Comparison of the degree of external root resorption of lower incisors and canines when using the Forsus Spring® over the arch or as part of a Crossbow® device in a RCT

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

Medical Sciences - Orthodontics

University of Alberta

ABSTRACT

Objective: Assess the degree of external root resorption among lower incisors and canines undergoing orthodontic movement with two Forsus® springs approaches.

Materials and methods: The sample of this RCT consisted of 23 patients treated with Forsus® springs over the arch and in 20 patients as part of a Crossbow® set up. CBCT imaging was taken before and after full orthodontic treatment completion. DICOMs were analyzed with ITK-Snap®. The volume of lower incisors and canine roots were assessed through an automated segmentation with manual adjustment on a 2D slice-by-slice basis. Their apical displacement was measured using 3D-Slicer®. Factors such as gender, treatment time, time with brackets were also considered. A MANOVA analysis was applied.

Results: No statistically significant difference on the percentage of root volume change in lower anterior teeth was found regardless of the treatment approach even when the above-listed co-variables were considered. The change was a decrease of 1.42% in the Crossbow® group and an increase of 0.27% in the Forsus® group.

Conclusions: Both treatment modalities produced similar amounts of root volume changes without clinically relevant differences. This can be interpreted as no significant root volume changes during orthodontic treatment or the proposed measure technique was not able to detect the minimal amount of root volume changes that may have occurred.

PREFACE

This thesis is an original work by Gaston Federico Coutsiers Morell (main author). The trial is registered at clinicaltrials.gov, under the number NCT01530516. The Human Ethics Research Office at the University of Alberta granted authorization (Pro00023805) for this study.

Chapters 1 (introduction) and 2 (methods) of this project were fully developed by the main author. The data collection and statistical analysis in chapter 3 (results) and the discussion and conclusions in chapter 4 are also the author's original work.

Dr. Kevin Chen helped as a secondary researcher. Dr. Heo supervised and corrected all the statistical analyses. Dr. Flores-Mir and Dr. Lagravère-Vich supervised and corrected the project in its entirety.

ACKNOWLEDGEMENTS

I would like to give special thanks to my supervisors and mentors: Dr. Flores-Mir and Dr. Lagravère-Vich; to Dr. Demirturk for participating in my project, to my stats professor, Dr. Heo; to my third-year colleagues with whom I worked closely during these last three years. To all the orthodontic team: instructors, staff, and residents. To the dental school as a whole, that has the most incredible atmosphere to develop dental professionals that I have never seen before; and last but not least, to my family who unconditionally supports me in every project I come up with.

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1 Chapter 1: Introduction

1.1 Class II Malocclusion, Diagnosis and Treatment

The first clear and simple classification of malocclusions was determined by Edward H. Angle in 1890:[1] He established that the upper first molars were the key to *normal occlusion* and that there were 3 types of malocclusions:

- Class I malocclusion,
- Class II malocclusion, and
- Class III malocclusion.

All of the proposed malocclusion types were based on the sagittal relationship of the lower molars relative to the upper first molars.

The main focus of this thesis is related to the Class II malocclusions, which Angle defined as the situation in which the lower first molar was distally positioned relative to the upper first molar. As the causes of this type of malocclusion are multiple, one of the first questions that the clinician should ask herself/himself while analyzing a Class II malocclusion case is the origin of the anterior-posterior discrepancy presented by the patient: is it caused by a jaw (skeletal) discrepancy, displaced teeth on well-proportioned jaws (dental Class II), or a combination of skeletal and dental displacements. Cephalometric analysis is advisable to determine the origin of the problem.[1]

After a correct and comprehensive diagnosis and the clarification of the cause of the Class II malocclusion, the clinician can elucidate different treatment options which should be patient specific. The range of age in which the patient is, will also narrow down the treatment possibilities. For instance, the treatment for an adolescent presenting a Class II malocclusion has two major possibilities:[1]

a) Differential growth management of the jaws, guided by extraoral force (headgear) or a so-called functional appliance (like Herbst) or

b) differential anteroposterior movement of the upper and lower teeth with or without differential closure of extraction spaces. This is known as camouflage and it should be considered when the patient presents reasonable jaw relationships, because it rarely succeeds in influencing growth according to Proffit.[1]

Once growth is completed or close to completion, the surgical treatment may also be a valid option for a lot of patients presenting a Class II. This treatment approach is addressed to adults and young adults.

The second type of treatment mentioned, which is also termed ‘camouflage’, includes three major ways to correct Class II:

1) Distal movement of the upper dentition,

2) differential anteroposterior tooth movement using extraction spaces, and

3) non-extraction treatment that consists primarily of forward movement of the lower dentition.[1]

The main focus of this thesis is related to the type of treatment that has the correction effects of 1) and 3) as listed previously. One way to achieve the correction is through the use of Forsus® springs. Forsus® springs are a specific brand of *intermaxillary springs.* While Class II intermaxillary elastics would depend on patient’s compliance, the Forsus® springs are fixed on the dentition, thus, require less patient cooperation. That is why they are also termed “compliance-free Class II correctors”.

Another classification of Class II correctors that helps to understand the Forsus® springs’ characteristics is as follows:

a) Active: The patient has to voluntarily move the mandible forward in order to avoid interference. For example: activator, bionator, twin-block and MARA.

b) Passive: The appliance restricts the patients’ mandibular motion to a specific forward path of closure. Within this category, both Herbst and Forsus® can be found.[1]

1.2 Forsus® Springs

The Forsus® spring consists of a nickel titanium alloy spring that pushes the lower dentition forward and the upper dentition backwards (Fig.1.1). The spring is assembled chairside: its superior part is introduced in the headgear tube of the bands on the upper first molars. On the lower arch, a pushrod is connected to the main archwire and it is usually placed either distal to the canine or distal to the first premolar. The ideal activation is around two mm of space between the compressed spring and the pushrod when the patient is biting in centric relationship. In order to activate it, the operator can use split spacers or modify the position of the pushrod.

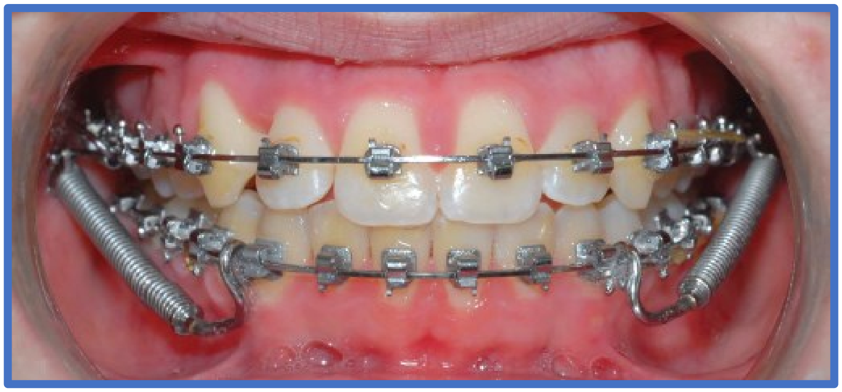

Figure 1.1: Bilateral Forsus® springs.

Normally, the Forsus® spring should correct an average Class II molar malocclusion in around six to eight months. In addition, the orthodontist has to account for one to two mm of possible relapse. Hence, once the correction is completed, the springs should be held in place in a passive form for a period of around 4 to 6 weeks. After removing the springs, the operator may identify adverse effects like posterior open bites or over-corrections into Class III, which is why posterior box elastics may be needed as follow-up after the springs have been removed.

To the best of our knowledge, the only systematic review that solely focuses on the dentoskeletal effects of the Forsus® spring was conducted by Linjawi et al.[2] The results stated that among the effects of the device, there was an increase on the occlusal plane inclination, protrusion with proclination and intrusion of the lower incisors, retroclination of upper incisors and distalization and intrusion of upper molars, with an associated reduction in overbite and overjet. Based on these effects, it seems that the lower anterior teeth will receive important significant forces. Among the resultant effects, it seems that we can expect that the lower incisors will end up proclined and intruded.

In order to start using the Forsus® spring in an orthodontic patient that requires it, the archwire sequence has to be advanced to a stage with a stiff rectangular wire, ideally a 19x25 Stainless Steel for 0.22 slot brackets. This is necessary for three reasons: there must be a certain control of the torque of the lower incisors to prevent further proclination when exposed to the anteriorly pushing forces from the springs, the wire has to be stiff enough to prevent unwanted bends while the force is applied and to transfer that force to the whole arch. For all these reasons, the Forsus® insertion has to be at a later stage of treatment, always when the level and alignment stages in both arches have been completed.

1.3 Crossbow® Appliance

A different treatment approach in order to use the Forsus® spring is as a component of the Crossbow® appliance, British Columbia, Canada. An issue that current orthodontic treatment presents is treatment duration. Being "in braces" implies a more difficult oral hygiene, and certain risks like dental decay or white spots or even OIERR (Orthodontically Induced External Root Resorption). Therefore, the less time the patient can be with bonded brackets to attain the treatment objectives, the better. For the reasons stated above, the inventor of the Crossbow®, D.W.H., introduced this philosophical approach that combines Forsus® fatigue resistant device (FRD) springs (3M Unitek, Monrovia, Calif), a palatal expander (hyrax) and mandibular lingual and buccal bows as it can be observed in Fig. 1.2.[3]

Figure 1.2: Crossbow ® appliance

Similar to a normal Forsus® spring device insertion, the maxillary part of the springs is inserted into the headgear tubes of the bands on the upper first molars. These bands are also part of a hyrax expander which usually has bands on upper premolars too. The mandibular part of the spring is connected to the lower buccal wire bow in the area of the canine and first premolar. The lower wire bow holds a Gurin lock (3M Unitek, Monrovia, Calif) which works as a stop for the spring and allows the activation of it. Both mandibular wire bows (lingual and buccal) are held together by bands on the lower first molars and by arm extensions coming from the lingual bow and bonded to the occlusal surfaces of the first premolars and sometimes second molars.[3]

The Crossbow® is conceptualized to allow for transverse (expansion) and antero-posterior corrections without the need to simultaneously use brackets on the patient. There is only one exception: if the patient presents lingually positioned or inclined maxillary incisors, these can be bracketed and aligned in a 2x4 arrangement.[3] This creates adequate overjet to allow for room for the Class II correction. Once both antero-posterior and transverse corrections have been achieved, the appliance can be removed, and full fixed appliances can be placed in order to finish the treatment by correcting the rotations, leveling the arches and finishing.

Theoretically, the total time in brackets would be reduced if the Class II correction has previously been done with Crossbow®. This is shown by one study in the literature that compares Forsus® to Crossbow®.[4] The mean treatment time was less with the Crossbow® when compared to Forsus® (24.2 and 30.2 months respectively, $p\text{-value} < 0.05$). This study also showed that the patients assigned to the Crossbow® appliance averaged ten fewer months of fixed edgewise appliances when compared to the patients assigned to Forsus®.

1.4 Orthodontically Induced External Root Resorption

Despite all the benefits of orthodontic treatments, these can also present some risks or adverse side effects. One of these risks is OIERR of the treated teeth (Fig. 1.3). Even if most of the time this side effect is not clinically relevant because it does not compromise the longevity of the affected teeth, the literature has proven that a high percentage of all orthodontically moved teeth are associated with histologically noticeable OIERR.[5-7]

Root resorption is defined as the destruction of the cementum or dentin by cementoclastic or osteoclastic activity; it may result in the shortening or blunting of the root. It is an inflammatory process resulting in an ischemic necrosis in the periodontal ligament when the orthodontic force is applied. Root resorption occurs when the pressure on the cementum exceeds its reparative capacity and dentin is exposed, allowing the multinucleated odontoclasts to degrade the root substance.[8]

There is a considerable amount of evidence that supports the association of orthodontic treatment with OIERR.[9] It also seems that OIERR is associated with increased level of orthodontic forces and increased orthodontic treatment time.[9] Therefore, the type of orthodontic appliance used, can cause more or less OIERR depending on the total time of use and the amount of force it exerts.

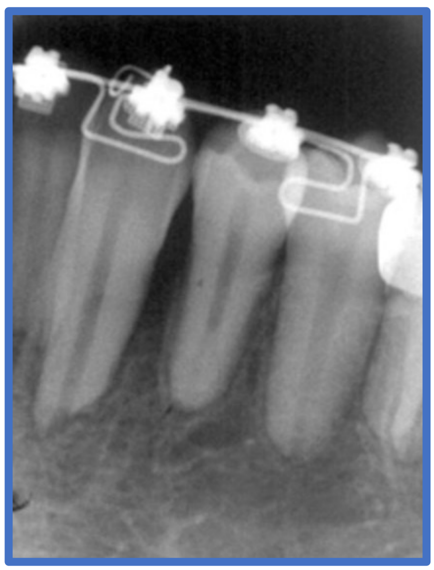

Figure 1.3: Example of OIERR caused by orthodontic forces.

OIERR can lead to significant consequences during or after orthodontic treatment. Among those, the most relevant ones would be mobility and loss of the affected teeth in severe cases. While posterior teeth are relatively unaffected, the most resorbed teeth are the maxillary anterior teeth. Twenty-five per cent of them undergo a level of resorption greater than two mm.[10] Consequently, it can generally be stated that OIERR is of greater clinical interest when found in the anterior segments.

OIERR is a multifactorial process.[11] A paucity of factors has been associated with this side effect of orthodontic treatment. For instance, increased overjet with no overbite was significantly associated with greater OIERR.[10] Logically, greater torque and larger root displacement is required to correct excess overjet. These are characteristics of the treatment requirements for the correction of Class II division one malocclusions.

Thus, quantifying and understanding how much OIERR is caused by certain devices can help the clinician to choose the adequate appliance for each patient. For instance, even if there is no difference in terms of OIERR in males and females, Hispanics and Caucasians are more prone than Asians to suffer from this clinical problem.[10] Therefore, in order to prevent complications, the clinician needs a deep understanding of the degree of OIERR caused by different appliances. This information would help to use the correct appliance to achieve efficient results with less OIERR risk.

The etiology of OIERR is widely discussed in Chapter 2, "Literature review". From the literature search, the maximum number of possible measurable independent variables was added to the initial hypotheses of our study. In addition, the analysis of all the different diagnostic methods historically used to assess OIERR was done in the same chapter. The limitations of two-dimensional methods were discussed as well as the benefits and limitations of three-dimensional methods, like the one employed in this study.

As it is explained in the chapter dedicated to the methods, traditionally, this orthodontic side effect has been known as External Apical Root Resorption (EARR). This term makes only reference to the decrease in tooth mass in the apical region of the tooth. Given the fact that this thesis is bases on three-dimensional measurements, the author of this thesis considers that EARR does not imply volumetric changes. That is why the term Orthodontically Induced External Root Resorption (OIERR) is proposed. This term intends to have a larger scope instead of being limited to the apical region, and it would also include resorption happening in any part of the root, not just on the apex.

1.5 Orthodontically Induced External Root Resorption & Class II Correctors

Patients that undergo major upper and lower incisors movements as part of a Class II camouflage treatment may undergo OIERR. This potential has not been extensively analyzed with newly available three-dimensional technology that allows improved, more accurate and more realistic quantification of OIERR. Using Cone-Beam Computed Tomographies (CBCT) of the patients treated in this randomized controlled trial (RCT), the author of this thesis intends to measure tooth volume of mandibular incisors and canines pre- and post-treatment. The patients underwent orthodontic treatment with one of the two following Class II camouflage approaches: a Forsus® group and a Crossbow® group. The author also analyzed the correlation between the amount of OIERR and other factors like sex, treatment time, time with brackets, and apical displacement.

1.6 Structure of this Master's Thesis Project

In chapter 2, a narrative literature review is going to be developed in order to put into context the process of OIERR within an orthodontic treatment in general and with the two studied appliances: Crossbow® and Forsus®. The already described in the literature risks factors for OIERR will be analyzed. The resolution of those hypotheses will help to understand the etiology of OIERR. In addition, the limitations of a two-dimensional versus three-dimensional diagnosis of OIERR will be analyzed and discussed.

In chapter 3, the methods that will be applied in the RCT to measure OIERR and other related variables that may influence the total amount of OIERR, will be presented and explained in detail. In addition to that, the whole RCT will be comprehensively explained. The described methods will be applied to the patients treated in the RCT as proof of concept in a clinical setting.

In chapter 4, the results of the methods' reliability, assessed in terms of reliability and measurement error, and the methods applied to the RCT sample will be presented. The CONSORT checklist was employed in order to prevent the missing of important aspects.[12]

In chapter 5, the final and general discussion of the whole project within the context of our current understanding and implications for future studies and clinical practice will be developed. Final conclusions will be added too.

1.7 Statement of the problem and study objectives

OIERR is a problem in orthodontically treated patients that can lead to catastrophic consequences in some cases. The Class II are common malocclusions and one of the usually employed methods to treat them consists in the differential dentoalveolar movement of the upper and lower teeth. Among the treatment philosophies to achieve that, the Forsus® and the Crossbow® are found. Both push the lower anterior teeth with significant amounts of force. Thus, the main purpose of this Master's thesis project is to determine the root resorption in the lower anterior teeth of the patients participating in a RCT which arms were Crossbow® and Forsus®. Given the possibility of using CBCTs from before and after treatment, the intention is to measure OIERR via a three-dimensional method instead of a two-dimensional method that would represent the traditional approach with all its limitations.

As far as we know, this is going to be the first study that assesses the amount of OIERR after the use of either the Crossbow® appliance or the Forsus® spring. In addition to that, this is the second study that compares Forsus® and Crossbow®;[4] however, it is the first one that compares them in a three-dimensional basis through the use of CBCTs.

The main objective of the study is to determine if there is a difference in the percentage of OIERR pre- and post-treatment considering all the jointly measured teeth. The secondary objectives are as follows: determine if there is a difference in the percentage of OIERR between the type of treatments, between sexes, and when the total treatment time, the time in brackets and the apical displacement are considered.

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2 Chapter 2: Literature Review

2.1 Given the fact that several systematic reviews have covered the topic of OIERR associated with different orthodontic therapeutic possibilities, as specific as for Class II malocclusions,[7] a narrative review of the literature was developed in order to try to answer the following questions:

- What does the literature suggest about Forsus® springs?

- What does the literature suggest about Crossbow®?

- What does the literature suggest about Forsus® and Crossbow® comparisons?

- What does the literature suggest about the relationship between OIERR and different orthodontic therapeutic options?

- What are the factors that may affect the amount of OIERR that can be seen in an orthodontic patient?

- What does the literature suggest about OIERR in Class II correction?

- Justification of the methods chosen for this study. Why 3D should be chosen over 2D analysis?

Our literature review is going to be based on systematic reviews unless no systematic review is found to answer a specific question, because this type of study "represents the most powerful tool to translate knowledge into action."[13] In addition, according to the systematic reviews published by Papadopoulos *et al.*,[14] and Segal *et al.*,[15] the correlation of OIERR and orthodontic therapy has a good level of evidence support.

2.2 What does the literature suggest about Forsus® springs?

Presently, only three systematic reviews were found discussing the effects of Forsus® springs or fixed Class II correctors as the main topic.

The first one relates to the additional appointments and discomfort associated with compliance-free fixed Class II correctors.[16] The authors concluded based on a low level of evidence with a weak recommendation strength that the main source of discomfort from Forsus®-type appliances appears to be soreness in the cheeks.

The second systematic review explored a comparison of the efficacy of fixed versus removable functional appliances in children with Class II malocclusion.[17] The authors concluded that "there is little evidence concerning the relative effectiveness of fixed and functional appliances or in relation to patient experiences and perceptions of these treatment modalities. Further well-designed clinical trials assessing the relative merits of both clinician- and patient-centred outcomes are needed".

The last related systematic review assessed the Forsus® dentoskeletal effects.[2] Among the results yielded, OIERR was not included. The reported effects of the device were an increase on the occlusal plane, protrusion, proclination and intrusion of the lower incisors, retroclination of upper incisors and distalization and intrusion of upper molars, as well as reduction in overbite and overjet.

Therefore, it seems that the teeth of the lower anterior region will be exposed to significant or large forces when this type of therapy is chosen. It appears that after using the Forsus® springs to correct a Class II malocclusion; one can expect that the lower incisors will end up proclined, protruded and intruded.

2.3 What does the literature suggest about Crossbow®?

Crossbow® appliance being a relatively new approach to treat Class II malocclusions, displays only a few results in the literature, eight in PubMed to be precise,[3,4,18-23] and none of them was a systematic review. None of studies about Crossbow® analyzed the amount of OIERR. Therefore, the general level of evidence about the Forsus® spring is higher than the one that can be found about the Crossbow®.

Those studies, however, allow us to understand the current concepts about Crossbow® presented in the literature. The conclusions of the relevant studies were as follows. The overall dentoskeletal effects of the Crossbow® measured in two-dimensional radiographs are: skeletally, a diminution of maxillary protrusion without mandibular advancement and an increase of the vertical dimension were found. Dentally, overjet correction was accomplished by an increase in mandibular incisor protrusion without maxillary incisor movement. The maxillary molars were distalized whereas the mandibular molars were mesialized.[3]

When compared to a Twin-block followed by fixed appliances both present a relatively similar combination of dental and skeletal effects. An average increase in mandibular incisor inclination of 9.5° for the Crossbow® group was noticed.[19] The treatment with the Crossbow® resulted in favorable increase in the oropharyngeal airway dimensions and volume when measured with CBCT.[20] The Crossbow® appliance has also a distalization effect on the maxillary molars. When distalizing maxillary first molars with a Crossbow® device, there is no difference in the amount of distalization in patients with erupted and unerupted maxillary second molars,[21] In relationship with the lower incisors, the Crossbow® will tend to procline them. However, there is a similar amount of incisor inclination when compared to Forsus® springs.[4] It seems that the average proclination is 3.04 degrees,[18] but the final amount cannot be predicted by the facial type of the patient.[23]

2.4 What does the literature suggest about Forsus® and Crossbow® comparisons?

One study in the literature has been found that compares Crossbow versus Forsus.[4] This study only compared final incisor inclination between both treatment modalities. The conclusion stated that there is no significant difference between groups. The mean change in lower incisor inclination was +3.39° and +4.80° for the Forsus® and the Crossbow® groups respectively. It was based on two-dimensional x-rays, lateral cephalograms, which is a main difference with this Master's thesis project in which CBCT was employed.

2.5 What does the literature suggest about the relationship between root resorption and different orthodontic therapeutic options?

Thirty-eight systematic reviews analyzed the relationship between different orthodontic treatment aspects that were related to OIERR. The pertinent reviews were classified by subjects as follows.

2.5.1 Extractions and OIERR

As summary, no difference in OIERR when *en masse* space closure is compared to a two-step retraction, when early is compared to late orthodontic treatment involving extractions. However, when extraction treatment is compared with nonextraction, a range of 0.26 to 0.3 mm difference in root length is found by different reviews, with more resorption in the extraction group. Indeed, it seems that extracting premolars may be an indicator of the severity of OIERR. This may be actually related to the amount of apical displacement of the affected teeth more than the fact that extractions were done or not as it will be explained later.

As previously mentioned in the introduction chapter, another way of dealing with Class II malocclusions is the camouflage type of treatment that involves extractions. The way the spaces are closed may influence the amount of OIERR. A recent systematic review explored, among other factors, the amount of OIERR when *en masse* space closure strategy is compared to a two-step retraction. The authors concluded that no significant difference was reported in the amount of OIERR between the two groups. Only two of the included studies reported the amount of OIERR. Both studies were found to be of low quality and a quantitative synthesis was not possible due to the difference in the measurements between studies. Maxillary central incisors: Reported no significant difference in the amount of OIERR between the two-step group (0.45 mm, SD 0.13) and the *en masse* group (0.42 mm, SD 0.12). Maxillary lateral incisors: Reported no significant difference in the amount of OIERR between the two-step group (0.60 mm, SD 0.11) and the *en masse* group (0.56 mm, SD 0.08). In any case, the study included measured OIERR on a two-dimensional basis as root length.[24]

Another systematic review analysed early vs late orthodontic treatment of tooth crowding by first premolar extraction.[25] Severe crowding caused by tooth size arch length deficiency may be treated at an early stage with serial extractions in the early mixed dentition or with later extractions in the permanent dentition. Of the six studies included only one study evaluated OIERR post–orthodontic treatment with serial extractions followed by mechanotherapy. This study suggested that there was no statistically significant difference between groups. The measurements on OIERR were linear; therefore, non-volumetric.

The systematic review published by Samandara *et al.* which was based only on CBCTs measurements, found that extraction treatment was associated with statistically greater OIERR of the upper anterior teeth than nonextraction treatment, which were 0.81 and 0.51 mm, respectively.[26] The explanation given by the authors is that space closure mechanics imply more treatment time, and treatment time is associated with the amount of OIERR. In any case, the difference is only 0.3mm which is one of the common voxel sizes of a full field of view CBCT used for comprehensive orthodontic assessment. Even if statistically significant, it may not be clinically relevant.

A Dutch clinical practice guideline about OIERR can be found in the literature.[27] In what concerns extraction versus nonextraction treatments, the authors concluded that there are indications that the extraction of premolars is an independent predictor of OIERR severity.

A meta-analysis published by Deng *et al.* focused on studies that measured OIERR only with the help of CBCTs.[28] The quantifications included in the meta-analysis were linear, more precise, according to the authors, because the CBCT does not present magnification. Treatments with extractions caused more OIERR than the one observed in the non-extraction treatments. The effect of tooth extraction on OIERR (1.03 ± 0.27) was greater than that in the non-extraction group (0.77 ± 0.40). A difference of 0.26 mm that is really close to the difference found in Samandara's review.

2.5.2 Bracket characteristics and OIERR

There does not seem to be evidence about the influence of the slot size in OIERR. Regarding self-ligating and conventional brackets, it seems that most reviews do not find any difference in terms of OIERR.

A systematic review assessing the effect of bracket slot size on the effectiveness of orthodontic treatment, found that none of the papers included measured the amount of OIERR, even if that was within the aims of the review.[29]

Forsus® springs can be combined with self-ligating or conventional brackets. A systematic review with meta-analysis tried to understand if there was a difference in the amount of OIERR of one type of ligation versus the other.[30] It seems that the only tooth that revealed a less amount of OIERR when treated with self-ligating was the maxillary central incisor, around 30% less compared to conventional. No differences were found in all the other incisors. Nonetheless, the main outcome was the reduction of root length that was either measured in millimeters or in percentage, which implies that only linear measurements were considered. No three-dimensional measurements were considered.

Another systematic review which was only based on CBCTs measurements did not find any difference in terms of OIERR when conventional fixed appliances where compared to self-ligating brackets.[26]

A previously published systematic review (2010) also assessed the different outcomes that self-ligating brackets can produce.[31] Only two studies included measured OIERR. One of them used panoramic x-rays,[32] and the other one, periapical radiographs.[33] The first one measured the root length in maxillary incisors and the second one in mandibular incisors. The amount of OIERR failed to reach statistical significance in both studies.

2.5.3 Treatment characteristics and OIERR

According to the following systematic reviews, the factors that may cause and increase the amount of OIERR are: high force level, increase treatment time, apical displacement, and intrusion movements.

The main objective of the following systematic review was to determine which evidence level supports the association of orthodontic force system and OIERR.[9] The authors concluded that "although a meta-analysis was not performed, from the available literature, it seems that positive correlations exist between increased force levels and increased OIERR, as well as between increased treatment time and increased OIERR. Moreover, a pause in tooth movement seems to be beneficial in reducing OIERR because it allows the resorbed cementum to heal." Interestingly, this is the only systematic review that addressed the OIERR evaluation by excluding studies that only used panoramic radiographs or lateral cephalograms. These exclusion criteria increased the methodologic quality assessment (mean of 72%, which corresponds to a high evidence level). The authors justified their choice explaining the inherent distortion and magnification problems that panoramic x-rays and cephalograms present when they are used to quantify OIERR.

Another systematic review that is related to the previous one, assessed the association between OIERR and orthodontic movement in patients with no history of OIERR.[5] The outcome in the inclusion criteria was OIERR measured either directly with histology or indirectly with a radiographic technique. Out of the eleven trials included in this study, six measured the amount of OIERR in extracted premolars, four in periapical radiographs and one study did not mention the technique employed. No study used CBCT to assess the amount of OIERR. The results drawn by this SR were: "Evidence suggests that comprehensive orthodontic treatment causes increased incidence and severity of OIERR, and heavy forces might be particularly harmful. OIERR is unaffected by archwire sequencing, bracket prescription, and self-ligation. Previous trauma and tooth morphology are unlikely causative factors. There is some evidence that a 2 to 3 month pause in treatment decreases total OIERR."

A well conducted meta-analyses by Segal *et al*. included 9 studies that assessed OIERR in maxillary incisors.[15] Exclusion criteria were history of trauma, prior endodontic treatment, and prior OIERR. The only criteria about the measurement of OIERR were pre- and post-operative x-rays. The conclusion of this meta-analyses pointed out that apical displacement ($r = 0.822$) and total treatment duration (r = 0.852) proved to be highly correlated with OIERR. The mean root resorption for eight of the studies was 1.421 ± 0.448 and the mean apical displacement was 2.382 ± 0.756.

Another systematic review also suggested a correlation between treatment duration and anteroposterior apical displacement and OIERR.[7] Nonetheless, the correlation was weak to moderate. The authors also suggested that factors that are associated with the duration of active treatment might result in increased levels of OIERR in the predisposed individual. OIERR in all the studies was measured in mm -linear measurements-, therefore, it can be deduced that all the studies measured the amount of OIERR in a two-dimensional basis. Data pooling of the selected reports was not possible because of methodological and clinical heterogeneity across studies. Consequently, an average value of OIERR could not be provided. In this review, mild to moderate root resorption is considered to be anything less than 1/3 of the original root length. Each study classified root resorption differently; however, all reported that the majority of teeth experienced mild to moderate resorption following treatment.

Treatment duration was associated to OIERR in the systematic review published by Samandara *et al.*[26] They found that the meta-regression showed a significant association of OIERR with treatment duration. The average increase in OIERR was 0.36 mm for every additional year of active treatment. The visual representation of their conclusions about treatment time can be observed in Fig. 2.1:

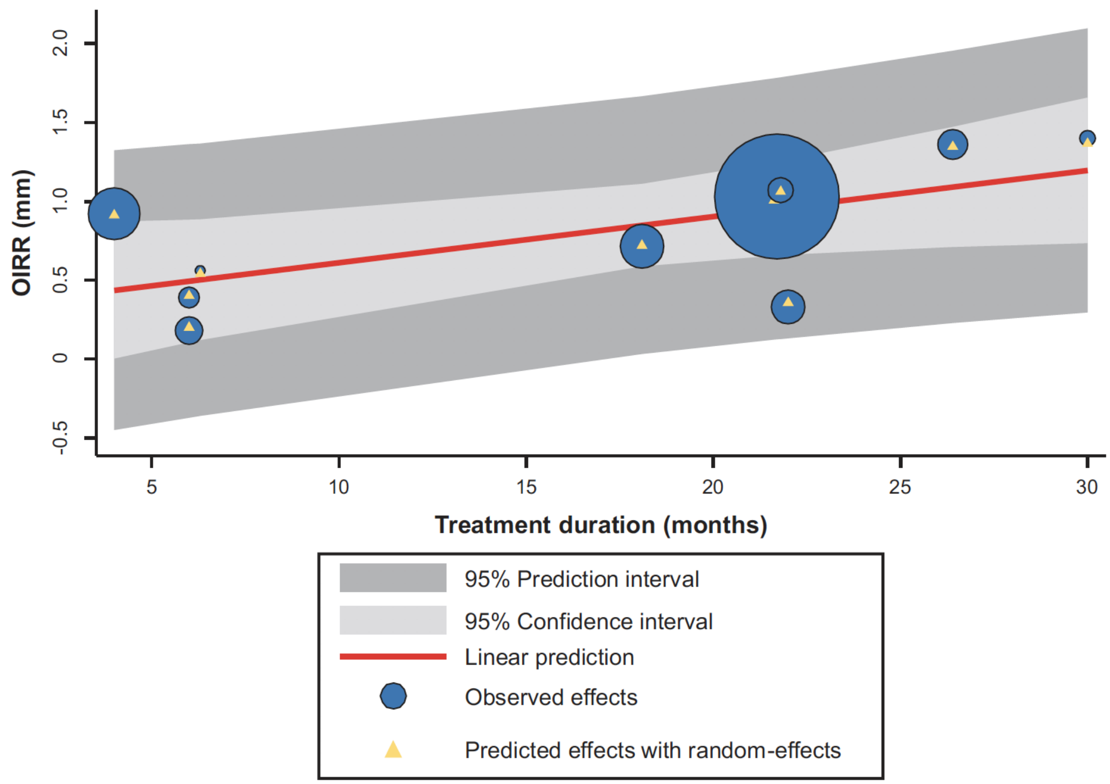


Figure 2.1: Graphic representation of the association of treatment time in months to the amount of OIERR

In the same systematic review, one randomized trial indicated that intrusion of upright incisors anchored from posterior mini implants yielded less OIERR than intrusion mechanics anchored anteriorly. The authors of this trial attributed the difference to the greater apical movement of the second group, which has already been proposed as risk factor for OIERR.[34,35]

Nine trials were included in a Cochrane systematic review which has as objective evaluating the initial archwires during orthodontic treatment with fixed appliances.[36] Even if it was stated on the initial objectives, none of the trials reported the amount of OIERR associated to the use of the initial archwires.

In the next systematic review, the authors attempted to answer to the following questions: In patients without a history of OIERR, does comprehensive orthodontic treatment, as compared with no tooth movement, result in a greater incidence of OIERR? What factors of comprehensive orthodontic treatment technique affect the severity of the observed OIERR?[37] The main conclusion of this review was: “The results were inconclusive regarding the clinical management of OIERR, but the evidence supports the use of light orthodontic forces, especially with incisor intrusion." In their final clinical advice for dental practice, they authors mentioned that "Assessing OIERR in a patient undergoing orthodontic treatment is best accomplished by means of periapical radiography of the anterior teeth." Even if we agree that this way of proceeding represents less radiation for the patient, we cannot think of periapical x-rays as gold standard to assess OIERR. The main reasons are discussed in later sections of this chapter.

2.5.4 OIERR and CBCT

Two systematic reviews that only included CBCTs for analysis of OIERR were identified.[26,28] However, most of the studies included in both of them used linear instead of volumetric measurements from the CBCT. Therefore, even if the researchers had the CBCTs they preferred or they chose to report linear values instead of volumetric values that may have given a more accurate and realistic information about the amount of OIERR given the fact that OIERR is a three-dimensional and not just a bi-dimensional issue.

As it could be noticed so far, all the systematic reviews are based on trials or retrospective studies that use two-dimensional x-rays. Nonetheless, there is one systematic review recently published (2019) in the European Journal of Orthodontics that only included studies with a CBCT assessment of OIERR.[26] The inclusion criteria, thought, comprehended linear or volumetric assessments of OIERR. All the RCTs that assessed OIERR through the means of CBCT should be included in this review. Nonetheless, none of them was similar to the present Master's thesis project in terms of therapeutic options.

Only 3 out of the 33 included studies reported volumetric measurements of OIERR from CBCT after fixed appliances. It seems that the average OIERR was 15.4 mm^3 95% CI=-4.1 to 35.0 mm^3. The authors mentioned in the limitations that the inclusion of retrospective studies was necessary due to the scarcity of randomized and prospective non-randomized trials. Indeed, the sensitivity analysis indicated that retrospective studies tended to show greater OIERR than prospective studies; 1.0 and 0.6 mm, respectively.

Among other conclusions, the authors stated that CBCTs seem to be a reliable tool to examine OIERR at the end of orthodontic treatment. It seems that the average OIERR across all studies involving fixed appliances was 0.79 mm for any treatment duration, and 0.86 mm from bonding to debond. There were important differences in the amount of OIERR between different groups of teeth. Interestingly enough, even if the measurements were made on a CBCT, only three studies reported a volumetric value after fixed appliances. Most of them reported a linear value.[26]

Another meta-analysis that only included OIERR measurements through CBCT, was published in 2018 by Deng *et al.* and it has already been cited in this project.[28] Most of the quantifications included in the meta-analysis were linear measurements, more precise than two-dimensional measurements, however, according to the authors. Some volumetric measurements were obtained. The results of the meta-analysis revealed that the root volume before and after orthodontic treatment was significantly different (mean difference = 23.12 mm3, 95% CI 17.88, 28.36) (Fig. 2.2)

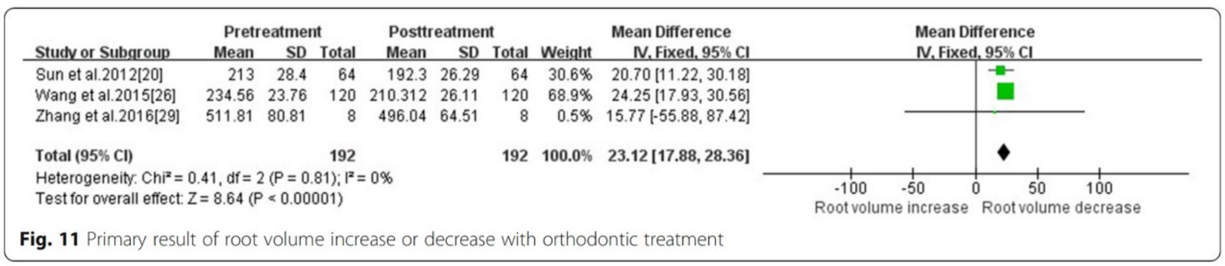


Figure 2.2: Forest plot of the volumetric changes before and after orthodontic treatment

2.6 What does the literature suggest about OIERR in Class II correction?

As far as we are aware of, there is only one systematic review in the literature that assesses OIERR after treatment in Class II patients, and it reflects the limited evidence in this subject.[7] According to the author's conclusions, the OIERR is not different in Class II treated cases when compared to the amount of OIERR in general orthodontic treatment.

This reviewed assessed radiologically determined OIERR in incisors after nonsurgical orthodontic treatment of Class II division 1 malocclusion. In the inclusion criteria, the outcome, OIERR, could be assessed by any kind of radiographic imaging; namely, periapical, cone-beam computer tomography images. Among the eight studies included in this systematic review, only one assessed OIERR with the help of a cephalometric x-ray. In all the other studies periapical x-rays were used with the same purpose. None of the included studies based its measurements on a CBCT.

The type of treatment to correct the Class II malocclusion varied from extractions to elastics, that is why the authors concluded that it seems that the treatment of Class II malocclusions with any of the treatment strategies, produces similar OIERR and the amount is at the same level to what is reported for orthodontic treatment of other types of malocclusions. In the discussion of this systematic review, the authors mentioned the limitation of using different two-dimensional techniques to assess a side effect that is three-dimensional. They also recommended that OIERR should be analysed with slices obtained in a CBCT. This would eliminate problems like magnification, superimposition of structures and would allow us to identify where the OIERR occurred.

2.7 Justification of the methods chosen for this study. Why three-dimensional should be chosen over two-dimensional analysis?

2.7.1 Limitations of the measurement of the tooth volume using two-dimensional techniques.

OIERR is a three-dimensional process that should be measured in a three-dimensional fashion. If measured through a two-dimensional approach, misleading conclusions may be obtained.[26] Dental roots can be reabsorbed simultaneously in different areas, namely: apical, buccal, lingual/palatal, mesial and distal. If the researcher or the clinician identifies and quantifies OIERR only based on a linear measurement, i.e., from the tip of the apex to the incisal edge, he or she may be missing an important part of the total amount of tooth mass loss that occurs in areas different than the apical segment. Overall, several studies that are going to be presented in this section suggested that the magnification degrees and the limitations of two-dimensional measurements of a three-dimensional process makes their accuracy questionable.

Orthodontic mechanics as part of a treatment approach can influence the location of the OIERR. For example, in a palatal expansion procedure, resorption seems to develop in the buccal-cervical surfaces. Nonetheless, this area remains undiagnosed as long as two-dimensional methods are used.[38] Some of the systematic reviews that analyze root resorption point at the same issue (see previous sections of this chapter).[7,9,26,39] One of them concluded that two-dimensional periapical radiographs do not fully reveal the amount of OIERR associated with maxillary expansion, except when there is a resultant frank apical OIERR.[39] Whereas, CBCT displays statistically significant OIERR associated with the same therapy.[39] Another systematic review also referred to the problems of measuring OIERR in cephalometric and panoramic x-rays.[9] "These issues may lead to inaccuracies in OIERR diagnosis and measurements", was one of the author's conclusions.

The limitations of two-dimensional methods in measuring OIERR were already described in a literature review back in 2004.[40] The authors stated that these methods of assessing OIERR have proven to be highly inaccurate because of magnification errors and their inability to be readily repeated and reproduced. Another study compared periapical x-rays (PAs), occlusal x-rays, panora1mic x-rays and CBCT scans.[41] They concluded that all the conventional radiographic methods demonstrated a more subjective procedure when compared to CBCTs when assessing root resorption. This last technique is more "accurate and precise".

Not only do CBCT techniques display clear advantages in general and apical OIERR, but also for external cervical resorption.[42] Treatment plans changed in the majority of the cases when periapical diagnosis was compared to CBCT imaging, given the fact that the CBCT provided with further information.

There is another *in-vivo* study that revealed this difference No significant differences between any incisors were observed in the two-dimensional analysis. However, the three-dimensional analysis revealed a significant difference in percentage root volume loss between the apical aspects of the central and lateral incisors, confirming that 2D analysis underestimates root resorption.[43]

- *Panoramic x-rays and OIERR measurements*

The main issues that panoramic x-rays present come from the foreshortening of the images, magnification issues and some structures being out of focus. In addition, the superimposition of different anatomic structures can create shadows or artifacts that can generate difficulties when reading of the x-ray.[44] An additional problem is that in patients with a severe Class II or III malocclusion or with proclined incisors, roots can be magnified or foreshortened.

Several studies pointed out the limitations of using a panoramic film to assess angulation of incisors and OIERR. In two studies,[45,46] the authors took panoramic x-rays of a skull in an ideal position and in several not ideal positions. The differences that resulted in the measurements of mesiodistal angulations were statistically significant even in just 5 degrees of positional changes. In the third study,[47] the buccolingual inclination was associated with the distortion of the root parallelism in panoramic x-rays. The most affected region was the canine area.

Another in vitro study that compared endo-oral radiographic techniques and panoramic x-rays in assessing OIERR, concluded that panoramic x-rays are not useful for the diagnosis of OIERR. The main reason is the increased distortion associated with that technique.[48] Another study compared different parameters on impacted upper canines, one of them being root resorption.[49] The radiographic assessment methods were panoramic x-rays and CBCT. Even if root resorption was evaluated just as “yes” or “no”, the authors reported that there was a very poor agreement between the two groups (panoramic x-ray and CBCT): the number of cases in which root resorption was not detected was 47 for the panoramic x-ray group and 6 for the CBCT group. Therefore, the authors concluded that three-dimensional imaging is more sensitive and provide a better detection of root resorption.

As it was reflected in the literature, the problem of measuring OIERR with panoramic x-rays does not come only from the fact that a three-dimensional process is measured in a two-dimensional manner. It also comes from the distortion and difficulty in visualizing several areas in the panoramic x-ray, which makes the task even more imprecise when a line has to be traced from the apex to the incisal edge.

- *Periapical radiographs (PAs) and OIERR measurements*

Other studies in other areas of dentistry, such as endodontics, have also examined and assessed the accuracy of CBCT compared to PAs in OIERR measurements.[50] One study assessed the accuracy of digital PAs and CBCT for diagnosis of natural and simulated OIERR.[51] The reference standard was the micro-computed tomography (micro-CT). They concluded that the CBCT was the best method to detect OIERR when compared to PAs, with a 20% difference in both natural and artificial OIERR cavities.

A systematic review reached to the same conclusions that the previously described papers: CBCT presents a higher diagnostic efficacy than PAs. In terms of sensitivity, CBCT had significantly higher sensitivity (0.89; 95% confidence interval [CI]: 0.77-0.96) than PAs (sensitivity: 0.68; 95% CI: 0.56-0.78).[52]

An *in vitro* study compared the diagnostic accuracy of CBCT and PAs but, this time, in internal root resorption. They found that even if the CBCT has a higher sensitivity, specificity, positive and negative predictive value in comparison with conventional radiography, the difference was not significant.[53]

A different study, in which traumatized teeth were analyzed, the authors also concluded that CBCT was superior to digital PAs in diagnosing external and internal root resorption after dental trauma.[54] It also seems that the CBCT superiority in diagnosis compared to PAs is extended to cervical resorption.[55]

The last study to be mentioned in this section suggested CBCT superiority in detecting multiple dental conditions, among them, incipient external root resorption, when compared to digital Pas.[56]

The two last studies of this section are based on histological measurements. The first one is a very comprehensive study that showed that CBCT is the most accurate technique when measuring root length and root resorption. CBCTs were compared to PAs in both perpendicular and bisecting technique and to Panoramic x-rays to the gold standard for this study, which was extraction and histology. Even if it seems that PAs can be as accurate as CBCT in measuring only root length, panoramic x-rays are not a good diagnostic tool for measuring root length or root resorption. This study used deciduous canines that had to be extracted for orthodontic reasons.[57]

Another *in vitro* study compared the diagnostic accuracy of OIERR among other pathologies, performed by CBCT, panoramic radiographs, and conventional and digital PAs. The authors also concluded that CBCTs showed the best results in the diagnosis of OIERR, whereas panoramic x-rays were considered not appropriate for the diagnosis of OIERR given their lack of accuracy.[58]

- *Lateral cephalometric x-rays and OIERR measurements*

It seems that even if the lateral cephalogram provides an accurate view of the length of the upper incisor, it is likely to be subjected to a 5-12% enlargement factor as a result of the radiographic set-up. In addition, the super-imposition of all the incisors, left and right side, increases the difficulty of obtaining precise measurements with this technique.[59]

The distortion, magnification and superimposition problems while measuring root length on lateral cephalograms were also detected and reported in the meta-analysis carried out by Segal *et al*. The authors concluded that these inaccuracies in OIERR measurements may lead to misleading conclusions.[15]

- *Conclusions of the limitations of two-dimensional x-rays when measuring OIERR*

It seems that although two-dimensional radiographs may be an appropriate diagnostic tool for several clinical and research purposes, their use while quantifying OIERR may be limited. Despite of all the limitations described, most of the studies about OIERR, and almost all of the studies included in systematic reviews about OIERR, used two-dimensional measurements. Interestingly enough, two-dimensional measurements were not only made when two-dimensional x-rays were taken, but also when CBCTs were taken and were available. Three-dimensional assessment should be the standard way for measuring a three-dimensional process.

2.8 Limitations of the measurement of the apical displacement using two-dimensional techniques.

- *Overall issues of measuring a three-dimensional process on a two-dimensional basis*

As seen in different systematic reviews, the amount of apical displacement seems to be related to the amount of OIERR.[7,15] Therefore, measuring and including the amount of apical displacement is necessary to confirm and better understand its correlation with OIERR.

Traditionally, before the CBCT era, the overall root and apical displacement was measured in two-dimensional x-rays. In a similar direction to what was explained for OIERR, the quantification of a three-dimensional process in a two-dimensional basis has limitations. The apices of the teeth during orthodontic treatment may move in any direction of the space, therefore, by using a two-dimensional imaging method, the third dimension is definitely missing.

Other problems with these types of measurements, like distortion, can be present in two-dimensional techniques like panoramic x-rays. The study developed by Bouwens *et al*., has shown that CBCTs would be superior in revealing true root angulations when compared to panoramic x-rays. The reason for that is that a panoramic x-ray can distort tooth position and inclination and the magnification can vary on different parts of the image. The authors concluded that "the assessment of mesiodistal tooth angulation with panoramic radiography should be approached with caution and reinforced by a thorough clinical examination of the dentition".[60]

As one of the meta-analysis analyzed in previous sections noted, there is a paucity of studies that use the apex as a reference point to determine the distance that a tooth has been displaced. It seems that most studies use angles such as SN to U1 or FH to U1 as a proxy.[14,15] The problem with that approach is that the proclination or retroclination of a tooth may not necessarily imply apical displacement. As well as a bodily displacement of the tooth many not imply changes in tooth inclination. The author of this thesis believes that a three-dimensional coordinate system based on CBCT segmentations and landmarks, would allow a spatial localization of the apices and the quantification of their displacement. The description of this method is in the following.

In the same discussion, the authors argue that one of the problems of measuring the apical displacement is the difficulty to pinpoint this landmark on cephalometric x-rays. A 1 mm discrepancy between measurements can alter the results in a significant way because the normal apical displacement seems to be in between 1.5 and 3 mm. Another problem seems to be that a lot of studies are retrospective so the researches cannot re-take x-rays.[15]

- Conclusions of the limitations of two-dimensional x-rays when measuring apical displacement

Some of the issues noticed in the literature could be solved by using the technique proposed in the following chapter that is based on CBCT measurements. By measuring the apical displacement in a three-dimensional basis, none of the dimensions is missing. The accuracy of measuring apical displacement of every single incisor in a three-dimensional basis is obviously superior than measuring the four incisors overlapping in a cephalometric x-ray.

2.9 Summary, justification and new methods proposed.

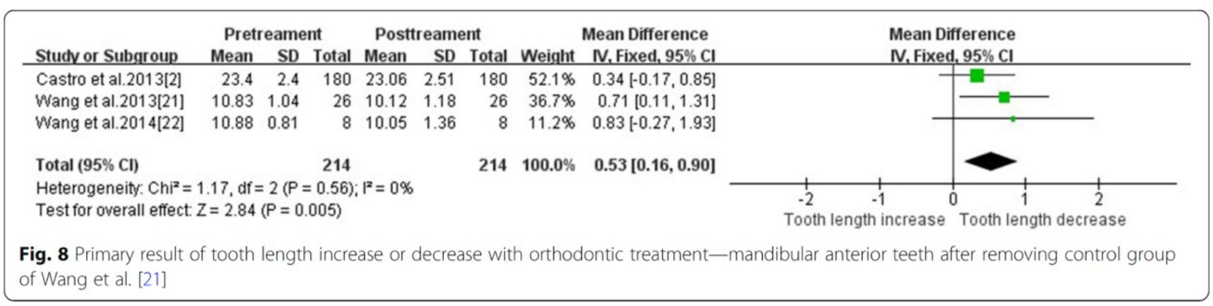
Chan, *et al.* in their literature review published under the title:
Exploring the third dimension in root resorption,[40] gives a concise summary of the limitation of two-dimensional techniques and the advantages of the three-dimensional techniques: "although two-dimensional radiography may be a good diagnostic tool, its use in the quantification of external root resorption should be avoided. With the evolution in computing technology and digital imaging, the vision of evaluating the extent of root resorption in three dimensions has materialized. It was demonstrated that three-dimensional volumetric quantitative evaluation of root resorption craters was feasible, and its accuracy and repeatability was high."

The two-dimensional measurements of both the volume of the teeth and the apical displacement seem to present several issues and not to be the most reliable and accurate way of quantifying both outcomes. Therefore, two techniques were needed in order to analyze those outcomes: The construction of three-dimensional volumetric label maps of lower incisors and canines from CBCT images in order to assess volume using the software ITK-SNAP®: "in-block" automatic segmentation with manual refinements; and the quantification of linear displacement of the apices of lower incisors and canines within the symphysis from CBCT images using the softwares ITK-SNAP® and 3DSlicer®. In the following chapter, both techniques are explained in detailed and tested through the inter- and intra-reliability analysis.

2.10 Conclusion, determination of the independent variables and statement of the problem.

The Forsus® that is used in both of the RCT groups, one as Forsus® itself and the other as Crossbow®, causes protrusion, proclination and intrusion of the lower incisors. In addition, it has been shown that there is a similar amount of incisor inclination when Crossbow® is compared to Forsus® springs.[4] The mean lower incisor proclination caused by Crossbow® has been quantified as much as 3.04°.[18] The Crossbow® also generates mandibular incisor protrusion.[3]

The lower anterior teeth seem to be one of the groups of teeth that suffer the most OIERR. According to the meta-analysis by Deng *et al.*,[28] statistically significant differences in OIERR were seen across the different regions within a jaw, with the anterior maxilla showing the greatest among of OIERR (0.82 mm), followed by the anterior mandible (0.60 mm), the posterior mandible (0.28 mm), and finally the posterior maxilla (0.22 mm). In conclusion, the sequence of OIERR from heaviest to lightest was maxillary lateral incisors, maxillary central incisors, mandibular anterior teeth, and maxillary canines. The tooth length of mandibular anterior teeth was reported by three studies (Fig. 2.3). The changes of tooth length in mandibular anterior teeth using CBCT were MD = 0.53 mm 95% CI 0.16, 0.90, P < 0.00001). Therefore, the teeth measured in this thesis RCT are actually subject to an important amount of OIERR relative to other groups of teeth; however, it may not be that relevant from a clinical point of view.



Study or Subgroup	Pretreament Mean	SD	Total	Posttreament Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Castro et al.2013[2]	23.4	2.4	180	23.06	2.51	180	52.1%	0.34 [-0.17, 0.85]
Wang et al.2013[21]	10.83	1.04	26	10.12	1.18	26	36.7%	0.71 [0.11, 1.31]
Wang et al.2014[22]	10.88	0.81	8	10.05	1.36	8	11.2%	0.83 [-0.27, 1.93]
Total (95% CI)			214			214	100.0%	0.53 [0.16, 0.90]

Heterogeneity: Chi² = 1.17, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.84 (P = 0.005)

Fig. 8 Primary result of tooth length increase or decrease with orthodontic treatment—mandibular anterior teeth after removing control group of Wang et al. [21]

Figure 2.3: Forest plot of the length change of the mandibular anterior teeth

Given the fact that the lower anterior teeth seem to be affected by the forces applied by the previously mentioned types of treatment and that they belong to the groups of teeth with higher OIERR, they are going to be measured in order to calculate the resultant OIERR pre- and post-treatment. The next natural question would be related to the amount of OIERR related to the type of treatment, Forsus® or Crossbow®. These two philosophies of Class II correctors are going to be the first independent variables. The corresponding hypotheses are **H_o1, H_a1, H_o2** and **H_a2.**

H_o1: There is no difference in the percentage of OIERR pre- and post-treatment considering all the measured teeth jointly.

H_a1: There is difference in the percentage of OIERR pre- and post-treatment considering all the measured teeth jointly.

H_o2: There is no difference in the percentage of OIERR between the type of treatments.

H_a2: There is difference in the percentage of OIERR between the type of treatments.

The following hypotheses, **H_o3** and **H_a3**, set sex as an independent variable. Some studies suggested that sex as risk factors for OIERR needs further study.[61] Therefore, the committee meeting responsible for this Master's thesis project decided that it would be worth to consider it.

H_o3: There is no difference in the percentage of OIERR between females and males.

H_a3: There is difference in the percentage of OIERR between females and males.

Nonetheless, some studies like a recently published Dutch clinical guideline based on a systematic review concluded that there are indications that gender is not an independent predictor of OIERR severity.[27] In other words, there is no correlation between gender and OIERR. They found a moderate level of evidence that supports that statement about gender and also about age.

As previously stated by several of the systematic reviews, active treatment time is a risk factor for OIERR.[7,9,26,] One of the main differences between the two groups of the study is the fact that the Forsus® approach starts with brackets that are initially not necessary for the anteroposterior correction with the Crossbow® appliance. In addition, the Dutch clinical guideline concluded that treatment duration was a potential risk factor of OIERR, rated with a 'low' evidence level.[27] Those points generate the following hypotheses: **H_o4, H_a4, H_o5** and **H_a5.**

H_o4: There is no difference in the percentage of OIERR when considered the total treatment time.

H_a4: There is difference in the percentage of OIERR when considered the total treatment time.

H_o5: There is no difference in the percentage of OIERR when considered the time in brackets.

H_a5: There is difference in the percentage of OIERR when considered the time in brackets.

Several studies that analyze the amount of apical displacement seems to be a proven clear risk factor for OIERR,[7,15,34,35] which generates the last two hypotheses: **H_o6** and **H_a6**. Nonetheless, the Dutch clinical guideline on OIERR developed by Sondeijker *et al.*[27] suggested that it is not clear whether horizontal apical root displacements are associated with OIERR severity. The included study reported a positive correlation; however, it presented a low confidence in that finding. Whereas regarding vertical apical displacement, the authors concluded that it is not clear whether vertical apical root displacements are associated with OIERR severity. The included study reported no association between vertical apical displacement and OIERR severity.

H_o6: There is no difference in the percentage of OIERR when considering apical displacement.

H_a6: There is difference in the percentage of OIERR between considered apical displacements.

Other risk factors of OIERR that could be found in this literature review, like level of the force applied,[5,37] could not be measured in this RCT.

As far as we know, this is going to be the first study that assesses the amount of OIERR after the use of either the Crossbow® appliance or the Forsus® spring. In addition to that, this is the second study that compares Forsus® and Crossbow®;[4] however, it is the first one that compares them in a three-dimensional basis through the use of CBCTs.

As it could be observed even if the number of studies that incorporates the accurate and more realistic measurements of OIERR is increasing, most of them are based on two-dimensional measurements instead of three-dimensionally. This is a way in which our study is a differentiator, providing with more evidence to the literature by using three-dimensional measurements of OIERR in a three-dimensional x-ray (CBCT).

It has been shown by sensitivity analysis that retrospective studies tended to show greater OIERR than prospective studies, 1.0 and 0.6 mm, respectively.[26] Indeed, the authors of that specific paper mentioned in the limitations that the inclusion of retrospective studies was necessary due to the scarcity of randomized and prospective non-randomized trials. This is another forte of our study, given the fact that it is a prospective RCT.

It seems also that there is limited evidence suggesting that OIERR does not vary in different approaches in Class II corrections.[7] Our study will provide a high level of evidence regarding this matter because it is a RCT.

The summary of the literature review regarding the comparison between two- and three-dimensional methods to study OIERR is as follows. The two-dimensional measurements of both the volume of the teeth and the apical displacement seem to present several issues and not to be the most reliable and accurate way of quantifying both outcomes. Therefore, two techniques were needed in order to analyze those outcomes: The construction of three-dimensional volumetric label maps of lower incisors and canines from CBCT images in order to assess volume using the software ITK-SNAP®: "in-block" automatic segmentation with manual refinements; and the quantification of linear displacement of the apices of lower incisors and canines within the symphysis from CBCT images using the softwares ITK-SNAP® and 3DSlicer®.

In a nutshell, this study is the first of its kind that measures OIERR in Class II patients through CBCT employing volumetric and not linear measurements. Specific three-dimensional measurement methodology will have to be created and tested for reliability. Only thereafter data from a completed RCT will be sued to apply the methodology in a real-life scenario.

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3 Chapter 3: Materials & Methods; Measurements of the Lower Incisors’ and Canines’ Volumes through the “In-Block” Technique, and their Apical Displacements within the Symphysis through CBCT Imaging Reconstruction: Inter- and Intra-Rater Reliability Analyses and RCT Methodology Explanation

3.1 Construction of three-dimensional volumetric label maps of lower incisors and canines from CBCT images in order to assess volume using ITK-SNAP software®: "in-block" automatic segmentation with manual refinements.

3.1.1 Software selection

The reasoning behind the software selection for this part of the project was as follows. To bridge the gap between methodological advances and clinical routine, ITK-SNAP® was developed as an open source, which is intended to make level set segmentation from CBCT imaging easily accessible to a wide range of users, including those with little or no mathematical expertise. ITK-SNAP® has been used in previous projects to segment structures from three-dimensional x-rays. The first time that the software itself was validated was while using it for segmentation of children's brains. The authors' conclusion was: "ITK-SNAP is a highly reliable and efficient alternative to manual tracing."[62]

For similar previous segmentation projects performed in this dental school the software Avizo® has been the choice, however, the interface is more difficult to use and less intuitive than ITK-SNAP®. This previous statement is the subjective opinion of the author of this thesis, who also recognizes that the same segmentation work and probably similar results could have been achieved with equivalent software. Dolphin® was not an option because it does not allow manual segmentation.

3.1.2 Study population and data collection for the volume measurements of lower incisors and canines for inter- and intra-reliability analyses.

Two orthodontic residents (KC and GCM) with the same background and experience developed an approach on how to segment teeth and obtain measurements of volume with the software ITK-SNAP®. Five patients from the studied sample were randomly selected using the software Microsoft Excel® and its randomization function. The patients were treated either with the Forsus® or Crossbow® appliances, as they belong to the RCT that is the main subject of this thesis. One of the two time points (T0 or T1) of the previously selected patients was also randomly selected using the same software and the same function.

Measurements were taken following the technique described in the next section of this chapter. Three consecutive measurements of the same six teeth were taken by the main researcher (GCM). Each set of measurements was taken one week apart from each other. The assistant researcher (KC) took only one set of measurements. All the consecutive measurements can be found on Table 3.1. For the inter-rater reliability analysis, KC's measurements were compared to GCM's second measurements.

Patient number	Tooth number	GCM 1st set of measurements (March 9th, 2019)	GCM 2nd set measurements (March 16th, 2019)	GCM 3rd set of measurements (March 23th, 2019)	KC unique set of measurements (March 9th, 2019)
1	3.3	393.9	399.1	383.2	358.4
	3.2	267.5	274	256.7	268.1
	3.1	232.6	235.6	222.6	212.7
	4.1	231.6	234.1	221.9	207
	4.2	266	269.7	256	248.3
	4.3	409.8	410.4	397.6	373.3
2	3.3	603.5	572	586.4	497.2
	3.2	337.3	317.8	331.6	294.7
	3.1	290.2	286.1	296.9	263.7
	4.1	284.8	270.1	279.1	273
	4.2	316.8	298	308.9	279.1
	4.3	566.5	528.2	536.4	467.3
3	3.3	667.9	626.8	648.7	670.9
	3.2	306.6	300.5	313.1	334.9
	3.1	225.1	224.3	234.5	230
	4.1	253.7	240.6	255.2	243

	4.2	319.5	303	320.7	316.1
	4.3	677.5	624.4	638.3	678.5
4	3.3	572.8	537.9	566.1	573.2
	3.2	389.9	348.3	373.2	375.7
	3.1	334.9	296.9	319	313.9
	4.1	324.6	286	303.7	305.9
	4.2	367.7	326.6	352.8	351.5
	4.3	564.3	519.1	545.6	542.7
5	3.3	450.6	449	468.8	472.1
	3.2	256.3	261.4	270.8	279.8
	3.1	219.8	225	236.2	243.9
	4.1	227.6	231.8	238.8	246.8
	4.2	268.2	271.2	273.3	300.5
	4.3	477.6	473	487.8	484.6

Table 3.1: Measurements from both researchers, GCM and KC, for inter- and intra-reliability analyses**.**

3.1.3 Step by step process of the segmentation for the volumetric measurements

Once ITK-SNAP Software® is launched, the display menu from File is used to open a main image, which, in this study, is a CBCT DICOM file. The volume selected is displayed in the three different planes: axial, sagittal and coronal (Fig. 3.1). Before starting the segmentation process, adjusting the contrast is suggested in order to better depict the image and distinguish the different tissues. The contrast taken to the extremes may difficult the visualization of the areas of interest.

Figure 3.1: Main imaged opened and volume displayed in the three planes.

Using the loop on the Main Toolbar, the anterior sector of the mandible is zoomed into. Once, a closer view of the tooth in all the three planes is obtained, the Active Contour Function, aka "Snake", is selected from the Main Toolbar in order to limit the area of the volume that is necessary for segmentation: lower incisors and canines. Thus, a rectangular parallelepiped is made as fit as possible to the aimed teeth (Figs. 3.2a and 3.2b).

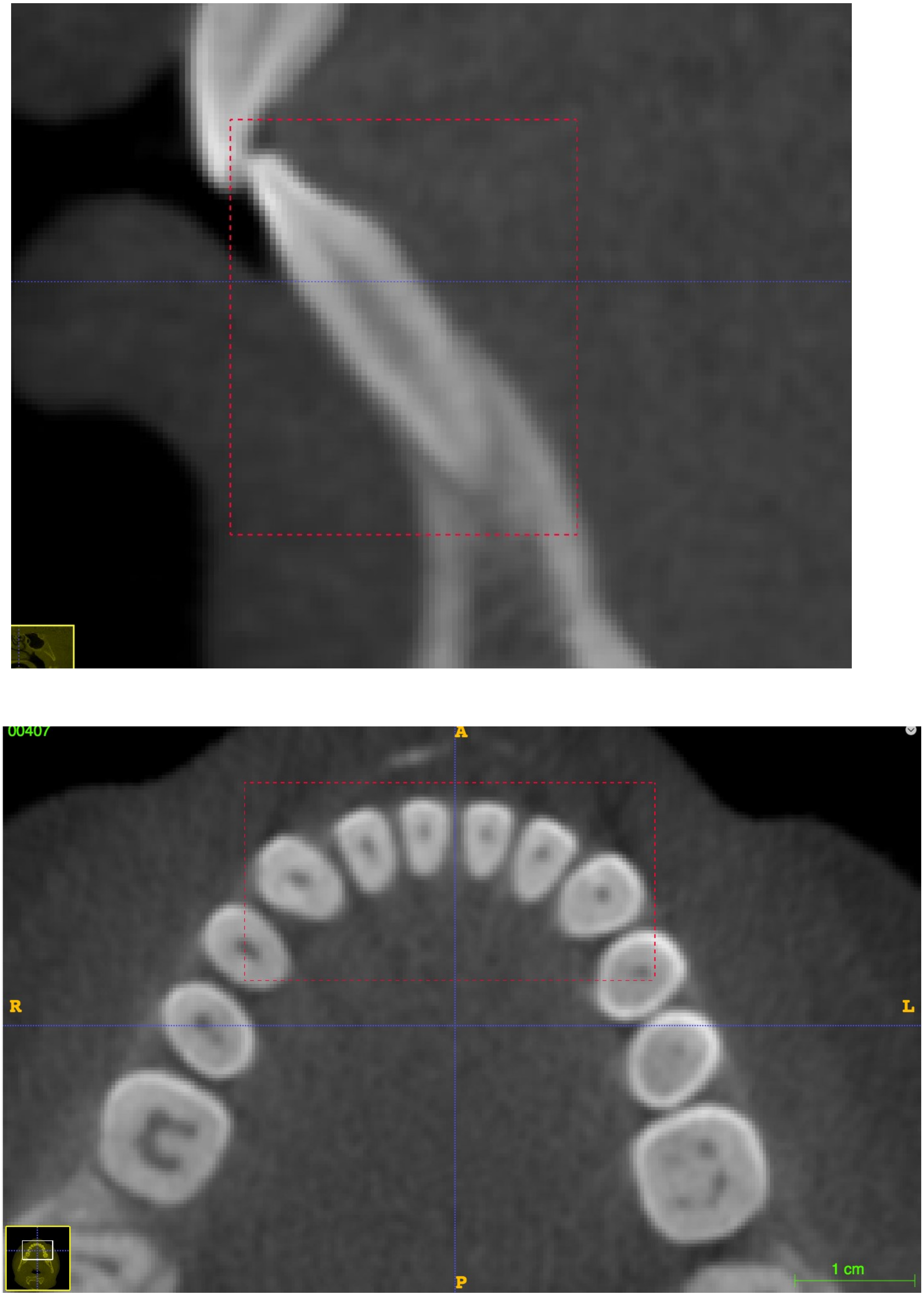

Figure 3.2(a and b): Fitting of the rectangular parallelepiped of the Active Contour Function.

The next step is to push the “Segment 3D” button on the left column. There are several segmentation methods available with ITK-SNAP®; the one used for this research is “Threshold”. On the right column, the threshold levels can be changed. The upper threshold is placed to the maximum, whereas the lower threshold is individually adapted for every patient. By arbitrary agreement between the researchers involved in this project, the lower threshold range was considered from 500 to 1500. Within that threshold, the operator chose the one that better allows the clearest visualization of the root and crown of the tooth to be measured without losing tooth structure (Fig. 3.3). From the author’s experience, switching between the blue and white and the grey scale images helps to gain some insight of the ideal threshold for the specific patient and tooth.

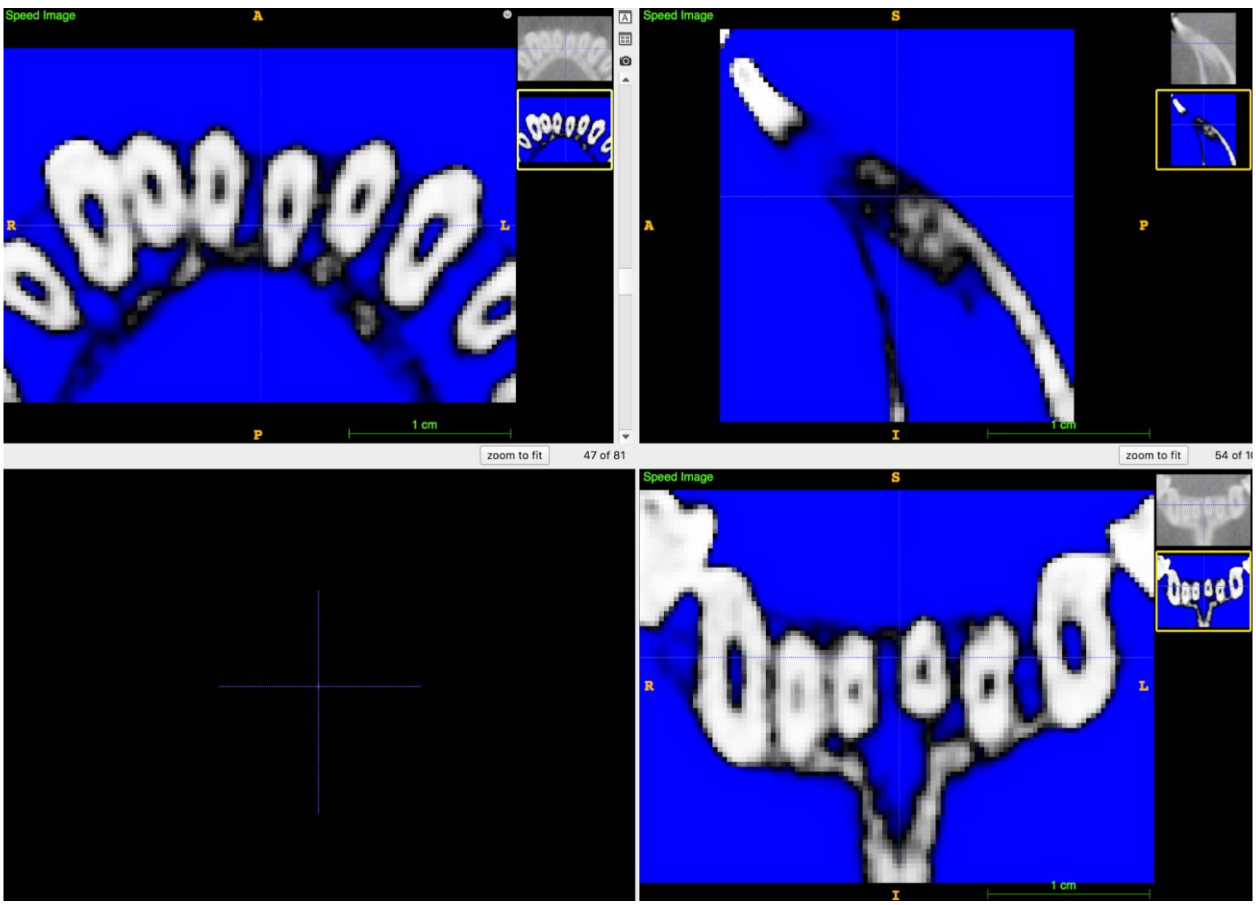

Figure 3.3: Lower threshold selection

Once the appropriate threshold is selected, the next step consists of adding bubbles or, as called by ITK-SNAP® developers, “seeds”. The seeds are centres of expansion of the segmentation colored label within the previously selected threshold. Their radius was chosen at around one because it is the size that approximately fits the thinnest areas of the root of a lower incisor, and also because with smaller seeds the researcher can better visually control the expansion of the segmentation as it occurs. Around four to five seeds per tooth are placed the most equidistant as possible from one to another. The seeds are added close to the center of the teeth, along their long axis and adjacently to the pulp canal and chamber, however, they have to remain within the hard tissue (Fig. 3.4). These bubbles are going to expand and automatically include the hard tissues of the tooth into the label. Then, the play button is pressed, and the seeds fill the volume of the tooth. In the parameters, the smoothing option has to be set at 0, otherwise, there may be modifications of the surface and volume of the tooth segmented.

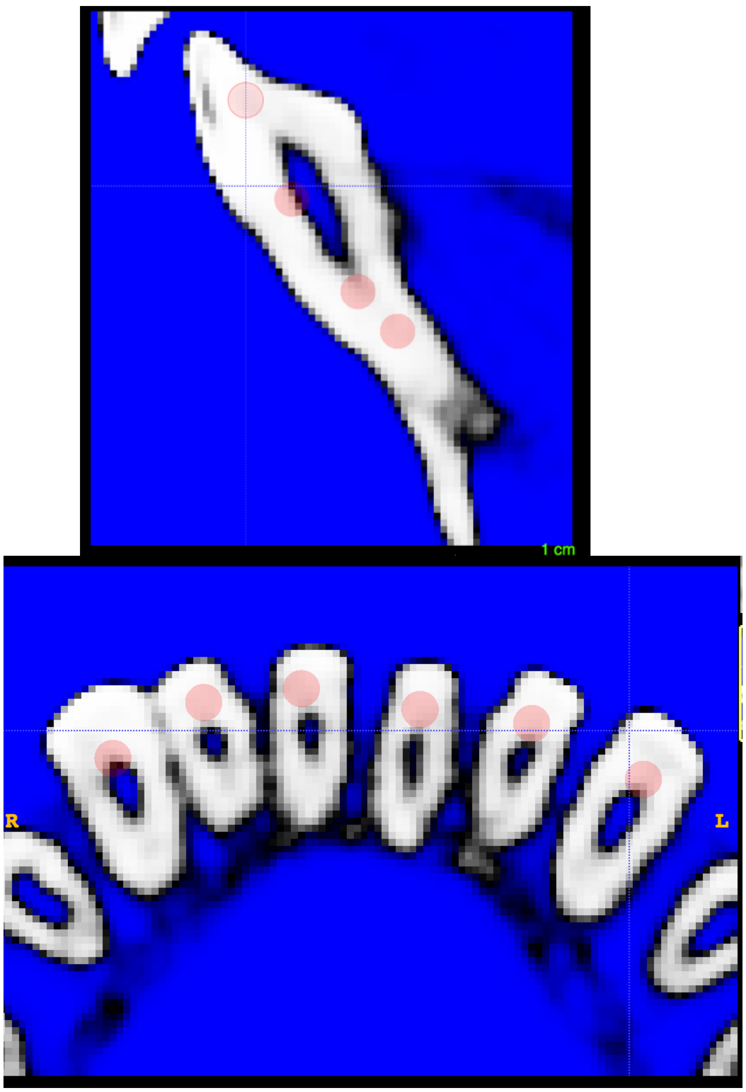

Figure 3.4: Seeds placed on the teeth

Once the tooth is filled, the automatic part of the segmentation is completed, and the researcher can proceed with the manual refinement (Fig. 3.5).

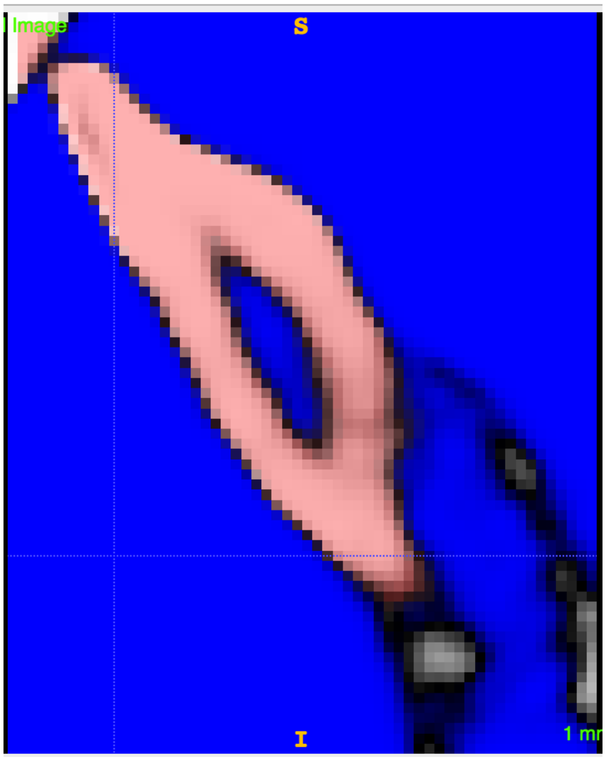

Figure 3.5: End of the automatic segmentation step

The manual refinement is necessary because the algorithm used in the automatic segmentation only distinguishes between pre-determined thresholds surfaces. Hence, for structures that are really closed in terms of radiopacity, like bone and cementum, the automatic segmentation alone will not be able to clearly differentiate them.

The manual refinement is done thanks to the Paintbrush Mode on the Main Toolbar, but before that, it is convenient to adjust the Overall Label Opacity. By reducing this parameter, the operator can better see the contours of the root and the crown of the segmented teeth, which will allow the operator to differentiate between the alveolar bone and the root. This function does not alter the amount of structure incorporated in the label; it just makes the label more translucent. With the Paintbrush Mode, the colored surface in the label, which is the one that is going to be included in the final volume calculation, can be increased or reduced.

The manual refinement is done in three planes, one at a time, to get the tooth surface and volume closer to the actual anatomy of the tooth (Fig. 3.6); normally the researcher starts by the axial and sagittal planes and the coronal plane is rarely used if the previous planes were segmented in detail. The size of the brush can be adapted accordingly to the necessity of adding or removing areas in a more efficient way. The size of the brushes used ranged from two to twelve. In this stage, it is important to also fill the pulp chamber because the volume calculation is performed including it for the reasons mentioned in the following sections. Overall, this is the most time-consuming step for the researcher.

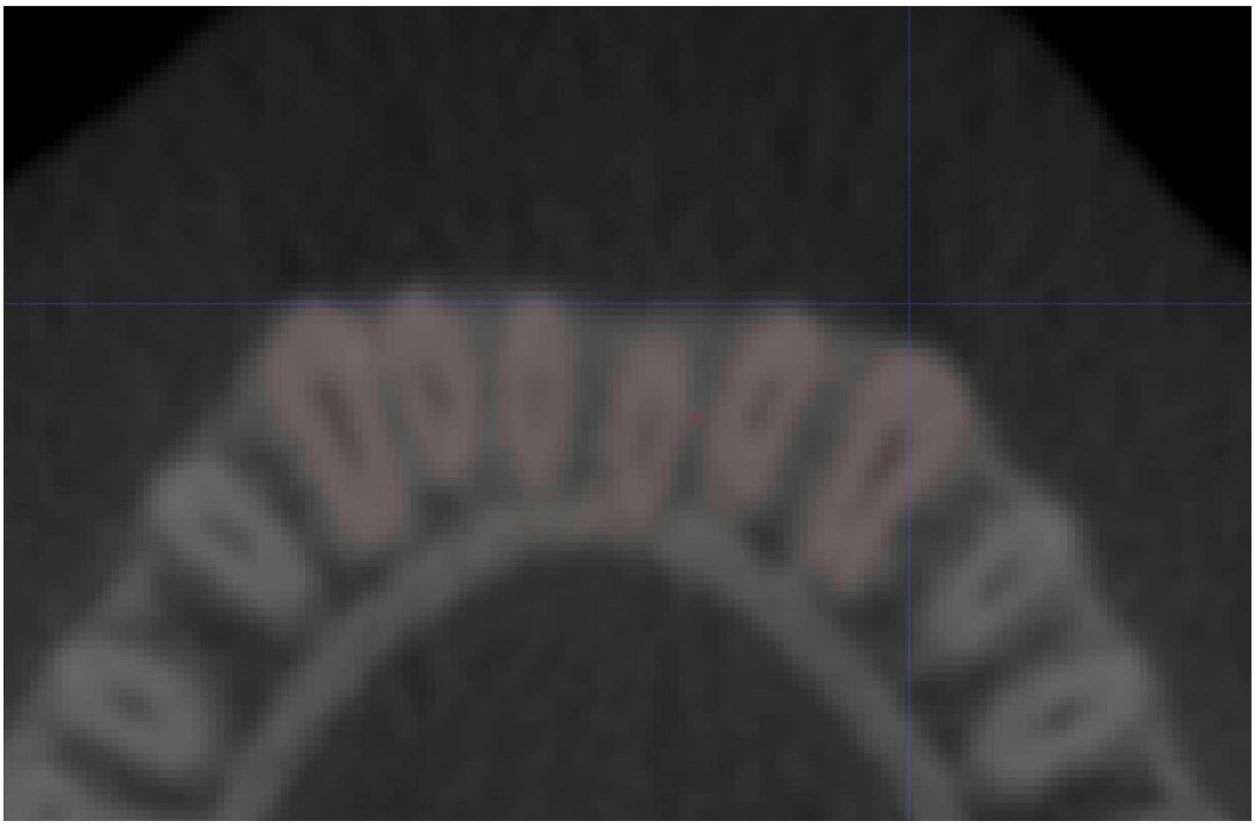

Figure 3.6: Manual refinement in the axial plane

After revision of the three planes, the update button is pushed in order to generate the three-dimensional volume of the six teeth together, which again, helps the researcher to assess if the correct anatomy was delineated (Fig.3. 7). Any anatomical aberrations that could be just the result of an improper segmentation process have to be corrected by coming back to the preceding step.

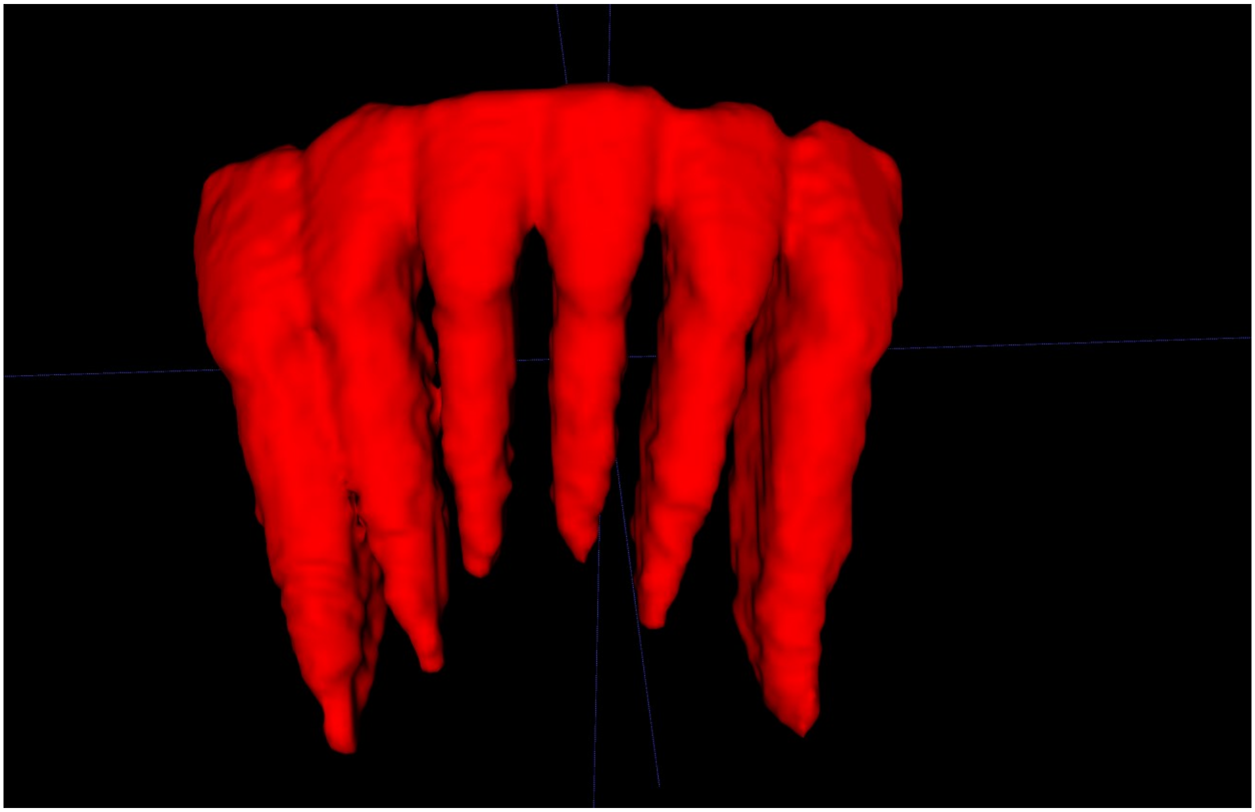

Figure 3.7: Three-dimensional volume of the teeth previously segmented

Using the Scalpel Mode (Figs. 3.8a and 3.8b) the teeth can be separated into different labels. This function allows the researcher to create a plane that divides one label into two. It works by tracing a plane in between two teeth and changing the label towards where the arrow points. To segment a specific tooth, more than one cut-plane may be necessary. A final manual refinement in the axial plane, especially at the level of the contact point area, after the use of the Scalpel Function allows to obtain the most precise tooth structure included in the label (Fig. 3.9). The final three-dimensional model of all the individual labels for all the teeth can be observed in Figures 3.10 and 3.11.

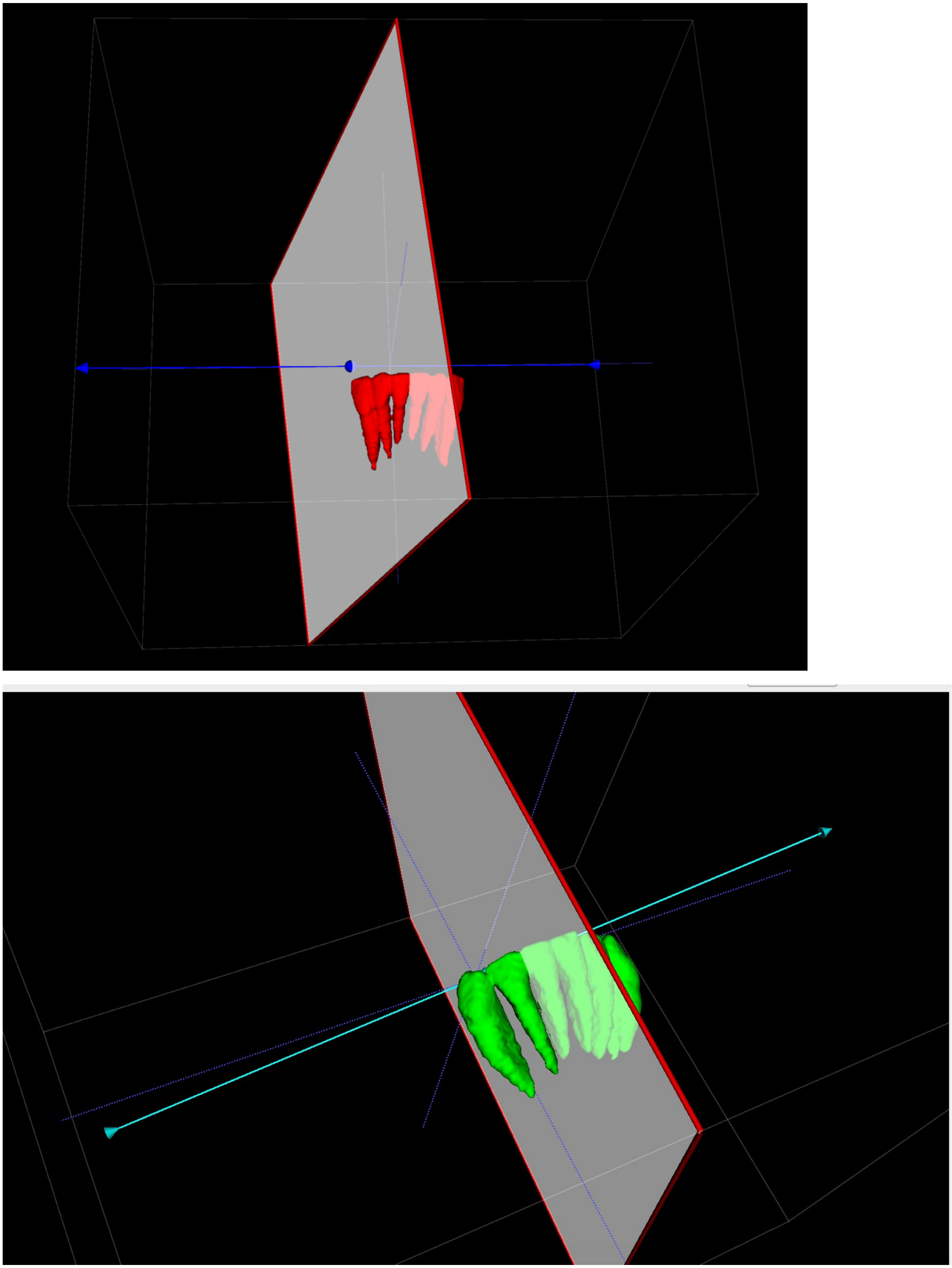

Figure 3.8(a and b): Scalpel Mode being used

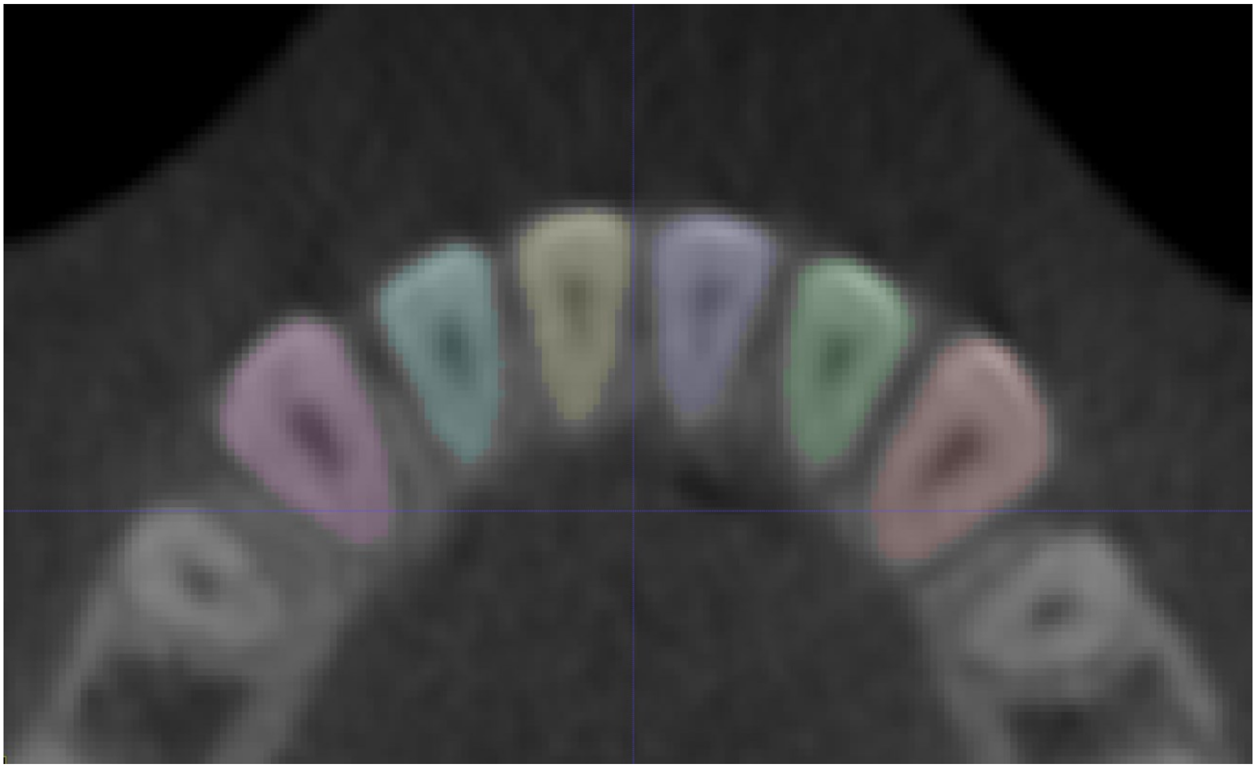

Figure 3.9: Refinement in the axial plane after using the Scalpel Mode

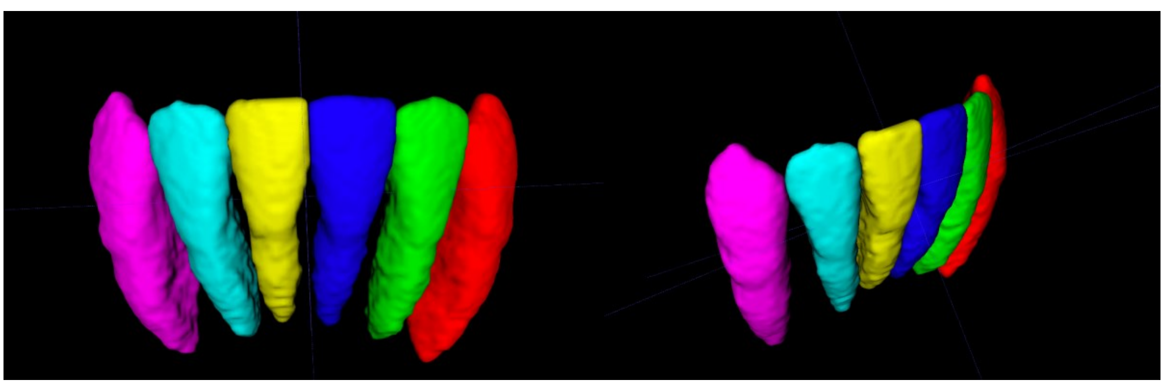

Figure 3.10 and Figure 3. 11: Teeth divided into individual labels with the Scalpel function and after the final axial refinement

Once the segmentation is completed, the software calculates the volume by clicking on Segmentation and then Volume and Statistics (Fig. 3.12). The volume is given in mm^3 for each label. Each label corresponds to each of the six measured teeth.

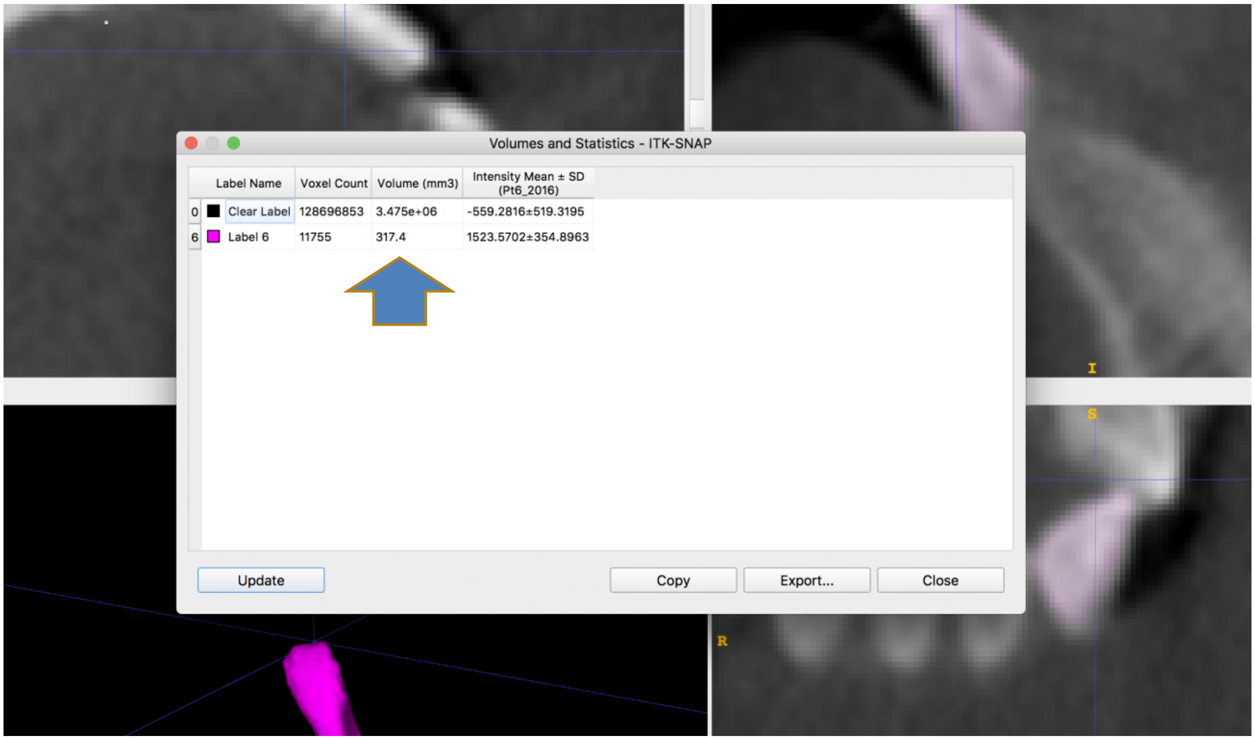

Figure 3.12: Volume calculation of the segmentation

3.1.4 Statistical analysis - hypotheses

In order to test the reliability of the volume measurements, before the beginning of the collection of the data for the main study, both inter- and intra-rater reliability tests were performed. In addition, the measurement errors were calculated for both inter- and intra-rater reliability comparisons.

The hypotheses of both reliability analyses are the following:

a) Intra-rater reliability:

H_0: The correlation is = 0 between the within-researcher measurement

H_a: The correlation is ≠ 0 between the within-researcher measurement

b) Inter-rater reliability:

H_0: The correlation is = 0 between the in-between-researchers' measurements

H_a: The correlation is ≠ 0 between the in-between-researchers' measurements

Once the hypotheses were answered, the next step was to describe the magnitude of the correlation, if one existed. Also, the Confident Intervals (CIs) were analyzed as well as the variance of ANOVA test related to the measurements. Using the software SPSS®, Interclass Correlation Coefficient (ICC) test was performed for both inter- and intra-rater reliability tests. A significance level of $\alpha=0.05$ was chosen for all statistical analyses. Values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively.[63] The measurement error was calculated through the percentage of variation between measurements regarding the total. The results can be found in the following chapter.

3.2 Quantification of linear displacement of the apices of lower incisors and canines within the symphysis from CBCT images using the softwares ITK-SNAP® and 3DSlicer®.

3.2.1 Software selection

The choice of the ITK-SNAP® as main software for the segmentation was previously explained. In order to calculate the distance between the apices of T0 and T1, the models have to be generated, then used and manipulated. The software chosen was 3DSlicer®. The main reason is because the software is well integrated with ITK-SNAP®. In addition, 3DSlicer® provides functions such as interactive visualization, image registration, and model-based analysis which are notably useful in neurological imaging and intervention. These functions, originally limited to offline use by technical factors, are integral to large scale, rapidly developing research studies, and they are being increasingly integrated into the management and delivery of care.[64]

3.2.2 Study population and data collection for the apical displacement measurements of lower incisors and canines for inter- and intra-rater reliability analyses.

Two orthodontist residents (KC and GCM) with the same background and experience, developed an approach on how to measure the linear displacement of the apices of lower incisors and canines with the help of the software 3DSlicer® and ITK-SNAP®. Five patients from the studied sample were randomly selected using the software Microsoft Excel® and its randomization function.

Measurements were taken following the technique described in the following section of this chapter. Three consecutive measurements of the displacement before and after treatment of the six apices were taken by the main researcher (GCM). Each set of measurements was taken one week apart from each other. The assistant researcher (KC) took only one set of measurements. The consecutive measurements can be found on table 3.2. For the inter-rater reliability analysis KC's measurements were compared to GCM's second measurements.

Patient number	Tooth number	GCM 1st set of measurements (March 9th, 2019)	GCM 2nd set measurements (March 16th, 2019)	GCM 3rd set of measurements (March 23th, 2019)	KC unique set of measurements (March 9th, 2019)
1	3.3	1.81	2.32	1.97	2.10
	3.2	2.85	2.41	2.29	2.44
	3.1	2.06	2.34	2.22	2.44
	4.1	1.47	1.42	1.42	1.49
	4.2	2.23	1.92	1.74	2.10
	4.3	2.42	1.73	2.17	1.73
2	3.3	1.62	2.09	1.79	1.93
	3.2	1.59	1.84	1.90	1.92
	3.1	1.59	1.84	2.02	1.59
	4.1	2.07	2.07	1.96	1.84
	4.2	2.66	2.10	2.12	2.13
	4.3	3.91	3.85	3.96	3.82
3	3.3	1.28	2.30	2.05	2.57
	3.2	1.88	1.72	1.89	1.59

	3.1	1.42	1.56	1.96	1.78
	4.1	1.67	1.56	1.56	1.56
	4.2	1.51	1.57	1.74	1.14
	4.3	1.59	1.75	1.44	2.05
4	3.3	3.63	3.70	3.61	3.55
	3.2	2.93	3.02	3.11	3.13
	3.1	2.75	2.65	2.55	2.44
	4.1	2.79	2.75	2.79	2.78
	4.2	2.76	2.58	2.47	2.26
	4.3	3.09	3.05	2.92	2.82
5	3.3	2.48	2.52	2.34	2.57
	3.2	2.27	2.18	2.27	1.97
	3.1	4.18	4.15	4.21	4.04
	4.1	3.43	3.56	3.56	3.48
	4.2	1.05	1.38	1.37	1.41
	4.3	1.12	1.27	1.15	1.11

Table 3.2: Measurements from both researchers (GCM and KC) for the inter- and intra-reliability analyses

3.2.3 Step by step process of the apical displacement measurements

The same segmentation process described for the lower incisors and canines is applied to the symphysis; however, one unique label is used for this structure. The combination of the labels of the lower teeth and the symphysis can be visualized in Figures 3.13 and 3.14. With the symphysis label, ITK-SNAP® allows the creation of a Model that is going to be transferred to 3D-Slicer®.[64] Both Models for T0 and T1 for every patient are generated and transferred in this fashion (Figs. 3.15 and 3.16).

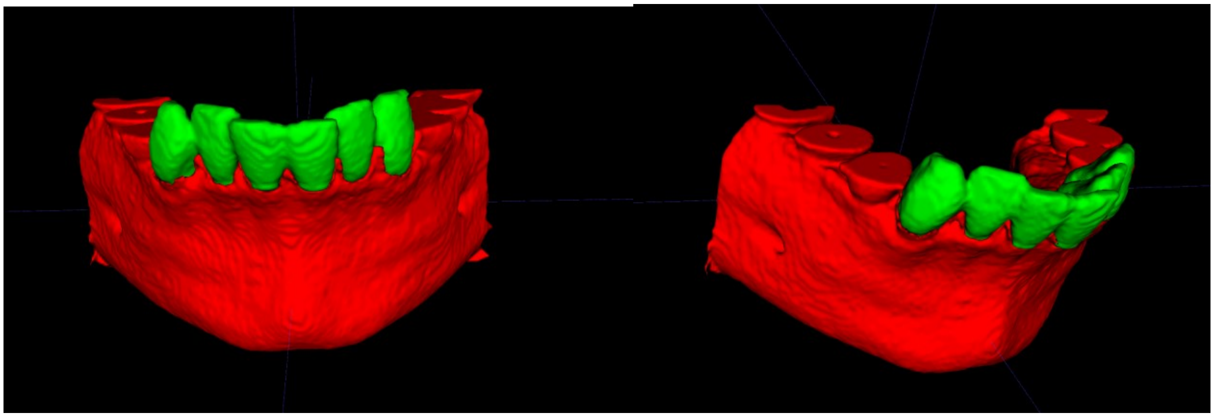

Figure 3.13 and Figure 3.14: Combination of the labels of the lower teeth and the symphysis

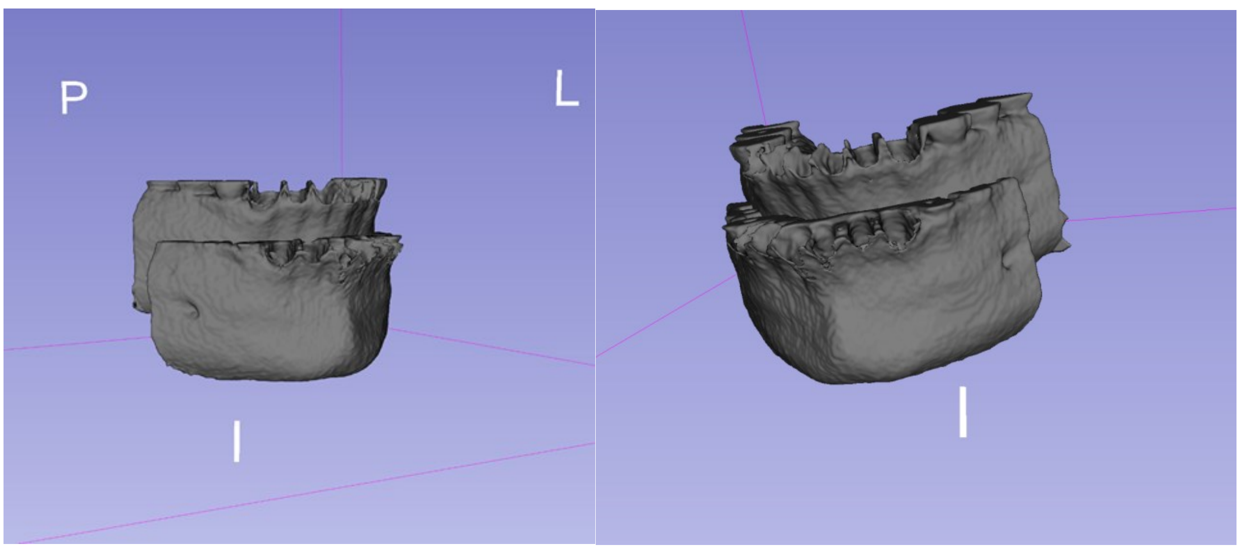

Figure 3.15 and Figure 3.16: Models of the symphysis of T0 and T1 in 3D-Slicer®

Using 3DSlicer® the symphysis model can be landmarked on its surface. The chosen points to be landmarked were mental foramina and B-point for both T0 and T1 symphyses models (Figs. 3.17 to 3.22). The size of the spheres that signal the reference points can be modified. However, the program only recognizes the centre of the sphere as the reference point. That is why the default size of the sphere was left as small as the software sets it by default. A sphere that is too big would make the visualization of the structures more difficult.

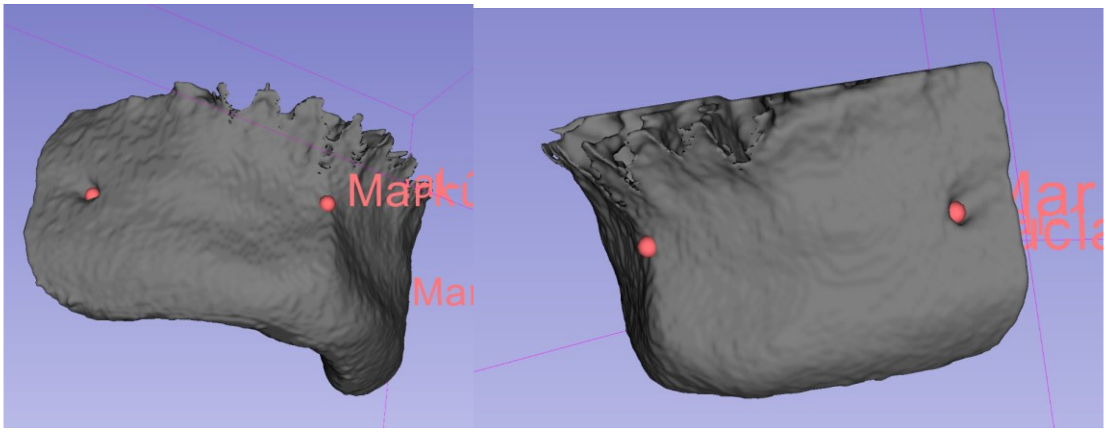

Figure 3.17 and Figure 3.18: Landmarking of the symphysis model of T1

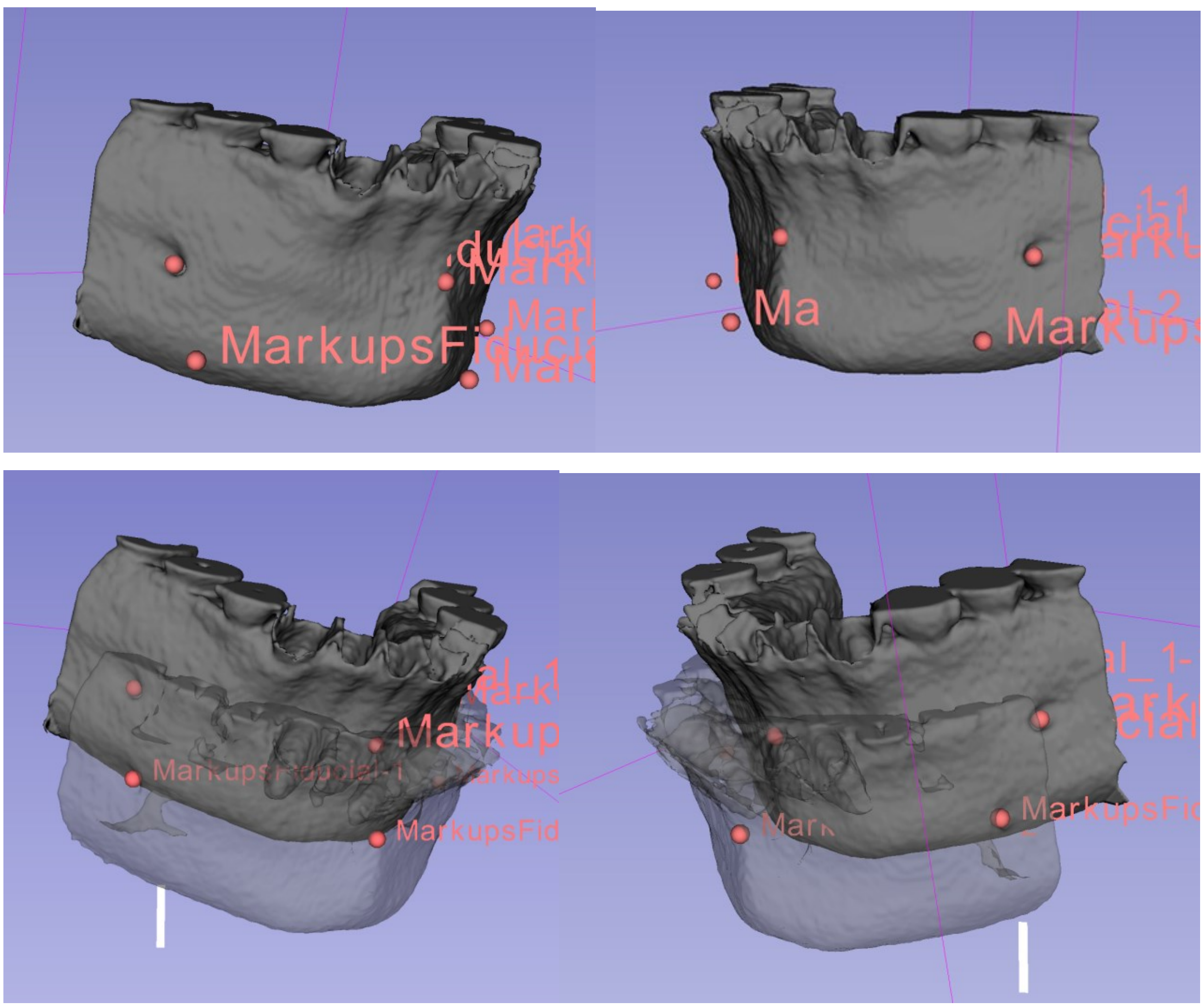

Figure 3.19, Figure 3.20, Figure 3.21, and Figure 3.22: Landmarking of the symphysis model of T0

The super-imposition of the T0 and T1 symphyses is performed by the software using the previous landmarks as a reference. This means that the 3DSlicer® is going to make correspond right mental foramen 0 to right mental foramen 1, left mental foramen 0 to left mental foramen 1 and B-point 0 to B-point 1. This process brings the symphyses together (Figs. 3.23 and 3.24). The super-imposition allows the generation of a matrix that will be applied to the incisors and canines' models.

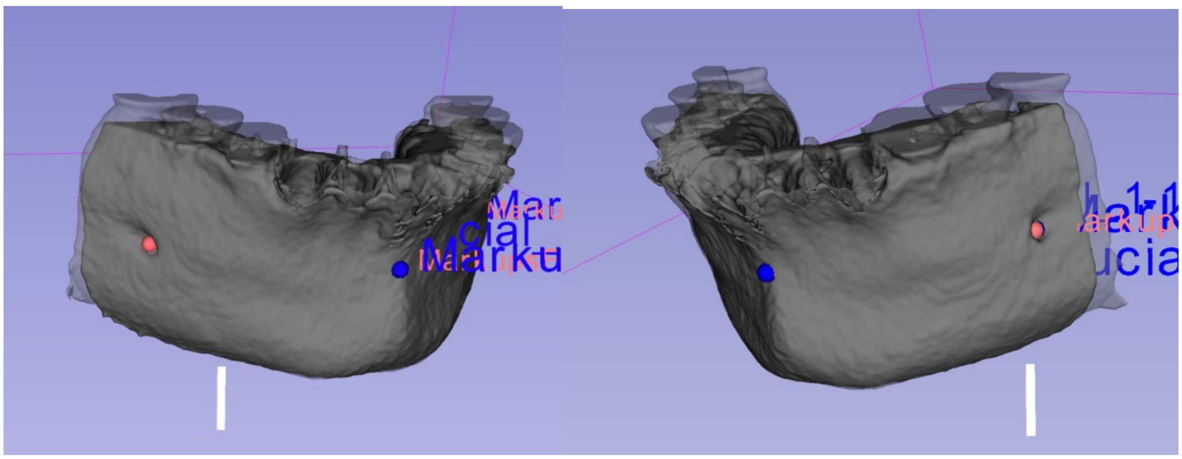

Figure 3.23 and Figure 3.24: Super-imposition of the T0 and T1 symphyses

The models of the incisors from T0 and T1 are generated after segmentation. These models are transferred to 3DSlicer® (Fig. 3.25). Both models are situated in the space in a pre-determined position by the software, however, the difference between the positions of T0 and T1 incisors and canines' models is arbitrary and it can only be related to the positions of the corresponding symphyses. That is why the matrix that related the position of symphysis 0 and symphysis 1 has to be applied to the teeth models.

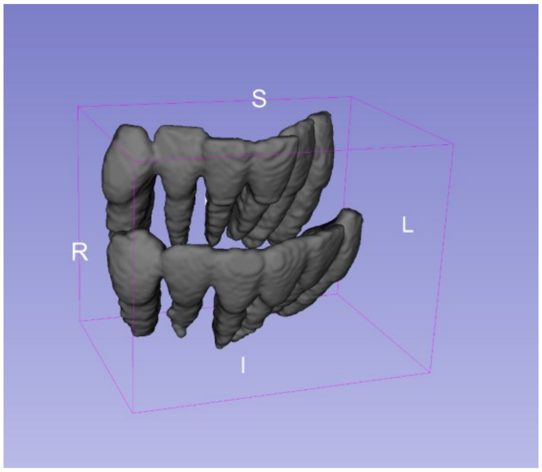

Figure 3.25: Models of the incisors of T0 and T1 transferred to 3DSlicer®

The next step consists of landmarking the tip of the apices of the twelve teeth (6 per T0 and 6 per T1) Figs. 3.26 and 3.27.

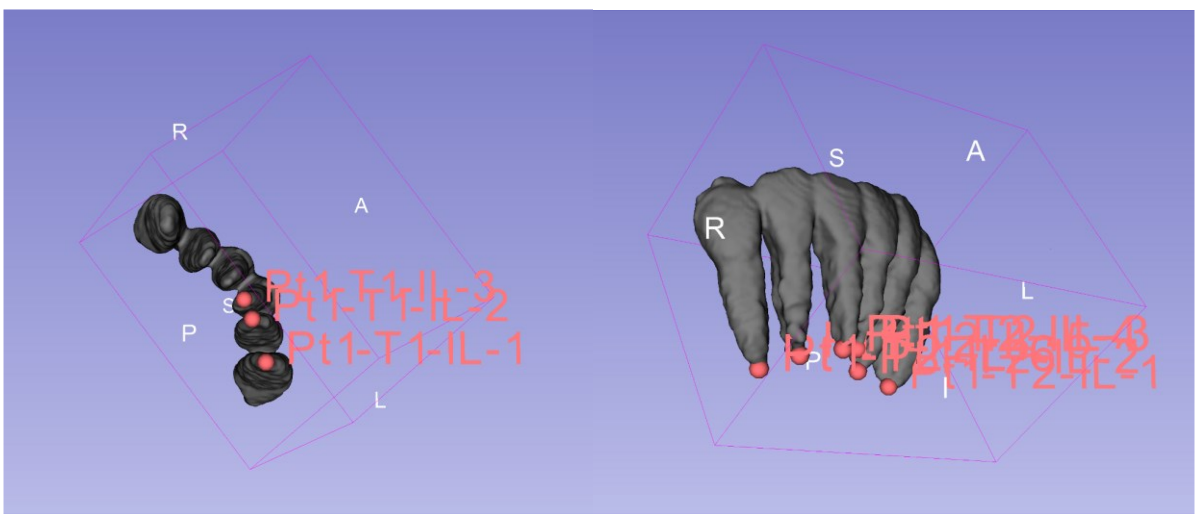

Figure 3.26 and Figure 3.27: Landmarks of the tip of the apices of the teeth of T0

Then, the matrix previously generated is applied to both models of teeth in order to allow the analysis of the displacement of the apices from T0 to T1 (Fig. 3.28). The software provides us with a table of all the displacements (Fig. 3.29). As it can be observed, the movement is decomposed in three spatial vectors.

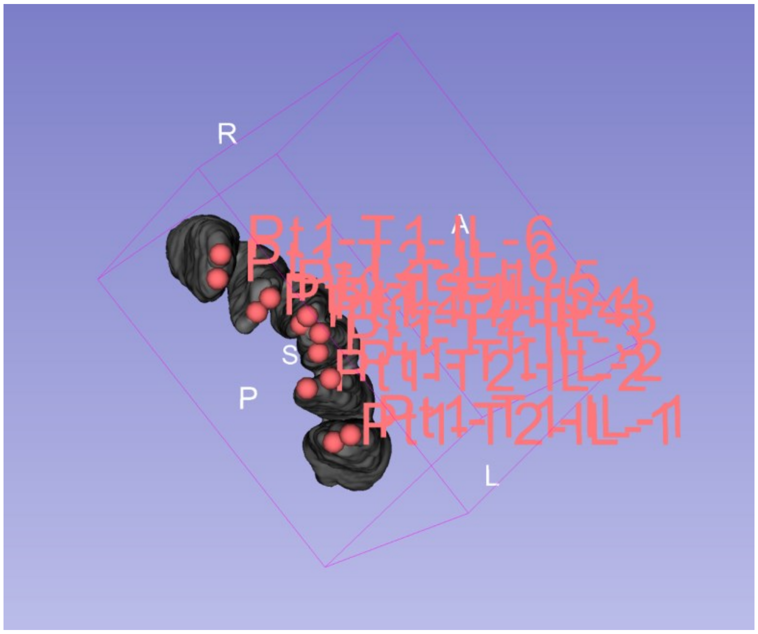

Figure 3.28: All the apices of the twelve teeth with their landmarks once the matrix is applied

distance

Landmark A - Landmark B	R-L Component	A-P Component	S-I Component	3D Distance
Pt3-T1-IL-1 - Pt3-T2-IL-1	-0.221	-1.659	1.19	2.054
Pt3-T1-IL-2 - Pt3-T2-IL-2	1.169	-0.171	1.382	1.818
Pt3-T1-IL-3 - Pt3-T2-IL-3	1.515	0.423	1.172	1.962
Pt3-T1-IL-4 - Pt3-T2-IL-4	1.182	-0.143	1.009	1.56
Pt3-T1-IL-5 - Pt3-T2-IL-5	1.441	-0.658	0.725	1.742
Pt3-T1-IL-6 - Pt3-T2-IL-6	-0.55	-1.271	-0.408	1.444

Figure 3.29: Table with the values of all the displacements (Pt for Patient, R-L for Right-Left, A-P for Anterior-Posterior, S-I for Superior-Inferior)

3.2.4 Statistical analyses – hypotheses

In order to test the reliability of the apical displacement measurements, before the beginning of the collection of the data for the main study, both inter- and intra-rater reliability tests were performed. In addition, the measurement errors were also calculated for both inter- and intra-rater reliability comparisons.

The hypotheses of both reliability analyses are the following:

a) Intra-rater reliability:

H_0: The correlation is = 0 between the within-researcher measurement

H_a: The correlation is ≠ 0 between the within-researcher measurement

b) Inter-rater reliability:

H_0: The correlation is = 0 between the in-between-researchers measurements

H_a: The correlation is ≠ 0 between the in-between-researchers measurements

Once the hypotheses were answered, the next step was to describe the magnitude of the correlation, if one existed. Also, the Confident Intervals (CIs) was analyzed as well as the variance of ANOVA test related to the measurements. Using the software IBM® SPSS® Statistics Version 2.3 64-bit edition, Interclass Correlation Coefficient (ICC) test was performed for both inter- and intra-rater reliability tests. A significance level of α=0.05 was chosen for all statistical analyses. The same values as previously indicated are used to classify the reliability as poor, moderate, good, and excellent.[63] The measurement error was calculated through the percentage of variation between measurements regarding the total. Results can be found in the corresponding section of the following chapter.

3.3 Randomized Clinical Trial (RCT) methodology

In order to report this randomized clinical trial (RCT), the CONSORT Statement was used as guideline. "CONSORT stands for Consolidated Standards of Reporting Trials and encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials."[12]

3.3.1 Objectives of this RCT[65]

The initial objectives that were stated for this randomized clinical trial were as follow:

Primary Outcome Measures:

1. Facial soft tissue, dental and skeletal changes [Time Frame: around 24 months]

Outcomes to be measured from Cone-Beam Computed Tomography data and dental casts.

Secondary Outcome Measures (adverse effects):

1. Root resorption [Time Frame: around 24 months]

   Evaluation of the magnitude of external root resorption as quantified/qualified from the CBCT data.

2. Treatment efficiency [Time Frame: around 24 months]

   Quantification of number of appointments, total treatment times, number of emergencies/comfort appointments, patients experiences (data obtained from clinical chart or patient's interviews).

The outcome that was chosen as objective for this Master's Thesis Project was the first of the two secondary outcomes: to assess the degree of external root resorption (OIERR) among lower incisors and canines undergoing orthodontic movement with two Forsus® springs approaches. Even if the hypotheses will be further developed and explained in the Statistical Methods section, the question that summarizes all of them would be: Is there a difference in the percentage of root resorption in lower incisors and canines when type of treatment, sex, total treatment time, time in brackets, and apical displacement are taken into account?

3.3.2 Trial design

This was a uni-centre, equal randomization (1:1), blinded, as much as the type of therapy allows*, controlled, parallel-group study conducted in Edmonton, Canada.

This study specifically was performed with a single blinded researcher, the author of this Master's Thesis (GCM). The data collection regarding the segmentation and the apical displacement was a masked process.

* Both therapies are physically different (see the figures on the Interventions section); the patients and the care provider, Dr. CFM, can clearly distinguish between them. That is why the masking of both treatment modalities was impossible.

3.3.3 Changes to trial design

This trial presented no changes from its original design to be reported.

3.3.4 Participants

Eligible participants presented a mild to moderate Class II division 1 malocclusion and an age ranging between eleven to fifteen years old. Both sexes were included. In total, 56 patients were enrolled. The inclusion and exclusion criteria were as follows:

Inclusion Criteria:

- Participants of either gender between eleven and fifteen years-of-age.
- Mild to moderate Class II division 1 malocclusions.
- Late mixed dentition or early permanent dentition.

Exclusion Criteria:

- Severe vertical facial growth tendency or clear syndromic cases.
- Craniofacial growth completed.

3.3.5 Study settings

This RCT took place at the Edmonton Kaye Clinic, Alberta, Canada, from October 2012 to December 2020. Eleven patients are currently in retention follow-up. To the best of our knowledge, there is no specific data about the prevalence of Class II malocclusion in the province of Alberta. The main care orthodontic provider was the responsible for and design of the study, Dr. CFM. Dr. CFM is an orthodontist with more than twenty years of clinical experience.

3.3.6 Interventions

The patients were randomly assigned to one of the two following interventions:

Crossbow® plus full brackets as intervention and brackets plus Forsus® springs as control. The first treatment methodology consisted of a Crossbow® (Figs. 3.30 to 3.34) followed by full edgewise appliances. The Class II malocclusion was overcorrected by 2-3 mm into Class

III. After the antero-posterior overcorrection, the springs were disarticulated, taken out, and a period for relapse allowed for around two to four months (3.64 months was the mean in this study). The next step was the full bonding with full brackets. Intermaxillary antero-posterior elastics were used, if needed, in the advancement of the treatment. If the relapse to Class II was significant, the springs could be added again until a satisfactory correction of the Class II was achieved.

The second one consisted of a Forsus® (Figs. 3.35 to 3.37), which is the standard of care, used in combination with full brackets. In both groups of the study, the same brackets were used: 3M Unitek® with a slot size of 0.22 inches. The archwire sequence was 0.14, 0.18, 0.16 x 0.22 NiTi, 0.17 x 0.25 TMA, and as a finishing wire: 0.18 x 0.25 SS (measurements given in inches). The finishing was intended to be similar, in terms of aesthetic and occlusal objectives, to the one that a normal clinician would obtain in a private practice. The Forsus® springs were inserted once the arch wire sequence reached a full dimensional stainless-steel wire of a size of 0.019 x 0.025 inches. Like in the previously described group, a similar overcorrection into Class III occlusal relationship was attained and antero-posterior elastics were applied when necessary.

Figure 3.30: Crossbow® maxillary occlusal view presenting the four banded Rapid Palatal Expander with Headgear Tubes to connect the Forsus® springs

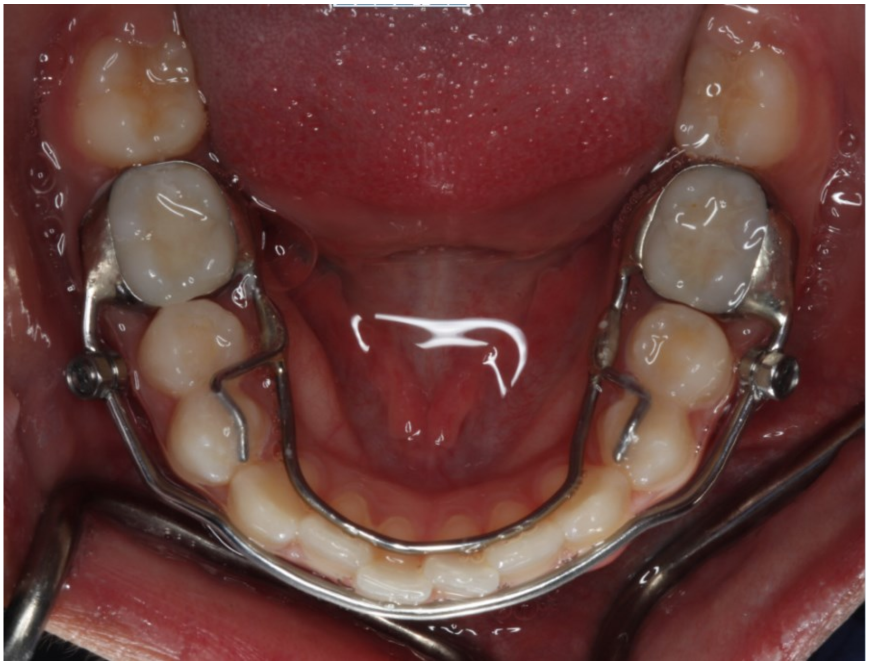

Figure 3.31: Crossbow® mandibular occlusal view of a lingual arch and buccal rail to support the pushrod and the Forsus® spring

Figure 3.32: Crossbow® view with Forsus® springs in centric-occlusion relationship

Figure 3.33: Forsus® spring connected to the Crossbow® device, lateral view of the patient's mouth

Figure 3.34: Forsus® connected to the archwire, frontal view

Figure 3.35: Forsus® connected to the archwire, lateral view

Figure 3.36: Forsus® connected to the archwire, lateral view

Full orthodontic records (digital volumetric images - Cone Beam Computer Tomograms, photos, and dental casts) were obtained for both groups at baseline and right after treatment was completed.

Pre-treatment (T0) and posttreatment (T1) full field of view (FOV) CBCTs at medium resolution were taken. A full field of view was chosen because from it a full orthodontic radiographic diagnosis for a treatment plan can be generated. From medium or small field of views, not a cephalogram, or a panoramic X-ray can be generated. Therefore, from a day-to-day clinical orthodontic perspective the type of CBCT that makes more sense is the full FOV. The same parameters were used for both pre-treatment and posttreatment CBCTs. T0 CBCT was taken at the same time as all the initial records. T1 CBCT was taken at the completion of treatment, usually, on the same day of the debond; however, for scheduling and x-ray technician availability, for some patients the T1 CBCT was taken up to four weeks after the debond date. T1 CBCT was considered necessary to assess hard tissue changes after treatment as significant dental compensation was expected. The response of the surrounding bone was to be assessed. The x-rays were taken in an i-CAT machine (see Figs. 3.37 and 3.38 in the appendix). The manufacturer is ISI, the model is ICAT, the serial number is ICU081752, the location is 8D. 126 Edmonton Clinic and the certification number is DX-080 (see the certificate in Fig. 3.39 in the appendix).

The specific settings of the acquisition of all the CBCTs in this RCT were as follows:

- Full FOV with these dimensions: 16 cm (w) x customized height up to 13 cm, from the roof of orbits to the inferior border of the mandible-level of cervical vertebra (C4). The one used in large patients with large mandibular angle/plane was 16 or 23 cm (w) x up to 17 cm (h): From the level of frontal bone / frontal sinus superiorly to the inferior border of mandible/level of C3-C5.

- Medium-low resolution:

Child: 0.3 mm voxel and 4.8 seconds

All the T0 and T1 CBCT files were coded and transferred via a ciphered hard drive to the main author of this Master's Thesis, GCM, who proceeded with the data collection following the methods exposed in the previous sections of this chapter. Once the CBCT segmentations and apical displacement measurements were completed, the codes of the patients were revealed to the main researcher so he could have access to the charts to collect the remaining data, like sex and treatment time, to complete all the predictive variables.

3.3.7 Outcomes

The initially stated outcomes in the trial design were:

a) Facial soft tissue, dental and skeletal changes,

b) Root resorption, which is the main focus of this master's thesis, and,

c) Treatment efficiency

The primary responsive variable measured in this study was the percentage of volume change of the lower incisors and canines as result of the treatment. Other predictive variables were considered and exposed in the next paragraph. Even if root resorption is the main focus of this Master's Thesis project, this is not the primary outcome of the RCT; it was a secondary one (see section <u>*Objective*</u>).

Therefore, this study has one primary research question, and five secondary research questions:

1. Are there any differences in the percentage of root volume loss between T0 and T1 and between the different types of incisors? If so,*
2. Does the type of treatment,
3. The gender of the patient,
4. The total treatment time,
5. The time with brackets, or

6. The average linear apical displacement per patient** make a difference in terms of amount of tooth volume loss?

If differences in the percentage of root volume loss are found, the magnitude of those differences is to be described.

The only assessor of the outcome was the main author of this Master's Thesis project, GCM. GCM is a third-year resident at the University of Alberta Master's in Sciences in Orthodontics program. The assessor learned how to use the required softwares, ITK-Snap® and 3DSlicer®, by being instructed by peers, by watching videos, and by reading referred articles from the sofwares' web pages.[66,67]

* Cervical Vertebrae Maturation (CVM) stage was thought as one of the possible independent variables. The thought behind that was that the closer to the mandibular peak of growth, the shorter the time frame needed the fixed Class II corrector because natural mandibular growth would help or facilitate the correction of the malocclusion. In the end, it was not added to the list of variables because it could not be measured in fourteen out of the 43 patients that were analyzed, which represents around 35% of the total sample. CVM stage calculation is a method developed for lateral cephalograms. Even if a lateral cephalogram can be generated from a Full FOV CBCT, the cervical vertebrae did not show completely to allow the proper measurement. Most of the time C4 was cut, but the cut could go as high as C3.

** About the apical displacement, the measurements were taken from the apex of T0 to the apex T1 for every tooth for every patient (see previous section of this chapter). Four measurements were recorded for every tooth: the linear distance plus the decomposition of that distance into the three planes of space. However, only one linear distance from the apex of T0 to the apex of T1 for every tooth and the average of the six displacements for every patient was taken into account for the final statistical analysis. Decomposing the measurement into three planes of the space would give more information about the direction of the displacement, as well as considering the displacements per tooth and not as an average per patient. Nonetheless, the main reason for this simplification is statistical: there were too many independent variables for a small sample size.

3.3.8 Changes to outcomes

There were no changes to trial outcomes after the trial commenced. There were neither major changes to the protocol, including unplanned changes to eligibility criteria, interventions, examinations, data collection, and methods of analysis.

3.3.9 Sample size

The sample size calculation was based on a statistically significant change in five degrees of the lower incisor inclination after treatment. A sample of 50 patients will be sought. Ideally, there should be 25 patients per treatment group, considering a twenty percent loss during follow-up so that the groups will not have less than 21 patients per group at the end of study. Assumptions were made with a Standard Deviation (SD) of five degrees of lower incisor inclination, as averaged from previous studies,[4,18,19] and a clinically significant difference of also five degrees. In total, 56 patients were enrolled in this trial.[65]

In other words, by recruiting that number of patients, this study should be large enough to have a high probability or power of detecting as statistically significant a clinically important difference of lower incisor inclination before and after treatment and between treatments, if such a difference exists. The sample was not initially calculated to detect the potential amount of root volume loss.

3.3.10 Interim analyses and stopping guidelines

There were no interim analyses nor stopping guidelines executed and planned for this study. The therapeutic techniques employed in both groups are similar in terms of force systems and widely used in academic[4,18,19] and non-academic orthodontic offices, therefore, they have been proven to be safe.

3.3.11 Randomization: sequence generation: Method used to generate the random allocation sequence

The researchers did not participate in the randomization as it was done by a statistician and only communicated by phone once a participant is deemed to have fulfilled the inclusion criteria and provided informed consent. Randomization sequence was generated by the statistician (Dr. GH), and the process was as follows: a sequence of random allocations of two treatments was generated by a block randomization using Excel® Software. Block randomization assures balance, equal sample size in two groups, as the data accumulate.[68]

3.3.12 Randomization: type

A 1:1 allocation was used in this study. "Simple randomization" was done and no restriction was used. No stratification, nor blocked nor minimization were used either.

3.3.13 Randomization: allocation concealment mechanism

Sequence was concealed in closed sealed envelopes with consecutive number types externally to know which envelope to open next.

3.3.14 Randomization: implementation

Statistician, Dr. GH, generated a randomization sequence and made the sealed envelopes to conceal the information. Patients were enrolled by the principal investigator, Dr. CFM. The envelopes were opened only by the treatment coordinator after the patient and the family decided to participate in the study and signed the appropriate paperwork.

3.3.15 Blinding

Participants and healthcare providers could not be blinded because the two therapies proposed are visually different (compare figs. 4 and 6). Allocation was blinded. In the case of our study, as well as the segmentation and the data collection as much as possible. The processes regarding the data collection were done by the same researcher, GCM, who was kept blinded.

The patients' CBCTs were numbered and the names and codes were only revealed when the charts had to be read in order to continue with the data collection. T0 and T1 CBCTs were not blinded because it did not make sense given the fact that the lower incisors and canines were clearly aligned after treatment (T1), and even sometimes, the lower fixed retainer showed up in the CBCT images. Therefore, the main researcher could visually identify and distinguish T0 from T1 CBCT images.

There was no data monitoring committee in this study. About the manuscript writers, the author of this Master's Thesis project, GCM and his supervisors, were not blinded.

3.3.16 Similarity of interventions

The interventions are not similar *per se*, and they are physically different. Thus, no blinding of participants or the healthcare providers can be done. Therefore, there was no need to state similarities of the characteristics of the treatment modalities.

3.3.17 Statistical methods

The statistical analysis was performed using version 23 IBM® SPSS® Statistics 64-bit edition. The statistical analysis used to analyze the outcomes was a five-way MANCOVA. A significance level of α=0.05 was chosen for all statistical analyses.

This study has five explanatory variables: types of treatment, which is nominal and has two levels (Forsus® springs and Crossbow®); sex, which is again nominal and has two levels (male and female); total treatment time, which is continuous and is expressed in months as well as the time with brackets; finally, the apical displacement which is continuous and is expressed in mm. There are also six continuous response variables: the percentage of volume loss, which was computed from the difference in volume measured in mm^3 before and after treatment (T0 and T1) of the six studied teeth: #3.3, #3.2, #3.1, #4.1, #4.2, #4.3. Given the fact that in this study two time points were measured (pre-treatment -T0- and post-treatment -T1-), a spreadsheet was used in order to calculate the amount of root resorption (T1-T0) and from that value, the percentage of root resorption ([T1-T0]*100/T0).

Since this study presents six dependent variables (multivariate) and three independent continuous variables (covariate) among the five independent variables, the correct statistical analysis is a five-way MANCOVA. The steps of the comprehensive planned statistical analysis are as follow:

1) Descriptive statistics.

2) Five-way MANOVA, assumptions, and its overall test to answer the primary research question of the study. The corresponding hypotheses for this test are:

H_o1: There is no difference in the percentage of root resorption pre- and post-treatment considering all the measured teeth jointly.
H_a1: There is a difference in the percentage of root resorption pre- and post-treatment considering all the measured teeth jointly.

3) Five-way MANCOVA overall test, which will provide answers to the hypotheses corresponding to every one of the secondary research questions. The hypotheses corresponding to the secondary research questions are:

H_o2: There is no difference in the percentage of OIERR between the type of treatments.
H_a2: There is difference in the percentage of OIERR between the type of treatments.

H_o3: There is no difference in the percentage of OIERR between females and males.
H_a3: There is difference in the percentage of OIERR between females and males.

H_o4: There is no difference in the percentage of OIERR when considered the total treatment time.
H_a4: There is a difference in the percentage of root volume loss when considered the total treatment time.

H_o5: There is no difference in the percentage of root volume loss when considered the time in brackets.
H_a5: There is a difference in the percentage of root volume loss when considered the time in brackets.

H_o6: There is no difference in the percentage of root volume loss when considered apical displacement.
H_a6: There is a difference in the percentage of root volume loss between considered apical displacement.

4) ANCOVA analysis: In order to understand on which teeth, the intervention could have had an effect on their corresponding amount of root resorption.

5) Regression analysis: to analyze the relationship between the independent variable/s and the root resorption in the teeth on which the relationship was significant at the level of the ANCOVA analysis.

Intention-to-treat analysis was not performed in this study. Per protocol analysis was used instead. A "complete case" (or "available case") analysis was used because only those patients whose outcomes are known were included. No outcomes were imputed of those subjects whose outcomes were lost. Therefore, analysis was restricted to only participants who fulfilled the protocol in terms of eligibility, interventions, and outcome assessment.

3.3.18 Additional analyses

There were no additional analyses, such as subgroup analyses and adjusted analyses.

Appendix

Figure 3.37: i-Cat x-ray machine used for the acquisition of the CBCT images

Figure 3.38: i-Cat x-ray machine used for the acquisition of the CBCT images

UNIVERSITY OF ALBERTA

Registration Certificate
for
Radiation Equipment

Equipment Type: Cone Beam CT
Manufacturer: ISI
Model: ICAT
Serial Number: ICU081752

Facility Type: Clinical
Location: 8D.126 Edmonton Clinic
Applicant: Dr. Anthea Senior
Department: Dentistry

Certificate Number: DX-080

Date of Issue: 31 Aug 2018
Expiry Date: 31 Aug 2021
(ext.)

Director, Environment, Health & Safety

Figure 3.39: Certificate of the i-CAT machine

3.4 References

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4 Chapter 4: Results; Degree Of External Root Resorption in the Lower Incisors and Canines When using the Forsus Spring® in Two Different Treatment Approaches to Treat Mild to Moderate Class II Malocclusions: Application into a Randomized Clinical Trial Sample.

RESULTS OF THE INTER- AND INTRA-RELIABILITY ANALYSES AND THE MEASUREMENT ERROR

4.1 Measurement error, inter- and intra-rater reliability of the measurements of volume of lower incisors and canines.

4.1.1 Intra-rater reliability results

The order of the results displayed is p-values, Intraclass Correlation Coefficients (ICCs), Confident Intervals (CIs), variances from the Analysis of Variance (ANOVA) test, and scatter plots.

The null hypothesis can be rejected (p-value <0 .001) for all the teeth. The ICC for all the measurements was >0.910. Therefore, this method displays an excellent reliability under the stated conditions (Table 4.1).[63]However, ideally, the limits of the CIs of every tooth measured should be above 0.90; this is not the case for the lower boundaries of the CIs of teeth #3.2, #3.1, #4.1, #4.2, and #4.3. Besides, the measurement error results for each tooth are also displayed in Table 4.1. The average measurement error for all the teeth together was 4.16%.

Tooth number	p-value	ICC value and CI	Measurement error (%)
3.3	<0.001	0.985 [0.927-0.998]	3.51
3.2	<0.001	0.937 [0.727-0.993]	4.44
3.1	<0.001	0.941 [0.742-0.993]	4.41
4.1	<0.001	0.912 [0.641-0.990]	4.52
4.2	<0.001	0.916 [0.654-0.990]	4.08
4.3	<0.001	0.976 [0.886-0.997]	3.98

Table 4.1: Intraclass Correlation Coefficients (ICCs) p-values, ICC values, Confident Intervals (CIs) and measurement errors for the intra-rater reliability analysis

The corresponding ANOVA for each tooth was also analyzed, and it confirms, again, the reliability displayed by the ICC values, showing high variance in the patients' measurements and relatively low variance in the repeated measurements of the same tooth (Table 4.2).

Tooth number	Variance in the patients' measurements	Variance in the repeated measurements
3.3	31852.78	558.00
3.2	6101.86	170.59
3.1	5399.94	98.49
4.1	3088.88	180.84
4.2	3610.75	247.60
4.3	23802.45	1013.97

Table 4.2: Variance in the patients' measurements and variance in the repeated measurements of the same tooth

The high magnitude of the intra-reliability can also be visually confirmed in the corresponding scatter plot for each tooth (Figs. 4.1 to 4.6).

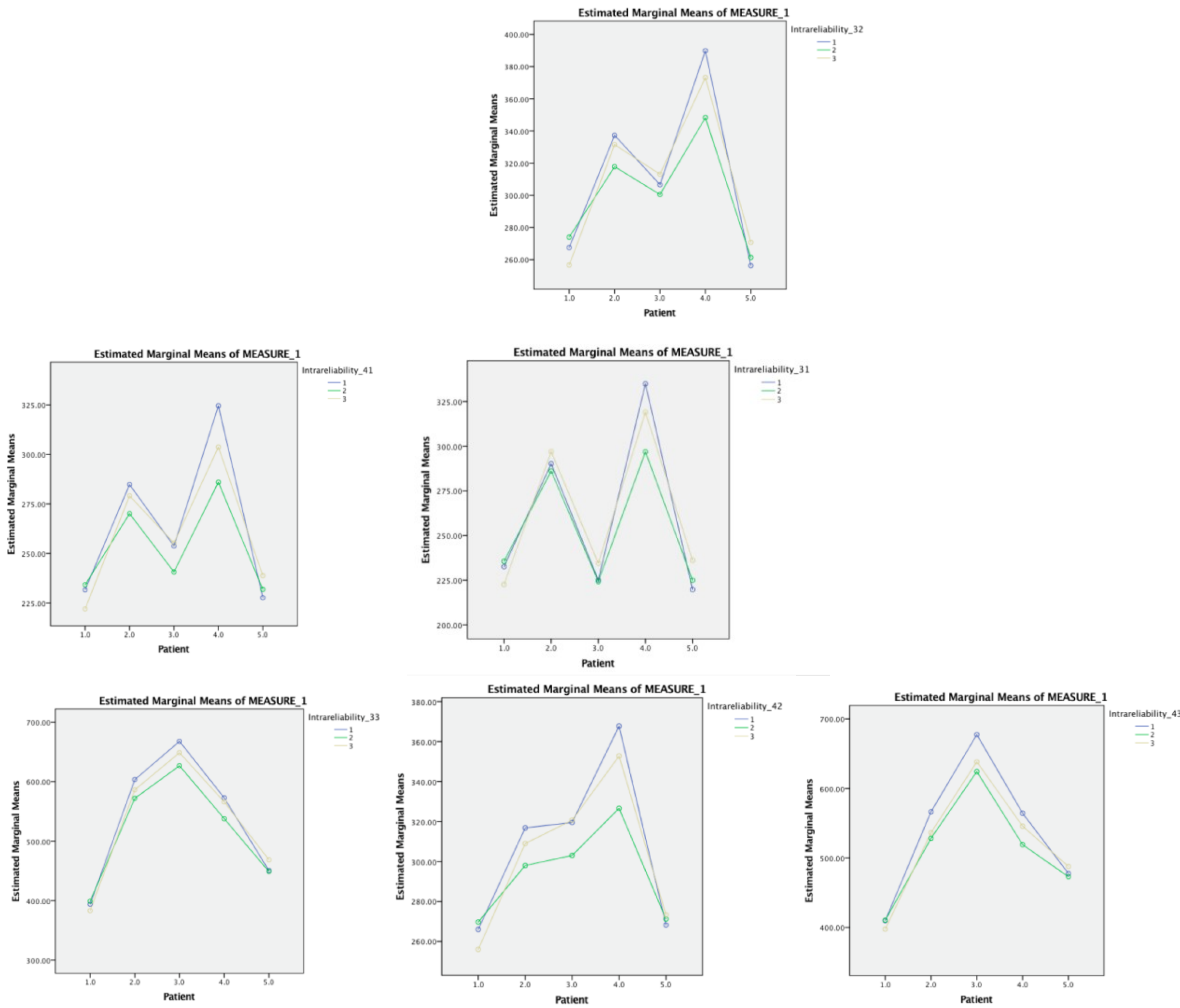


Figure 4.1, Figure 4.2, Figure 4.3, Figure 4.4, Figure 4.5 and Figure 4.6: Scatter plot for the three measurements for each tooth

4.1.2 Inter-rater reliability results

The null hypothesis can be rejected (p-value <0.05) for all the teeth except for tooth # 4.2. The ICC values reflect a good reliability for all the teeth except for tooth #4.3, which presents an excellent reliability (Table 3.3). Nevertheless, the limits of the CIs of every tooth measured should be, at least, above 0.75 in order to be good.[63] Besides, the measurement error results for each tooth are also displayed in Table 4.3. The average measurement error for all teeth together was 7.11%.

Tooth number	p-value	ICC value and CI	Measurement error (%)
3.3	<0.05	0.898 [0.269-0.989]	8.58
3.2	<0.05	0.820 [0.145-0.979]	6.98
3.1	<0.05	0.872 [0.133-0.986]	6.90
4.1	<0.05	0.855 [0.095-0.984]	5.47
4.2	=0.53	0.752 [-0.199-0.971]	7.33
4.3	<0.05	0.905 [0.307-0.990]	7.38

Table 4.3: Intraclass Correlation Coefficients (ICCs) p-values, ICC values, Confident Intervals (CIs) and measurement errors for the inter-rater reliability analysis

The corresponding ANOVA for each tooth was also analyzed, and the variances in the patients' measurement regarding the variances in the repeated measurements confirm, the overall good level of reliability displayed by the ICC values (Table 4.4), except for tooth #3.2, which presents a higher variance in the repeated measurements.

Tooth number	**Variance in the patients' measurements**	**Variance in the repeated measurements**
3.3	20735.49	16.9
3.2	2873.23	262.14
3.1	2534.89	1.37
4.1	1775.75	17.16
4.2	1781.82	72.9
4.3	17763.86	7.57

Table 4.4: Variance in the patients' measurements and variance in the repeated measurements of the same tooth

The good level of the inter-rater reliability can also be visually confirmed in the corresponding scatter plot for each tooth (Figs. 4.7 to 4.12).

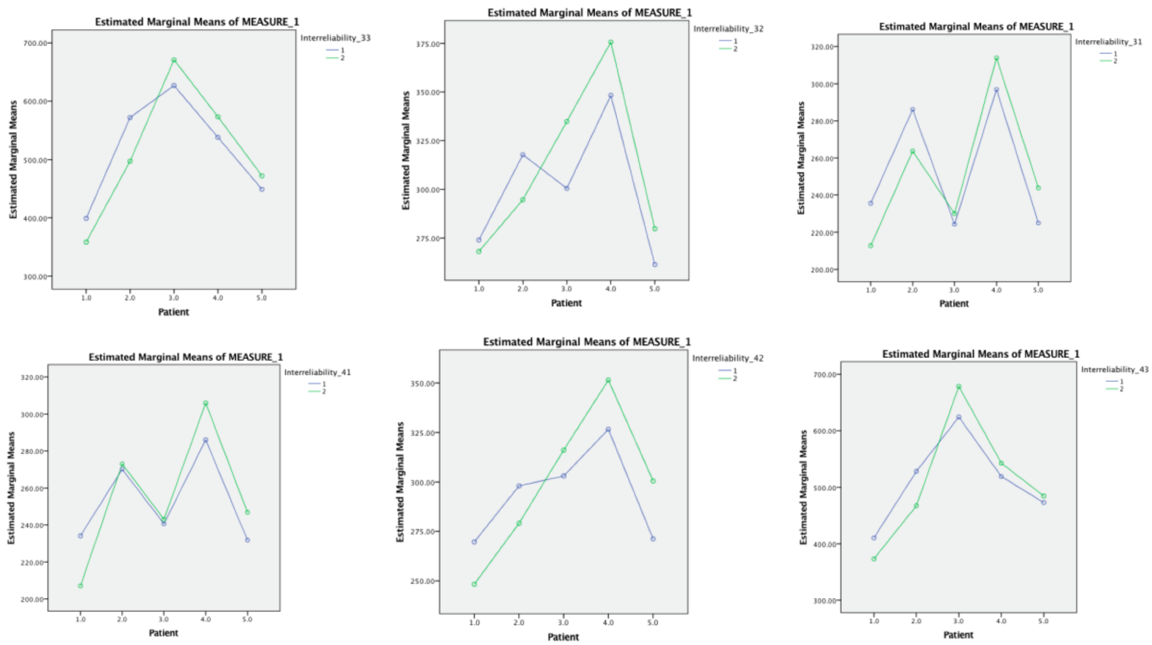


Figure 4.6, Figure 4.7, Figure 4.8, Figure 4.9, Figure 4.10, Figure 4.11 and Figure 4.12: Scatter plot for the two measurements for each tooth.

4.2 Measurement error, inter- and intra-rater reliability of the measurements of the apical displacement of lower incisors and canines.

4.2.1 Intra-rater reliability results

The null hypothesis can be rejected (p-value = or <0 .001) for all the teeth. The ICC values for teeth #3.3, #3.1, #4.1, and #4.3 indicated an excellent reliability. Whereas the ICC values for the teeth #3.2 and #4.2 indicated a good reliability (Table 4.5). Therefore, this method displays good to excellent reliability overall. Nonetheless, ideally, the limits of the confident intervals (CI) of every tooth measured should be above 0.90 or 0.75 in order to be good or excellent,[63] this is not the case for the lower boundaries of the CI of teeth #3.3, #3.2, and #4.2. Besides, the measurement error results for each tooth are also displayed in Table 3.5. The average measurement error for all the teeth together was 9.91%.

Tooth number	p-value	ICC value and CI	Measurement error (%)
3.3	<0.001	0.920 [0.666-0.991]	15.26
3.2	<0.001	0.894 [0.583-0.987]	07.77
3.1	<0.001	0.975 [0.879-0.997]	10.31
4.1	<0.001	0.995 [0.977-0.999]	02.83
4.2	=0.001	0.841 [0.438-0.980]	13.50
4.3	<0.001	0.970 [0.861-0.997]	09.80

Table 4.5: Intraclass Correlation Coefficients (ICCs) p-values, ICC values, Confident Intervals (CIs) and measurement errors for the intra-rater reliability analysis

The corresponding ANOVA for each tooth was also analyzed, and it confirms, again, the good to excellent reliability displayed by the ICC values, showing high variance in the patients' measurements and relatively low variance in the repeated measurements of the same tooth (Table 4.6).

Tooth number	Variance in the patients' measurements	Variance in the repeated measurements
3.3	1.71	0.22
3.2	0.81	0.01
3.1	3.09	0.05
4.1	2.25	0.00
4.2	0.85	0.04
4.3	3.65	0.01

Table 4.6: Variance in the patients' measurements and variance in the repeated measurements of the same tooth

The high magnitude of the intra-reliability, good to excellent, can also be visually confirmed in the corresponding scatter plot for each tooth (Figs. 4.13 to 4.18).

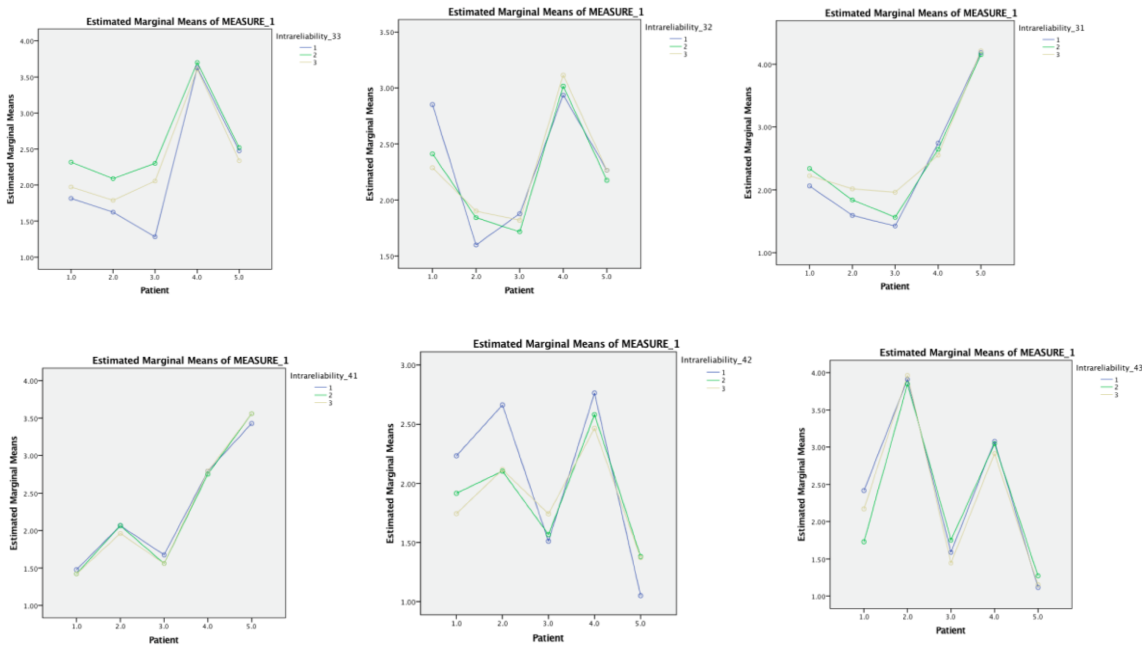


Figure 4.13, Figure 4.14, Figure 4.15, Figure 4.16, Figure 4.17 and Figure 4.18: Scatter plots for the three measurements for each tooth

4.2.2 Inter-rater reliability results

The null hypothesis can be rejected (p-value = or < .05) for all the teeth. The ICC for all the measurements was >.90 except for tooth #4.2 whose ICC was >.75 (Table 4.7). Therefore, this method displays an excellent reliability for all the teeth analyzed except for tooth #4.2 which presents a good reliability. However, ideally, the limits of the CIs of every tooth measured should be above .90 or .75, this is not the case for the lower boundaries of the CI of teeth #3.3, #3.1, and 4.2. Besides, the measurement error results for each tooth are also displayed in Table 4.7. The average measurement error for all the teeth together was 7.33%.

Tooth number	p-value	ICC value and CI	Measurement error (%)
3.3	<0.05	0.957 [0.674-0.995]	7.02
3.2	<0.05	0.974 [0.788-0.997]	5.37
3.1	<0.05	0.957 [0.674-0.995]	8.42
4.1	<0.05	0.992 [0.939-0.999]	3.98
4.2	<0.05	0.862 [0.273-0.984]	11.57
4.3	<0.05	0.985 [0.866-0.998]	7.64

Table 4.7: Intraclass Correlation Coefficients (ICCs) p-values, ICC values, Confident Intervals (CIs) and measurement errors for the inter-rater reliability analysis.

The corresponding ANOVA for each tooth was also analyzed, and it confirms, again, the reliability displayed by the ICC values, showing high variance in the patients' measurements and relatively low variance in the repeated measurements of the same tooth (Table 4.8).

Tooth number	Variance in the patients' measurements	Variance in the repeated measurements
3.3	0.79	0.00
3.2	0.61	0.00
3.1	3.09	0.00
4.1	1.53	0.00
4.2	0.44	0.03
4.3	2.23	0.00

Table 4.8: Variance in the patients' measurements and variance in the repeated measurements of the same tooth

The good to excellent inter-rater reliability can also be visually confirmed in the corresponding scatter plot for each tooth (Figs. 4.19 to 4.24).

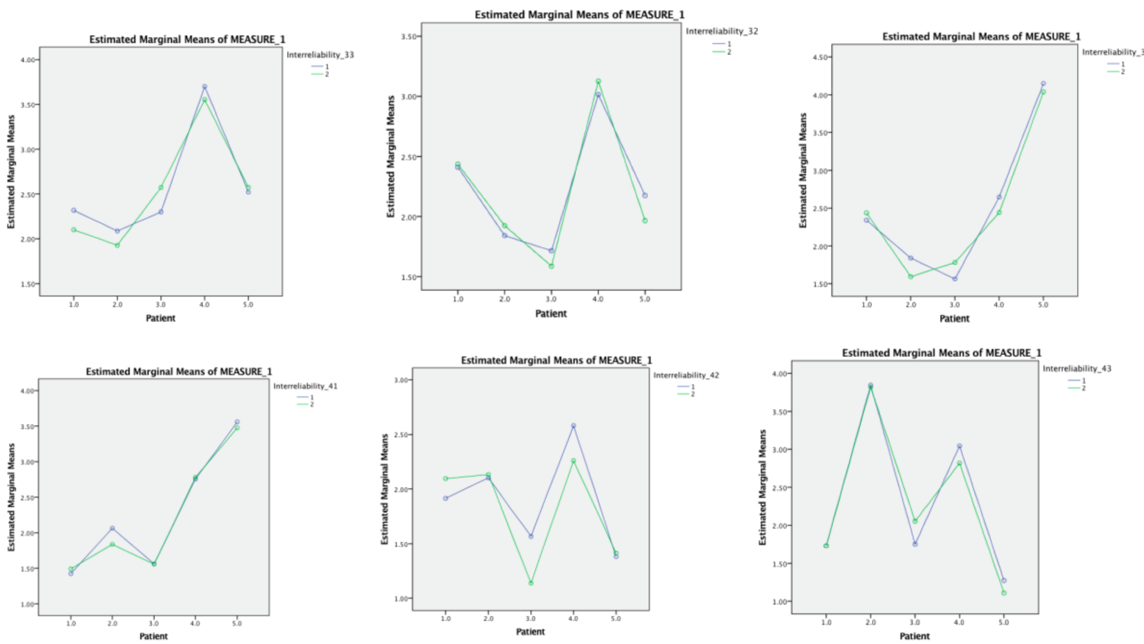


Figure 4.19, Figure 4.20, Figure 4.21, Figure 4.22, Figure 4.23 and Figure 4.24: Scatter plots for the three measurements for each tooth.

Overall results

Table 4.9 presents a summary of the reliability results.

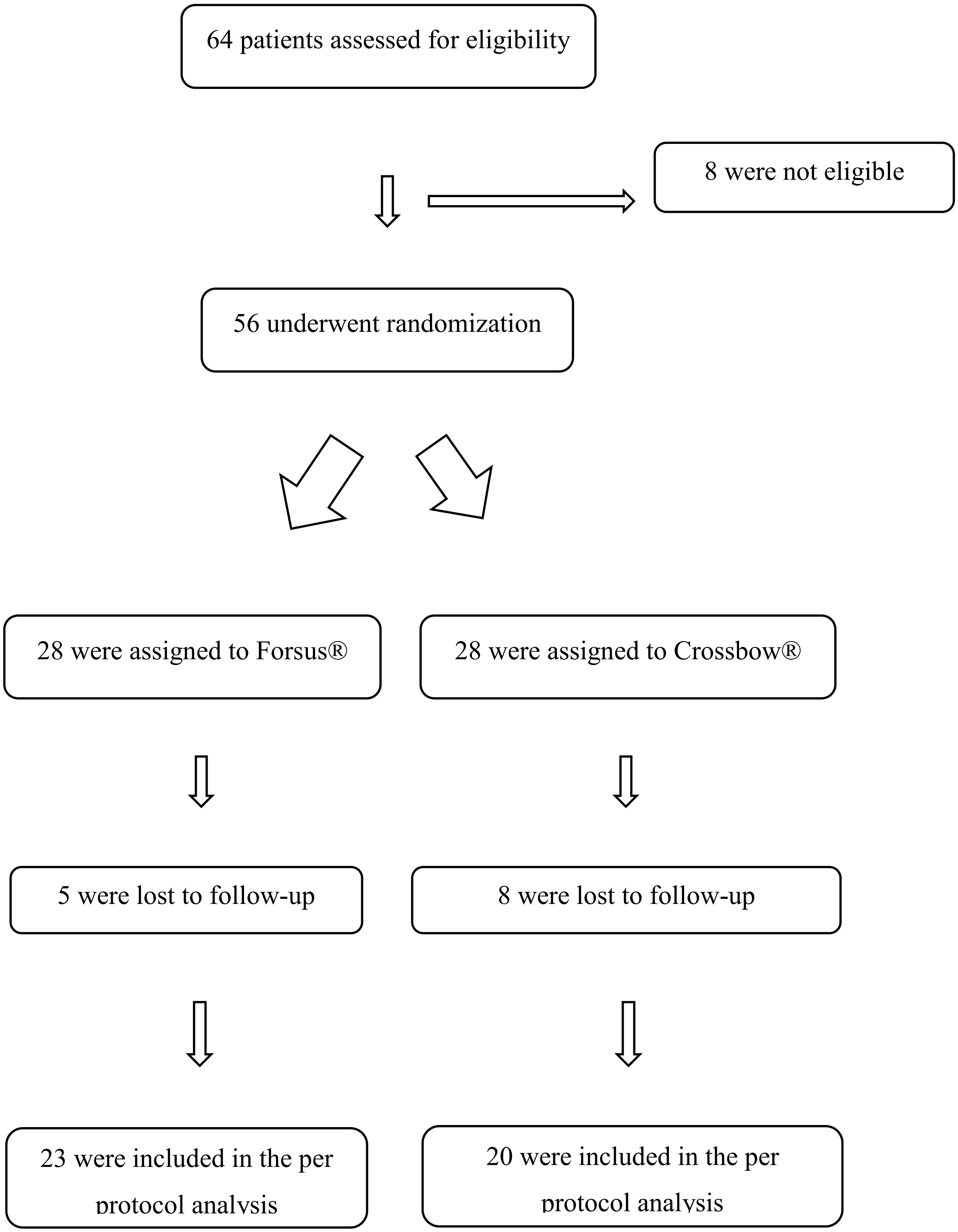
Technique	Inter- / Intra-rater	Reliability	Measurement error
Volume	Intra-	Excellent	4.16%
	Inter-	Good	7.11%
Apical displacement	Intra-	Good to excellent	9.91%
	Inter-	Good to excellent	7.33%

Table 4.9: Summary of the results of all inter- and intra-reliability analyses

RESULTS OF THE RCT

Participant Flow

In the following diagram, the participant flow of the study can be observed.



4.2.3 Losses and exclusions

Description of the patients lost to follow-up in both groups is as follows:

a) All initial 64 patients were already identified as having a Class II malocclusions at an appropriate age per screening notes. However, 8 were not eligible after full consideration of the records, and the reasons were: they did not fulfill the inclusion criteria, or they declined study participation.

b) In the Forsus® group:

- One needed a change in the treatment plan after the correction: the patient and his/her family were not satisfied with the results and extractions were performed, which increased the treatment time.
- Another patient had initial records not found.
- For the other three patients, once the alignment was completed, the sagittal malocclusion discrepancy was so minimal that Forsus® was not needed nor used.

The percentage of loss to follow-up out of the total participants of this group was 17.86%

c) In the Crossbow® group:

- The final CBCT of one of the patients was distorted and could not be used for the assessment.
- CBCT imaging of five patients, either initial or final, could not be found.
- Two patients abandoned the treatment. One of the patients suspected that he had an allergy to the appliance; however, even after the lack of allergies was confirmed, the family decided not to continue with the Crossbow® appliance and selected the Forsus® springs. The other patient moved to a different country before treatment completion.

The percentage of loss to follow-up out of the total participants of this group is 28.57%. The percentage of loss to follow-up out of the total participants in the study is 23.21%

4.2.4 Recruitment

Age-eligible participants were recruited from eleven to fifteen years of age.

4.2.5 Reason for stopped trial

The trial was not stopped nor ended, and there was no plan for it.

4.2.6 Baseline Data

Given the fact that this was a randomized controlled trial, it can be considered that all the factors were equal among groups. Thus, the only difference between groups was the treatment applied. However, due to chance, the baseline characteristics of both groups could be significantly different and that may affect the treatment results. That is why, the following variables were analyzed at T0 in order to make sure that the groups were similar regarding the baseline values at the beginning of the treatment. The values analyzed at the baseline were: FMA at T0, average volume of lower incisors at T0, average incisor inclination at T0, average alveolar volume at T0, and age at T0. An OMNIBUS MANOVA test was employed to detect the differences between groups. The resultant p-value was 0.11, therefore, there are no significant differences between the two groups of the study in all of the pre-treatment parameters included in this baseline analysis. Gender, being a dichotomous variable, could not be included in the OMNIBUS MANOVA test. A test of two proportions using the X^2 test of homogeneity revealed no differences in gender between Forsus® and Crossbow® groups ($p = 0.94$). Therefore, the groups can also be considered equal in terms of gender distribution.

The means and standard deviations (SD) of all the parameters as well as gender can be found in Table 4.10.

	Crossbow®		Forsus®		Total	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
FMA	19.54	6.43	21.31	6.52	20.49	6.46
Alveolar volume	1787.93	482.37	1936.82	815.51	1867.57	677.70
Incisor inclination	131.48	13.59	128.78	10.44	130.03	11.93
Volume lower incisors	272.61	39.89	276.61	42.38	274.75	40.80
Age	13.1	0.92	13.9	1.26	13.53	1.18
	Females	**Males**	**Females**	**Males**	**Females**	**Males**
Gender	11	9	15	8	26	17

Table 4.10: Baseline characteristics of each group (FMA for Frankfurt Mandibular plane Angle)

4.2.7 Numbers analysed

Analysis was restricted to only participants who fulfilled the protocol in terms of eligibility, interventions, and outcome assessment. This analysis is known as an "on-treatment" or "per protocol" analysis.

Twenty-three patients out of the 28 randomized in the Forsus® group were analysed, whereas in the Crossbow® group, the end was twenty out of 28. See the previous flow diagram of the patients for more details.

4.2.8 Outcomes and estimation

The statistical results are shown in the same order as planned and explained in the *Statistical Methods* section.

1) Descriptive statistics

The descriptive statistics are as follows. The average percentage in volume change, dependent variable and main objective of this Master's Thesis project, was + 0.27% and -1.42%, for the Forsus® and the Crossbow® patients respectively. The total average percentage in root volume loss for all the patients of the study was -0.55% (see Table 4.11). None of them were statistically significant, as it will be described in the following sections. The author of this Master's Thesis project decided to assign positive sign, "+", when an increase in the root volume was found and a negative one, "-", when the opposite situation occurred. This was an arbitrary decision and it was intend to be a more intuitive match for the reader.

	33	**32**	**31**	**41**	**42**	**43**	**ALL**
Forsus®	+ 0.36	+ 0.64	- 0.42	- 0.15	+ 0.44	+ 0.78	+ 0.27
Crossbow®	- 0.34	- 1.58	- 1.50	- 1.72	- 1.78	- 1.57	- 1.42
All	0.02	- 0.45	- 0.95	- 0.92	- 065	- 0.37	- 0.55

Table 4.11: Percentage in volume change (%)

The number of patients per group of the study, the gender of those patients as well as their age, were described in previous section (Baseline Data)

In terms of time, the spams were calculating by adding the number of days, dividing by 30, and that gives the corresponding number of months. The average time with Crossbow® was 5.51 months, and the allowed relapse time for the same group of patients before the full bonding was 3.64 months. The relapse time for the Forsus® appliance was not calculated *per se* because it was within the total active treatment time with full fixed appliances. However, the main clinician, Dr. Flores-Mir, overcorrected the Forsus® cases until an anterior edge-to-edge occlusion was obtained, and then he let the springs without farther activation for approximately four to six months. The average total active treatment time was 21.95, and 23.63 months for the

Forsus® and the Crossbow® patients respectively. The total average treatment time for all the patients in the study was 22.73 months.

For the calculations of the average total treatment time for Crossbow® and all the patients, the relapse time after the use of Crossbow® was not taken into account. The average treatment time with brackets was 21.95, and 18.12 months for the Forsus® and the Crossbow® patients respectively. The total average treatment time with brackets for all the patients of the study was 22.73 months (see Table 4.12).

	Average time with Crossbow®	**Average relapse time after Crossbow®**	**Average time with brackets**	**Average total active treatment time**
Crossbow®	5.51	3.64	18.12	23.63
Forsus®			21.95	21.95
Total			20.17	22.73

Table 4.12:Time with Crossbow®, relapse time after Crossbow®, treatment time with brackets, and total treatment time for both groups of the study and for all the patients. All the values are presented in months

The average linear apical displacement, as independent variable, was 2.17mm and 1.93mm, for the Forsus® and the Crossbow® patients respectively. The total average linear apical displacement for all the patients of the study was 2.05mm (see Table 4.13).

Group of patients		**33**	**32**	**31**	**41**	**42**	**43**	**Average**
Forsus	R-L	-0.43	0.13	0.61	0.36	0.50	0.57	0.29
	A-P	-1.12	-0.44	-0.23	-0.15	-0.81	-1.46	-0.70
	S-I	0.90	0.82	0.25	0.20	0.65	0.68	0.58
	3D	2.35	2.28	1.88	1.79	2.07	2.64	2.17

Crossbow	R-L	-0.49	-0.33	0.64	0.25	0.72	0.45	0.21
	A-P	-0.62	-0.18	0.23	-0.02	-0.14	-0.84	-0.26
	S-I	0.71	1.29	0.79	0.70	0.96	0.58	0.84
	3D	1.81	1.95	1.71	2.03	2.04	2.03	1.93
Overall	R-L	-0.46	-0.10	0.63	0.31	0.61	0.51	0.25
	A-P	-0.88	-0.31	0.00	-0.09	-0.48	-1.16	-0.49
	S-I	0.80	1.05	0.51	0.44	0.80	0.63	0.71
	3D	2.08	2.12	1.80	1.91	2.06	2.34	2.05

Table 4.13: Average apical displacement per tooth, per type of movement, per type of treatment, and overall averages. All are given in mm

2) Five-way MANOVA, assumptions and overall test

Prior to performing the overall MANOVA test, the model assumptions for this analysis were checked. The four assumptions for MANOVA include:

First, independence, which is met because the patients of this RCT were sampled independently from one another and the acquisition of the volumes from one patient does not influence the acquisition of the volumes from other patients.

Second, multivariate normality: univariate normality was assessed thanks to the matrix of each pair of dependent variables (Fig. 4.25) and the boxplots of all the dependent variables (Fig. 4.26). We can observe that, overall, the variables appear not normally distributed due to the presence of univariate outliers. In any case, MANOVA is robust to violations of multivariate normality if the size of the groups is equal or close to be equal, which is the case in our study because the Forsus® group contains twenty patients and the Crossbow® group contains 23. Even if seven outliers were detected in the univariate dimension, there were no multivariate outliers as determined by the p-value of the Mahalanobis distance being greater than 0.001 for all dependent variables.

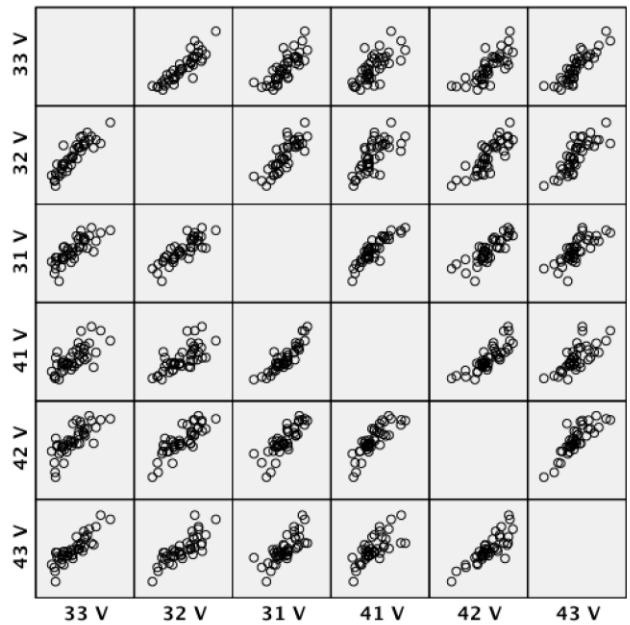


Figure 4.25: Scatter plot of the matrix of the pairs of responsive variables

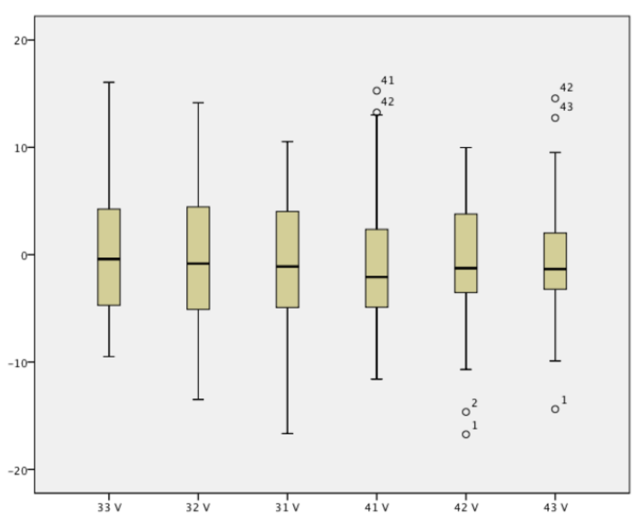


Figure 4.26**:** Boxplots of all the dependant variables (percentage of volume change of all the six lower anterior teeth)

Third, equal variance-covariance matrices were not assessed because none of the independent variables were added to this model. Fourth and last, linearity of all pairs of response variables can be visually assessed thanks to the scatter plot displayed in Fig. 4.25. All the cells display a linear or elliptical pattern, and given the fact that the contours of the multivariate normal density are ellipsoids, this assumption is also met.

The hypotheses for the overall test are:

H_o1: There is no difference in the percentage of root resorption considering all the measured teeth jointly.

H_a1: There is difference in the percentage of root resorption considering all the measured teeth jointly.

The matrix representing these hypotheses can be found Table 4.14.

$$H_0 \begin{Bmatrix} \mu\ \%V\ \#3.3 \\ \mu\ \%V\ \#3.2 \\ \mu\ \%V\ \#3.1 \\ \mu\ \%V\ \#4.1 \\ \mu\ \%V\ \#4.2 \\ \mu\ \%V\ \#4.3 \end{Bmatrix} = \begin{Bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{Bmatrix} \qquad H_a \begin{Bmatrix} \mu\ \%V\ \#3.3 \\ \mu\ \%V\ \#3.2 \\ \mu\ \%V\ \#3.1 \\ \mu\ \%V\ \#4.1 \\ \mu\ \%V\ \#4.2 \\ \mu\ \%V\ \#4.3 \end{Bmatrix} \neq \begin{Bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{Bmatrix}$$

Table 4.14: Matrix of the hypotheses of the MANOVA overall test

After analyzing the MANOVA overall test, the resulting Wilks' Lambda p-value was 0.82 (Table 4.15), therefore, the null hypothesis cannot be rejected. The conclusion is that, when all the measured teeth are considered jointly, no statistically significant percentage of volume change was noted between T0 and T1. The statistical analysis arrests at this point; given the lack of statistical significance of the MANOVA overall test, no further statistical tests are necessary, nor performed.

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	.073	$.485^b$	6.000	37.000	.815
	Wilks' Lambda	.927	$.485^b$	6.000	37.000	.815
	Hotelling's Trace	.079	$.485^b$	6.000	37.000	.815
	Roy's Largest Root	.079	$.485^b$	6.000	37.000	.815

Table 4.15: Overall MANOVA analysis.

4.2.9 Binary outcomes

There were no binary outcomes in this study.

4.2.10 Ancillary analyses

No other analyses were performed, including subgroup analyses and adjusted analyses.

4.2.11 Harms

There were no important harms or unintended effects in any of the groups of the trial. Nonetheless, it is convenient to mention that one of the patients suspected that he/she had an allergy to the Crossbow® appliance; however, even after it was confirmed the lack of allergies, the family decided not to continue with the Crossbow® treatment and selected the Forsus® springs instead.

Also, it is worth mentioning, the number of unscheduled appointments (may be emergencies or discomfort appointments) per group were as follows:

- Forsus®: In this group, the number of patients that did not experience unscheduled appointments was three. The average of unscheduled appointments per patient was 3.04.

- Crossbow®: In this group, the number of patients that did not experience unscheduled appointments was one. The average of unscheduled appointments per patient was 3.95.

4.2.12 Registration

The trial is registered at clinicaltrials.gov, under the number NCT01530516.[65] The Human Ethics Research Office at the University of Alberta granted authorization (Pro00023805) for this study.

4.2.13 Protocol

Full details of the trial protocol can be found at https://clinicaltrials.gov/.[65]

4.2.14 Funding

The University of Alberta, Graduate Orthodontic Program was sponsor and collaborator. The sponsor had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

4.3 References

63. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016;15(2):155-63.

65. Clinical Trials Gov Canada [Available from: https://clinicaltrials.gov/ct2/show/NCT01530516?term=Flores-mir&draw=2&rank=2.]

5 Chapter 5: Discussion and Conclusions

5.1 Class II malocclusion generalities

Angle established three types of malocclusions in 1890, all of them based on the sagittal relationship of the lower molars relative to the upper first molars:

- Class I malocclusion,

- Class II malocclusion, and

- Class III malocclusion.[1]

The main focus of this Master's Thesis project is related to the comparison of two different approaches to treat Class II malocclusions, which Angle defined as the situation in which the lower first molar was distally positioned relative to the upper first molar. So we will center our discussion among our understanding of Class II malocclusion diagnosis, treatment planning and management.

In general terms in an adolescent presenting a Class II malocclusion there are two major treatment possibilities:

a) Either facilitate differential growth of the jaws, guided by an extraoral force or a functional appliance,

b) Or differential anteroposterior movement of the upper and lower teeth with or without differential closure of extraction spaces. This is known as camouflage and it should be considered when the patient presents relatively reasonable jaw relationships.[1]

The 'camouflage' type of treatment includes three major management approaches:

1) Exclusive distal movement of the upper dentition,

2) Differential anteroposterior tooth movement using extraction spaces, and

3) Non-extraction treatment that consists primarily of distal movement of the upper dentition and forward movement of the lower dentition.

5.2 Forsus® springs

The Forsus® springs, which are specific brand of fixed *intermaxillary springs,* would accomplish the Class II correction by the effects of option #3 listed above. While Class II intermaxillary elastics would depend on patient's compliance, the Forsus® would require less patient cooperation as they are attached to the dentition during the active treatment phase. Patients cannot remove them which a major differentiator with intermaxillary elastics. That is why these types of intermaxillary springs are also termed "compliance-free Class II correctors".

Two different treatment approaches that include Forsus® springs are the main focus of this Master's Thesis project: Forsus® over the archwires and as part of a Crossbow®. Those two were the groups of the RCT on which this study was based.

The Forsus® spring consists of a nickel titanium alloy spring that pushes the lower dentition forward and the upper dentition backwards. Normally, the Forsus® spring should correct an average Class II molar malocclusion in around six to eight months. The only systematic review that solely focuses on the dentoskeletal effects of the Forsus® spring shows the following effects:[2] There is a resultant increase on the occlusal plane inclination, protrusion with proclination and intrusion of the lower incisors; retroclination of upper incisors and distalization, and intrusion of upper molars, with an associated reduction in overbite and overjet. Based on these effects, it seems that the lower anterior teeth will receive significant anterior pushing forces.

Regarding adverse effects outside the dentoalveolar effects one to be noted is the continuous rubbing of the springs over the cheeks.[16] This is not observed when using intermaxillary elastics. As I am going to explain later this discomfort occurs quite frequently and hence needs to be clearly conveyed to the patients if this is the type of approach they choose. A systematic review that investigated additional appointments and discomfort associated with compliance-free fixed Class II correctors was developed by Phuong et al.[16] The authors concluded that low level of evidence with a weak recommendation strength suggested that the main source of discomfort from Forsus®-type appliances appears to be soreness in the cheeks. In our study, the numbers of emergencies per group were as follows: Forsus®: the number of patients that did not experience emergencies was three. The average of emergencies per patient was 3.04. Crossbow®: the number of patients that did not experience emergencies was one. The average of emergencies per patient was 3.95. This information is not a goal of this Master's Thesis project but it was considered something worth mentioning.

One of the conditions to start using the Forsus® spring in an orthodontic patient that requires it, the archwire sequence has to be advanced to a stage with a stiff rectangular. Because of that, the Forsus® insertion will be delayed at a later stage of treatment, always when the level and alignment stages in both arches have been completed. An alternative would be to employ a Crossbow® appliance.

5.3 Crossbow® appliance

The Crossbow appliance allows the correction of the antero-posterior and transversal mild discrepancies with one appliance before the full fixed appliances are bonded. Historically, an issue that orthodontic treatment presents is its relatively long duration. Being "in braces" implies a more difficult oral hygiene, and certain risks like dental decay or white spots or even increase risk of OIERR. Also, it has to be kept in mind that general patients' desire of having the orthodontic appliances bonded for the shortest possible time. For the reasons stated above, the Crossbow was invented and it combines Forsus® springs, a palatal expander (hyrax) and mandibular lingual and labial bows.[3] Once both antero-posterior and transverse corrections have been achieved with the Crossbow® appliance, it can be removed, and full fixed appliances can be placed in order to finish the treatment. At this stage no need other that alignment and leveling of teeth is needed. Hence, the total time in brackets should be reduced if this philosophy of treatment is used.[4] The mean treatment time was less with the Crossbow ® when compared to Forsus®.as well as the average number of months of fixed edgewise appliances when compared to Forsus® springs (ten less).

Given the fact that the Crossbow® is a relatively new treatment approach, the overall level of evidence about its effect cannot be compared to the one of Forsus®. Nonetheless, the effects described so far are, a diminution of maxillary protrusion without mandibular advancement and an increase of the vertical dimension. Overjet correction was accomplished by an increase in mandibular incisor protrusion and proclination without maxillary incisor movement. The maxillary molars were distalized whereas the mandibular molars were mesialized.[3]

5.4 Orthodontically Induced External Root Resorption

A high percentage of all orthodontically moved teeth are associated with histologically noticeable OIERR.[5-7] (Root resorption occurs when the pressure on the cementum exceeds its reparative capacity.[8] OIERR can lead to significant consequences during or after orthodontic treatment. Among those, the most relevant ones would be mobility and loss of the affected teeth in severe cases. Therefore, OIERR is of greater clinical interest when found in the anterior segments. Quantifying and understanding how much OIERR is caused by certain devices can help the clinician to choose the adequate appliance for each patient.

According to the literature, even if not always by consensus, OIERR is associated with increased level of orthodontic forces, amount of apical displacement, increased orthodontic treatment time, and gender predisposition. Patients that undergo major upper and lower incisors movements as part of a Class II camouflage treatment may suffer from OIERR. This potential has not been extensively analyzed in general, and even less with the use of CBCT technology.

One challenging situation is the fact that not all OIERR requires action or has meaningful consequences. Different classifications have been presented in this regard. Even if scales have been presented, studies should be developed in order to support their clinical significance. So the big question is: How much is a percentage of volume decrease that triggers clinically significance? Glenn Sameshima who considered an expert in OIERR, has stated that "if the patient or the general dentist can see it [the root resorption], then, maybe that is considered severe or at least moderate". During the same lecture, he also explained that there are no consensus standards on what constitutes severe OIERR. Dr. Sameshima's opinion is that, generally, for a normal length, non-periodontally involved tooth, any amount that compromises the longevity of the tooth may be considered severe. In Fig. 5.1, the different degrees of root resorption can be observed.

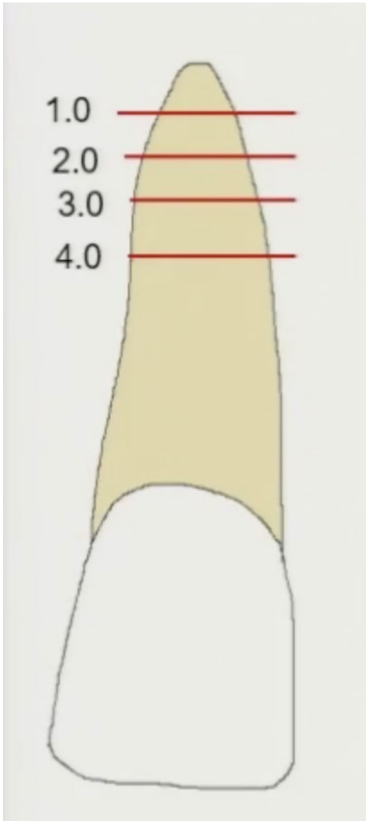


Figure 5.1: Image from Glenn Sameshima's lecture determining different degrees of root resorption

A different classification approach would be the following. Severe resorption, defined as exceeding 4mm, or a third of the original root length, is seen in 1% to 5% of teeth. By using graded scales, OIERR is usually classified as minor or moderate in most orthodontic patients.[37]

From the Samandara *et al*. systematic review, the average OIERR across all studies involving fixed appliances was 0.79 mm for any treatment duration and 0.86 mm from bonding to debond.[26] The authors concluded that this effect probably has no clinical relevance in terms of attachment loss, tooth mobility, or tooth prognosis. However, according to the same authors, this degree of OIERR falls in the category of "clinically important".

From the Dutch clinical practice guideline, "clinically relevant OIERR" was defined as a loss of 2mm or more root length.[27] Between 48 and 66% of orthodontically treated teeth show mild to moderate OIERR (less than 2.5 mm), and only 1 to 5% of all moved teeth end up with severe apical root resorption, defined as a loss of 4 mm of the original root length or more than one-third of the root.[5-7] Weltman *et al.* concluded that the OIERR detected through CBCT probably has “little clinical relevance”, which makes the added exposure to ionizing radiation through high-resolution CBCT protocols questionable in terms of risk to benefit ratio.[5]

As it can be observed, in the literature, several scales of severity of OIERR have been proposed. However, most of them are based on two-dimensional measurements. Only one could be found by the author of this Master’s Thesis project that classifies the severity of OIERR by means of volumetric measurements. In Samandara *et al*. systematic review, that was solely based on CBCT, the authors set that the cut-offs of minimal clinical important, large, and very large effects for linear OIERR were arbitrarily defined a priori as 0.75, 1.50, 3.00mm and 10.0, 20.0, and 40.0mm^3 for volumetric OIERR. These scales were used to augment the produced forest plots with contours of effect magnitude. The authors concluded that it might be useful in the future to categorize OIERR into clinically relevant categories of magnitude and use this as an outcome in clinical research.[26]

Even if those classifications could be an option, a study that relates a specific classification to different clinical endpoints does not exist and should be developed. A hypothetical clear example would be: if a specific treatment causes “severe” OIERR that may mean that the patient has a 50% increase risk of losing that tooth in the next ten years.

In summary, based on this background information the author of this Master’s Thesis project compared both Class II management approaches using the Forsus® springs in terms of amount of OIERR generated on lower incisors and canines. Those teeth, even if receiving forces, are not bonded with brackets until their Class II is fully corrected through the Crossbow® approach; whereas they are bonded before, during and after the Class II correction through the Forsus® approach. Variables associated with increased risk of OIERR listed before were included in the hypotheses of this Master’s Thesis project.

5.5 RCT methodological considerations

a) Randomization and similarity of the baseline characteristics

The randomization was strictly respected and properly performed. This would set equivalent baseline characteristics of both groups. However, in order to be certain that those characteristics were the same, adequate statistical analyses were performed. In addition, blinding was carried out to the maximum extent that was possible taken into account the noticeable physical differences between the two treatment modalities. All that stated, the reader can be certain that the only possible differences in any outcome found at the end of the trial, can only be attributed to the differences in the intervention.

b) Population

The portrayed results between the two treatment approaches were not significantly different regarding the outcomes of interest. However, they can be generalized to a population similar to the sample that participated in this RCT: the patients presented a mild to moderate Class II division 1 malocclusion and an age ranging between eleven to fifteen years old. Both genders were included. It has to be noted that the participants were in the late mixed dentition or the early permanent dentition.

5.6 Clinical study results

In the first study that measured three-dimensional changes in the volume in the intrusion of incisors in adults with marginal bone loss, the authors used pre- and post-treatment CBCT scans, like in this thesis project. As commented in a previous chapter, the authors divided the OIERR by areas, and they obtained the following results: The mean root volume significantly decreased on the labio- and palato-apical aspects of 1.2 and labio-apical aspects of 2.1 and 2.2. Palato-apical segment volume loss was greater on lateral than central incisors. Nonetheless, the authors used a limited field-of-view (80 x 40mm) CBCT with a 0.125mm voxel size which has an influence (increased definition of the image) in the final outcome as described in the previous section.[43] Probably, being the FOV and the voxel size far apart from the ones used in this thesis project, the results cannot be compared. Besides, the teeth measured were upper incisors, which present a higher likelihood of OIERR. In any case, this study may help to put the results of this project into perspective.

Something important to be considered when analyzing the results is that the way in which the methods of this study were designed do not allow to differentiate the area where the actual root resorption occurred. The previously mentioned study could make that difference by dividing the roots into different sections. So in our study, an overall change in the volume of the root was reported without distinguishing the root areas that could have suffered more or less volume loss.

In a meta-analysis that included only studies that used CBCTs to measure OIERR, most of the studies measured tooth length as reported in the literature review chapter.[28] However, three studies reported changes in root volume after fixed appliances using CBCT. The results of computing the measurements coming from those three studies, revealed that the root volume before and after orthodontic treatment was significantly different (MD = 23.12 mm^3, 95% CI 17.88, 28.36 P < 0.00001). The root volume experienced reduction after treatment. The meta-analysis results are shown in Fig. 5.2. Even if statistically significant, maybe the results found by the authors are not clinically relevant. The reason being is that if we calculate the percentage in change that that amount of OIARR represents, it results in a decrease of 7.23%. The question that may rise is, is that a clinically significant result? Given the fact that this is a new research method, there are not clear cuts of what is a clinically significant root loss in terms of volume.

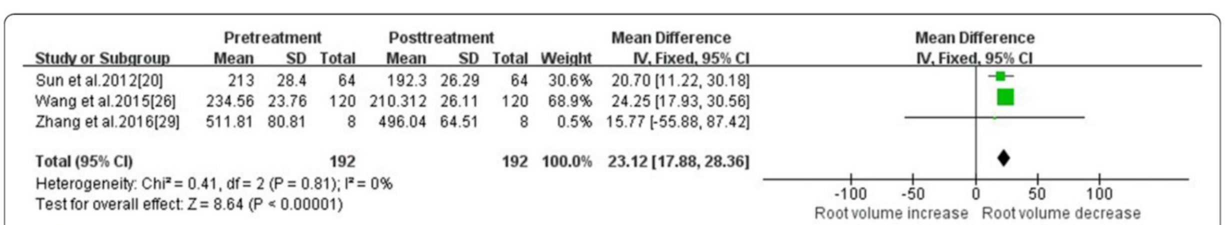
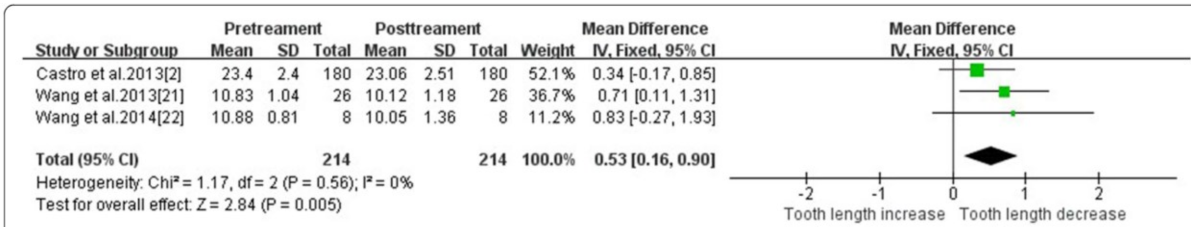


Fig. 11 Primary result of root volume increase or decrease with orthodontic treatment

Figure 5.2: Forest plot of root volume change before and after fixed orthodontic treatment

From the same meta-analysis, the two-dimensional analysis revealed that the lower anterior teeth seem to be one of the groups of teeth that suffer the most OIERR. Statistically significant differences in OIERR were seen across the different regions within a specific jaw, with the anterior maxilla showing the greatest among of OIERR (0.82mm), followed by the anterior mandible (0.60mm), the posterior mandible (0.28mm), and finally the posterior maxilla (0.22mm). As conclusion, the sequence of OIERR from heaviest to lightest was: maxillary lateral incisors, maxillary central incisors, mandibular anterior teeth, and maxillary canines.

The length of mandibular anterior teeth was reported by three studies. The change in length of mandibular anterior teeth using CBCT was MD = 0.53 mm 95% CI 0.16, 0.90, P < 0.00001). The forest plot of this part of the meta-analysis can be seen in Fig. 5.3. Therefore, the teeth measured in this RCT are actually subject to an important amount of OIERR relative to other groups of teeth. However, maybe, those absolute results may not be that relevant from a clinical point of view.



Study or Subgroup	Pretreament Mean	Pretreament SD	Pretreament Total	Posttreament Mean	Posttreament SD	Posttreament Total	Weight	Mean Difference IV, Fixed, 95% CI
Castro et al.2013[2]	23.4	2.4	180	23.06	2.51	180	52.1%	0.34 [-0.17, 0.85]
Wang et al.2013[21]	10.83	1.04	26	10.12	1.18	26	36.7%	0.71 [0.11, 1.31]
Wang et al.2014[22]	10.88	0.81	8	10.05	1.36	8	11.2%	0.83 [-0.27, 1.93]
Total (95% CI)			**214**			**214**	**100.0%**	**0.53 [0.16, 0.90]**

Heterogeneity: Chi² = 1.17, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.84 (P = 0.005)

Fig. 8 Primary result of tooth length increase or decrease with orthodontic treatment—mandibular anterior teeth after removing control group of Wang et al. [21]

Figure 5.3: Forest plot of lower anterior roots' length change before and after orthodontic treatment.

Indeed, the author of this Master's Thesis project, decided to calculate the percentage change, as done previously with the three studies that used volumetric measurements. The result is 3.52% loss in length. If the six studies were similar, the percentage of OIERR detected with the three-dimensional method would have been more important than the one detected with a linear measurement.

From the meta-analysis published by Samandara et al. that was commented in the literature review chapter,[26] the average overall increase in OIERR was noted as 0.36mm for every additional year of active treatment. The average OIERR across all studies involving fixed appliances was 0.79mm for any treatment duration, and 0.86mm from bonding to debond. Only six of the 33 included studies were RCTs. Out of the six RCT, only three reported volumetric measurements from CBCT. It seems that after fixed appliance treatment the average OIERR was 15.4 mm^3 95% CI = -4.1 to 35.0 mm^3. This result is not statistically significant therefore not clinically significant either. It coincides with the non-statistically significant results of this Master's Thesis project.

5.7 Limitations associated to the proposed methodology

Even if traditionally, the measurements of OIERR and apical displacement have been accomplished through two-dimensional x-rays, this approach implies certain limitations, as described in the literature review chapter (Chapter 2). A superior manner of proceeding would be a three-dimensional approach, for instance through the use of CBCT imaging.

Therefore, two techniques were developed in order to analyze OIERR and apical displacement: *the construction of three-dimensional volumetric label maps of lower incisors and canines from CBCT imaging reconstruction in order to assess volume using the software ITK-SNAP®: "in-block" automatic segmentation with manual refinements*; and *the quantification of linear displacement of the apices of lower incisors and canines within the symphysis from CBCT imaging reconstruction using the softwares ITK-SNAP® and 3DSlicer®.*

For statistical reasons, only the linear distances of the apical displacements of the lower anterior teeth were used, even if the vectors, one per each plane of space, would have given more details about the displacements. The statistical issue arises from the important increased number of independent variables regarding the relatively small sample size. If the linear distance between apex 0 to apex 1 is considered instead of the three vectors per tooth, the number of independent variables decreases enough to allow a more adequate statistical analysis.

In order to test the reliability of the techniques developed, the CBCTs of five randomly selected patients were used. A main and a secondary researcher proceeded with the two methods described in order to obtain the data. Inter- and intra-rater reliability analyses were performed as well as calculations of the respective measurement errors.

According to the results, the technique developed to measure the volume, overall presents a good to excellent reliability and a mean measurement error of 5.64%. The technique developed to measure the apical displacement overall presents a good to excellent reliability and a mean measurement error of 8.62%. The ICC values in this Master's Thesis project were as observed in Table 5.1.

Technique	Inter- / Intra-rater	Reliability (average)
Volume	Intra-	Excellent (.94)
	Inter-	Good (.85)
Apical displacement	Intra-	Good to excellent
	Inter-	Good to excellent

Table 5.1: ICC values in this Master's Thesis project

5.8 ICC values in other studies

About the apical displacement, no similar methods were found in the literature, therefore, a comparison could not be made. Nonetheless, ICC values in other studies that employed volumetric measurements of teeth are going to be discussed.

In an *in vitro* study that compared laser scans to CBCT scans,[70] the inter-rater reliability measurements were perfect, ICC=1, which is higher than the one in this Master's Thesis project, 0.85. In the same range, after segmenting twenty volumes from two CBCT scans with different voxel sizes, CBCT 200 µm and CBCT 300 µm, Maret *et al.* found inter-rater reliability ICCs values of 0.999 and 0.988.[71] In another similar study, Ahlbrecht *et al.* segmented maxillary incisors and they found that the inter-observer reliability for both surface area and volume of the repeated models yielded an ICC of 0.98.[72] However, lower values are found in another study including segmentations from CBCTs. For the inter-observer reliability, the ICC obtained by Liu Y. *et al.* was 0.86.[73] This last value is really close to the one obtained in this Master's Thesis Project. Consequently, it could be argued that the current inter-rater reliability values are within reasonable reach of previous relatively similar approaches.

About the intra-rater reliability, the ICC value found in this thesis was 0.94, which corresponds to the level of excellent. After segmenting twenty volumes from CBCT 200 µm and CBCT 300 µm, Maret *et al.* found ICCs of 0.998 and 0.999 [71] which are slightly higher than ours but all still fall in the range of excellence. In another study in which upper incisors were segmented, developed by Puttaravuttiporn et al., the intra-class correlation coefficient for intra-rater reliability of tooth volume was >0.90,[43] again, similar to this Master's Thesis project's results. Therefore, it can be considered that our intra-rater reliability values are within the range of previous related studies.

5.9 Measurement errors in other studies

In an *in vivo* study conducted by Liu *et al.*,[73] the validity of the tooth volume determinations from CBCTs was explored. The measurements were given and even if the measurement error was not calculated by the authors, it was done by the author of this Master's Thesis project. All the data can be observed in Table 5.3 in the Appendix. The resulting measurement error was 8.24% for the inter-observer analysis, which is really close to the value yielded from the current Master's Thesis project, 7.11%.

About the apical displacement, no similar methods were found in the literature; therefore, a comparison could not be made.

If the measurement error is 5.64% for one of the time points, a more significant and cumulative measurement error is logically applied when the difference between T0 and T1 are calculated, because the measurements errors of two time points are added. The measurement error is a variability that indicates that changes of around its value or less in the root volume could be explained by either measurement error or by an actual change in the measured outcome.

5.10 Threshold and contrast employed in the segmentation processes

In this method the upper threshold is placed to the maximum, whereas the lower threshold is individually adapted for every patient and every time point. By arbitrary agreement between the researchers involved in this project, KC and GCM, the lower threshold range was considered from: 500 to 1500. What is found in the literature is that in other *in vitro* studies the thresholds were set at 56 to 3071 Hounsfield units (HU), minimum and maximum respectively. If the HU threshold is set too high, the tooth contour cannot be completely obtained, and tooth volume tends to be smaller. If the HU threshold is set too low, the surrounding tissues will have a significant impact on tooth contour, and the tooth volume tends to be larger.[70] Standardized consensus-based ranges have not been developed so far because off the characteristics and the variability between CBCT machines, even within the same machine in different acquisitions, and among patients, as well as bone and teeth densities.

Indeed, Liu *et al*. concluded that visual adjustments of threshold parameters resulted in different threshold levels for different teeth in the same DICOM data sets, as well as between different data sets.[73] Therefore, the individual adaptation of the threshold within arbitrary limits is the best solution that can be currently supported. Furthermore, the use of a global threshold for each segmentation is not supported by Liu *et al.*[73]

Finally, the density of teeth is very different from the crown to the apex. If a single parameter was applied for the segmentation of the whole tooth, it may not be possible to clearly visualize the crown and the root apex at the same time. The researchers of the previously mentioned study adjusted the threshold level at least three times. Based on this, it was decided that tooth segmentation would require more than one threshold level.

As described in the methods section, the contrast selection was similar to the threshold selection: through a subjective visual assessment of the structures to be segmented. The intention was to better see and segment the regions of interest. The contrast selection as well as the threshold selection may have affected the final results. Probably, despite the good reliability results obtained for both techniques developed, a completely different study would be necessary in order to be able to precisely quantify the influence of contrast and threshold selection 0n the final results.

5.11 Smoothing option provided by the software

As explained in the step-by-step segmentation process in the methods chapter (Chapter 3), the smoothing options offered by the software ITK-SNAP® were turned off. Smoothing enhances the visual appearance of the three-dimensional model. Nonetheless, it can also reduce the volume from three to twelve percent according to the first study that tested the validity of *in vivo* tooth volume determinations from CBCT.[73]

5.12 Percentage as main outcome of tooth mass loss

Different ways of analyzing the results could have been used. Mean differences of the volumes, surface reduction, shape change analysis, etc.[72] Our choice was the percentage of total volume loss or increase: negative and positive values respectively. The author of this Master's Thesis project thinks that in the frame of new concepts and measurements in the third dimension, nothing is fully agreed and accepted, therefore, using percentages is more intuitive for the clinician and the researcher than using the previously mentioned format outcomes. Indeed, there is a study that already employed this format to report the outcome.[43] Puttaravuttiporn *et al.*

[43]calculated the root volume loss between T0 and T1. The percentage of root volume loss was calculated as:

$$\frac{\text{Root volume of } T0 - \text{Root volume of } T1}{\text{Root volume of } T0} \times 100$$

The only difference with this Master's Thesis project is that the numerator was inverted so the negative values will reflect "loss" and the positive values will reflect "increase" of root volume.

5.13 Structures included in the segmentation process for the volumetric measurements

When considering the structures that should be included in the segmentation, the main question that arises is: should the whole tooth be considered or just the root? Considering only the roots presents the difficulty of separating the root from the crown. Under normal anatomy, the anatomical crown structure ends at the cementum-enamel junction (CEJ) level. Below it, the root begins. This CEJ limit is curved. The segmentation tools that are employed in this study allow an easy straight line or plane segmentation, thanks to the Scalpel function, but not a curve one (Scalpel mode cannot be applied).

The curve segmentation, if done manually, would be more challenging and would require a much significant effort without necessarily resulting in an increase in the accuracy of the measurement; maybe it would even decrease it. The reasons being are because it may increase the number of sources of error and subjectivity in the segmentation process, and because the CEJ is not clearly visible with the voxel size that has been employed, which hinders the identification of the limits of the root-crown transition.

In addition to the technical issues that a curve segmentation to separate the root from the crown generates, it seems that the whole tooth segmentation is more precise than the root segmentation according to a study developed at the University of Alberta.[74]

In addition to the previous arguments, the enamel is not expected to change considerably during the average orthodontic treatment time. The attrition wear, also called occlusal-contact-area wear, of human enamel per year is about 29 microns for molars, and about 15 microns for premolars,[75] and the average time of an orthodontic treatment consisting of comprehensive fixed appliances is 24.9 months.[76] In our RCT, the average treatment time was 22.73 months. Hence, the amount of enamel wear could be estimated to reach a maximum of around 60 microns for the two years of treatment, which equals to 0.06 mm. The voxel size of the CBCT used in this study was 0.3 mm. Ergo, a normally expected enamel wear difference would not be detectable by the radiographic approach employed in this RCT. Any changes of the overall volume between T0 and T1 detected in this study can, therefore, be almost completely attributed to the changes in the root volumetric dimensions.

One of the issues with including the crowns in the volumetric assessment was the fact that interproximal reduction (IPR) of lower incisors and canines is a commonly used technique in orthodontic treatments. That procedure would reduce the volume of the crowns, and that change cannot be attributed to the reduction due to root resorption. Thus, knowing if there was or there was not IPR in the patients of this trial is an important point to validate and understand the results. Several thorough revisions of the charts of all the participants in the RCT was performed by the main author of this Master's Thesis project (GCM). No IPR was noted for any of the patients.

For the same technical reasons for which the crown was included, the pulp was included too. The segmentation of the pulp separately from the rest of the tooth structure can be really challenging and time consuming. Besides, the changes in the volume of the pulp do not affect the total volume of the tooth, consequently, it was included in the segmentation. The inclusion of the pulp chamber in the segmentation label has already been described in a previous *in vitro* study.[70] The authors used the "cavity fill" tool in Mimics®, a different segmentation software, to fill the pulp chambers.

It has to be kept in mind that the volume of the pulp decreases with age.[77] Indeed, the pulp to tooth volume ratios of anterior teeth can be used as a forensic instrument to estimate the age of the cadaver. The next scatter plot (Fig 5.4) shows the estimated line representing a linear regression relation between mean pulp to tooth volume ratios of anterior teeth and age.[77]

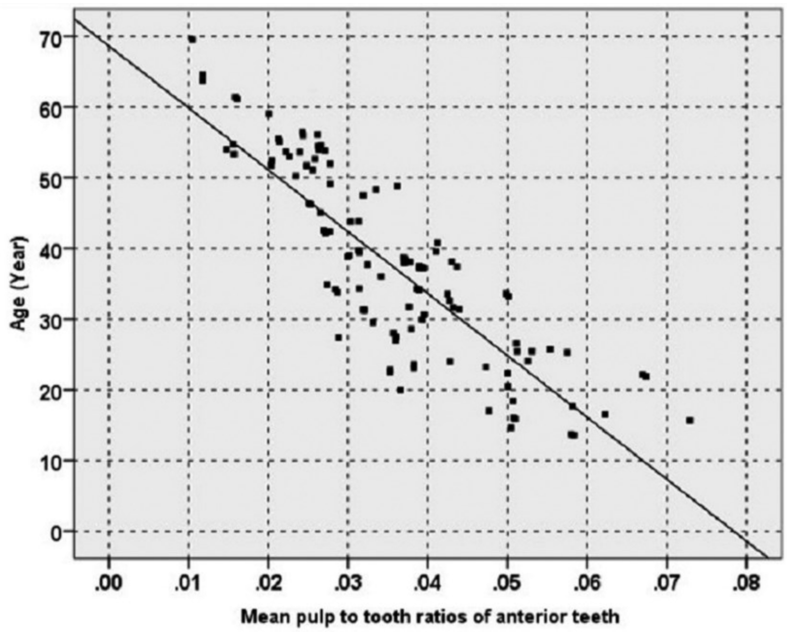


Figure 5.4: Scatter plot of linear regression relation between mean pulp to tooth volume ratios of anterior teeth and age

5.14 Structures included in the segmentation process for the apical displacement measurements

Besides the previously segmented teeth for the volumetric measurements, a reference structure or structures have to be segmented in an independent label. Those structures must be easily identifiable and stable from T0 to T1. They also have to be a reliable reference plane to situate in space the teeth and quantify the displacement of the apices of lower incisors and canines from T0 to T1. A parallel Master's Thesis project was being developed by Dr. KC, who has as aim to quantify the volumetric changes of the symphysis from T0 to T1 from the same sample of patients. Thus, the segmentation of those symphyses with the respective models were used as reference to quantify the apical displacements. Three points define a plane, therefore, three specific points on the surface of the symphysis would allow the researchers to have a reference to quantify the displacement of the apices from T0 to T1. The landmarks chosen were mental foramen right, mental foramen left, and B-point for both T0 and T1 symphyses models.

Mental foramina have been proven to be reliable as anatomical landmarks in three-dimensional cephalometric analyses using CBCT.[78] B-point is a classic and repeatable mandibular reference point for two-dimensional cephalometric analyses in orthodontics. It has also been chosen to be used in this study given the fact that B-point identified in a CBCT seems to be highly reliable when compared to the B-point traced in a two-dimensional lateral cephalogram generated from the same CBCT.[79] Indeed, B-point as a three-dimensional reference in CBCT has already been used to assess the stability of orthognathic surgery,[80] and in the assessment of the antero-posterior jaw relationships.[81]

There were no analyses performed to exclusively assess the reliability of the placement of the three symphyseal reference points. The two main reasons for that are: the points have already proven to be reliable in other studies and the reliability of the points was indirectly tested by the reliability analysis of the whole technique.

5.15 Other possible ways of measuring OIEARR in three-dimensions

As mentioned before, the fashion in which the OIERR was measured in this Master's Thesis project has already been employed according to the literature. It should be kept in mind that this may be only an initial way of assessing this endpoint in the "three-dimensional era". Other authors are already exploring different options. Two alternative options are presented in this section.

Shape analysis is one of those alternative options. Indeed, there is a study exploring three-dimensional incisor root morphology, by applying a three-dimensional surface mapping technique.[72] This would allow the researchers to determine the shape of the roots of right central and lateral incisors. Application of this morphological characterization in additional studies may allow improved understanding of factors affecting development of root shape or the influence of root morphology on OIEARR (Figs.5. 5 and 5.6).[72]

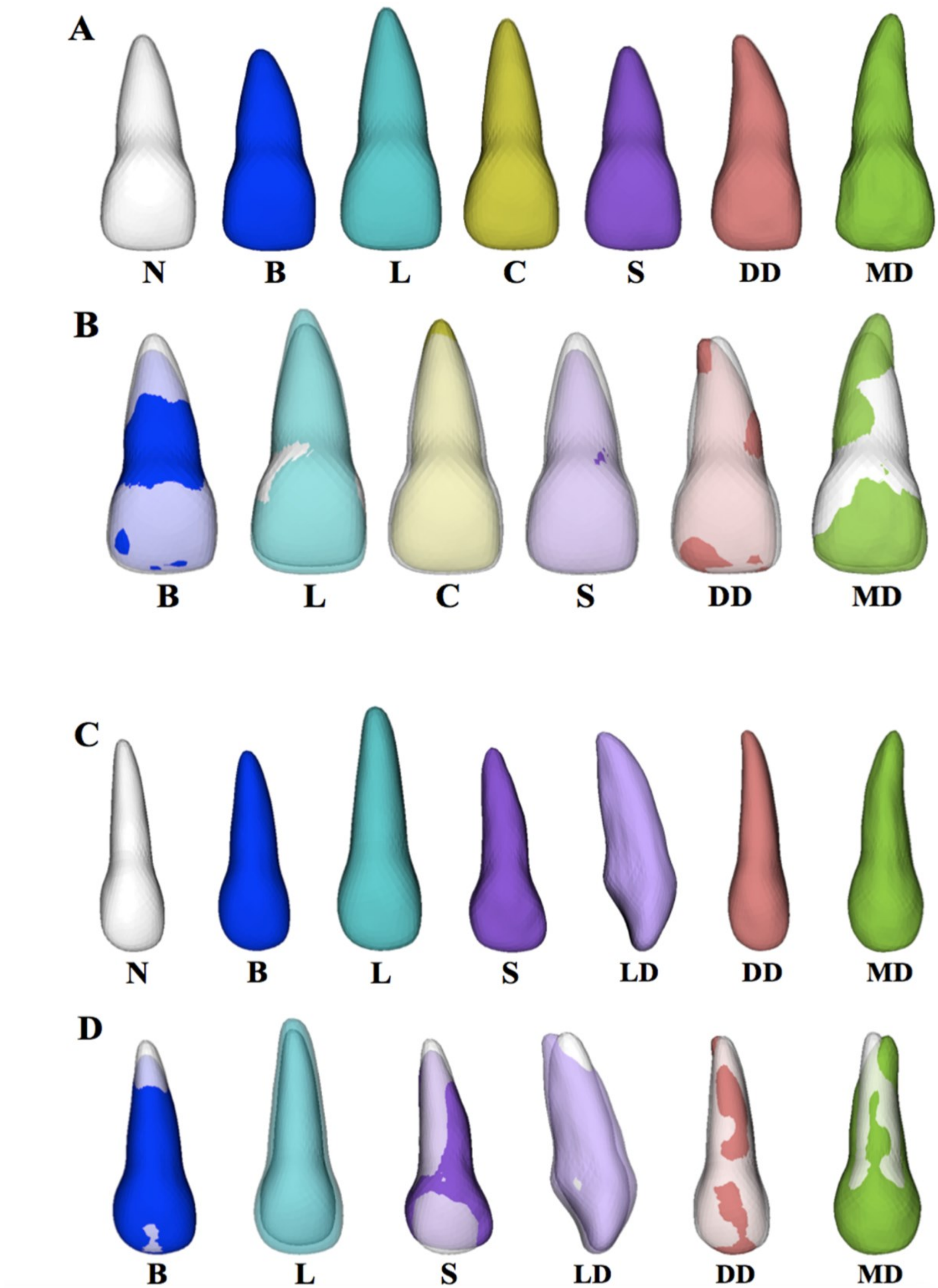


Figure 5.5: Shape analysis

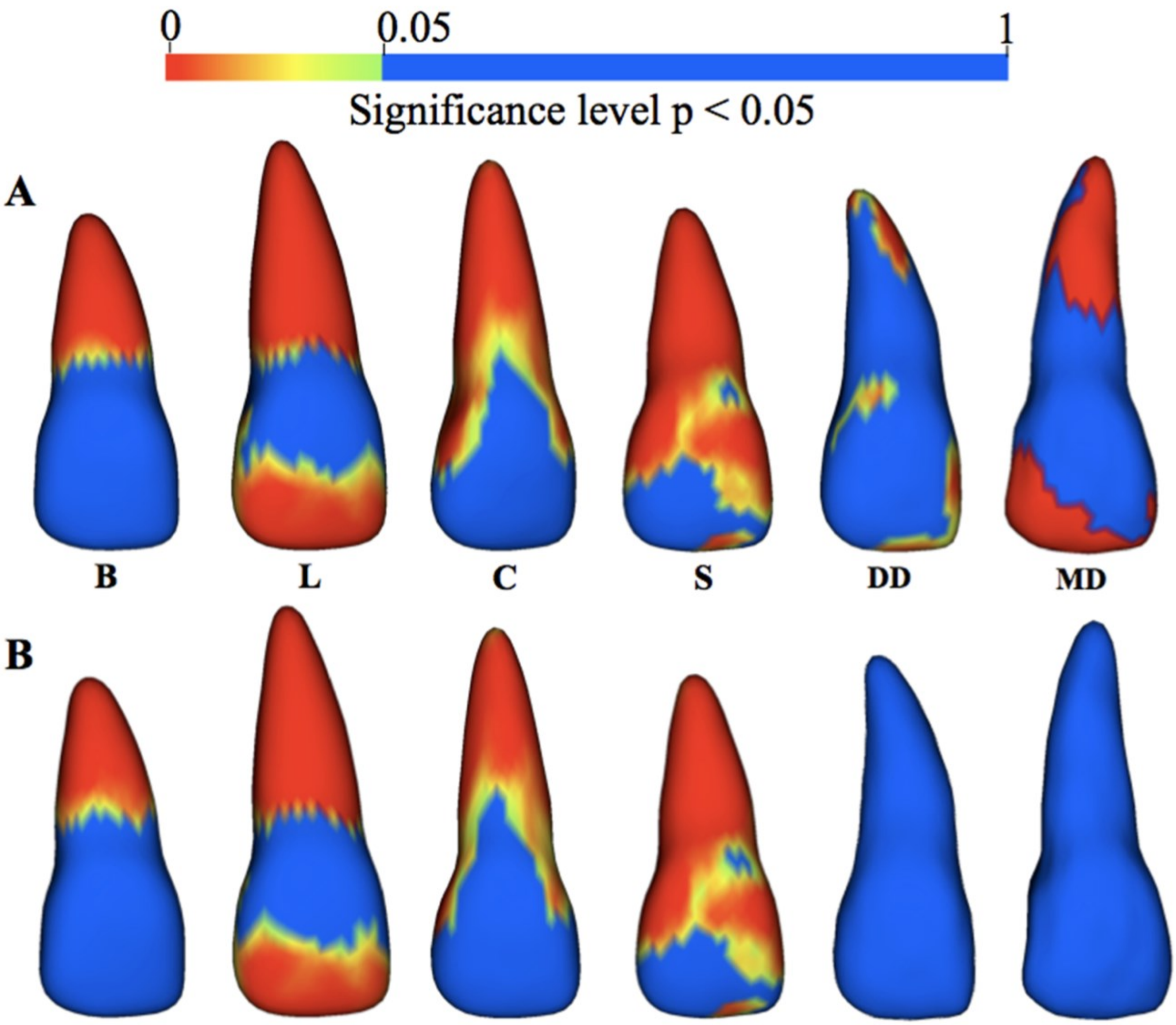


Figure 5.6: Shape analysis

Another completely different way of measuring OIEARR is the one described by Puttaravuttiporn *et al*.[43] After a usual segmentation like the one described in this Master's Thesis project, the roots were separated into cervical, middle, and coronal thirds (lengths) along the reference plane 2 and three planes parallel to the reference plane 1 (as it can be observed in Fig. 5.7). In this manner, six segments were generated from the root: labio- and palato-apical, middle, and coronal thirds. Root volumes were computed and calculated for the six portions of each root.

This type of analysis, even if it requires more work from the researcher, gives a more accurate location of where the OIEARR is located.

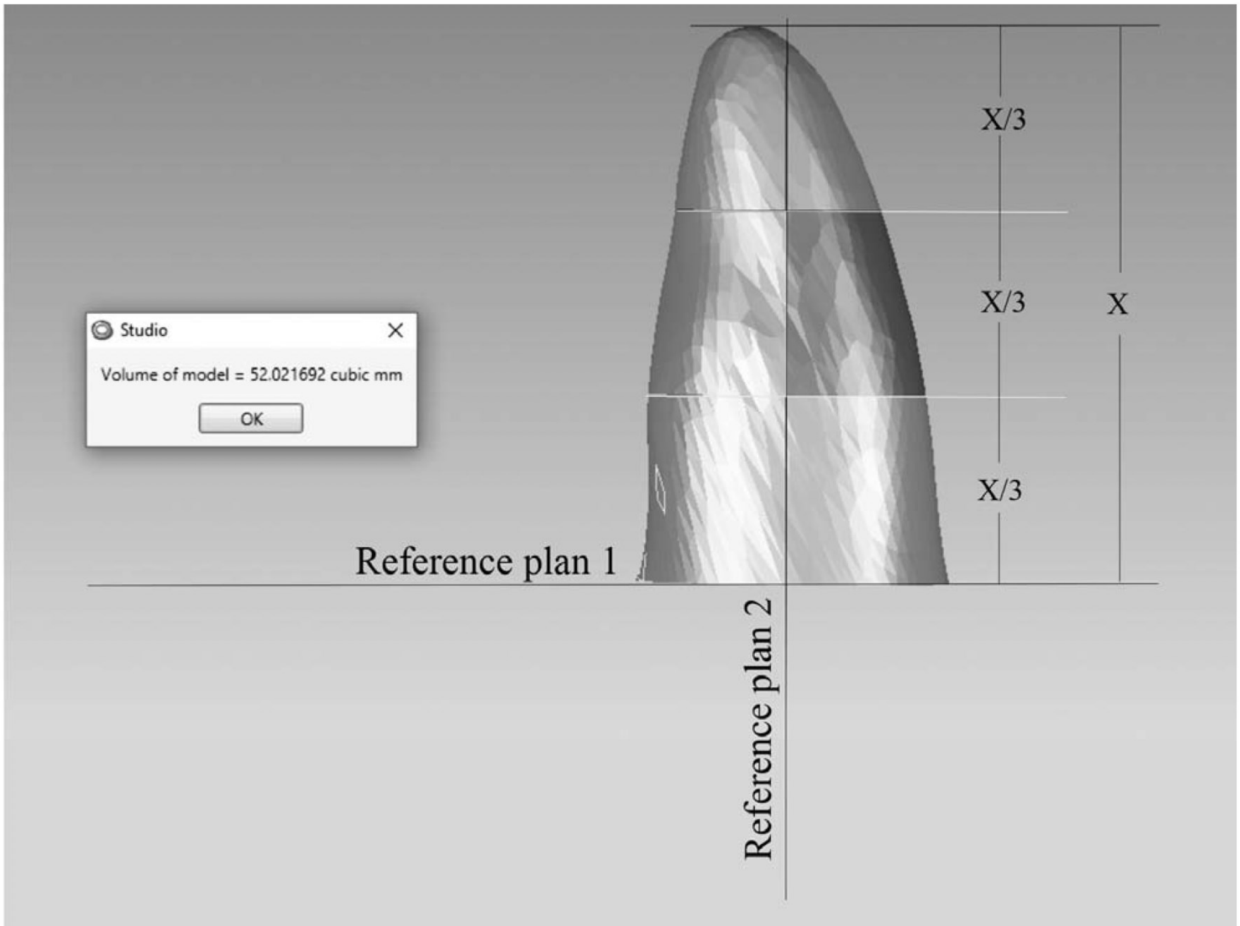


Figure 5.7: Reference plane 2 and three planes parallel to reference plane 1

5.16 Limitations of the methods employed

a) Voxel size, partial-volume effect, surrounding artifacts, and scatter x-rays

The definition of the images generated by the CBCT with the voxel size used in our study, 0.3mm, may not be accurate nor precise enough to detect minor amounts of volume change in the root. Thus, this can lead to wrong diagnostic conclusions. The problem with smaller voxels, which would provide higher definition and more accurate results, is that longer scanning times and a greater patient exposure to radiation are required within the same range of FOV.

Large field-of-view CBCT scans can currently be taken at four resolutions (voxel size): super high (0.125mm), high (0.2 mm), medium (0.3 mm) and low (0.4 mm). Whereas super high- and high-resolution CBCT are reserved for research purposes and generally are not used in private clinical settings, lower-resolution CBCTs are more commonly employed in private clinical orthodontic settings (29). In this RCT, the CBCT imaging employed was a Full FOV with 0.3mm voxel size. As previously stated, the full FOV had the following dimensions in our study: 16 cm (w) x customized height up to 13 cm, from roof of orbits to the inferior border of the mandible-level of cervical vertebra (C4). The one used in large patients with large mandibular angle/plane was 16 or 23 cm (w) x up to 17 cm (h): From the level of frontal bone / frontal sinus superiorly to the inferior border of mandible / level of C3-C5.

The definition of the images generated by the CBCT with the voxel size used in this RCT, 0.3mm, may not be accurate or precise enough to detect minor amounts of root volume changes. Nevertheless, these stings, previously explained, better represent the conditions faced by clinicians in private practice. This voxel size and exposure time is adequate to obtain a full FOV CBCT in order to help the clinician to get a useful diagnostic and treatment planning tool. Besides, the principle of “as low radiation as reasonably achievable” in dental radiography suggested by the ADA, should be kept in mind. This issue related to the voxel size has already been described in the literature. In addition, missing small amounts of root volume loss are unlikely to have a major clinical impact.

The first study that tried to validate *in vivo* tooth volumes from patients’ CBCT images was published by Liu *et al.*[73] In that project, CBCTs were taken from patients who needed premolar extractions for orthodontic purposes. Segmentation and volume calculation of all the extracted premolars were performed. Once extracted, the real volume of the premolars was measured with the water displacement technique. There was a statistically significant difference between the physical volumes and the CBCT segmentations. This difference varied from -4% to

+7%. These values are really close to the measurement error of the segmentation noticed in this Master's Thesis project.

The voxel sizes used in that study were 0.292, 0.25, 0.3, and 0.4mm in two different CBCT machines. The voxel size used in our RCT was 0.3mm. The fact that two different machines were used could have contributed to the heterogeneity in the measurements, as the authors discussed. These values obtained from extracted teeth tend to validate our results even though real root volume measurements were not completed in this Master's Thesis project (no gold standard employed as reference). Our reliability variation is quite similar to that reported by Liu *et al.*[73] In any case, a range of the variation from the gold standard of 12% (from -4 to 7%) is clearly significant, and results from individual CBCT segmentations may lead to wrong conclusions that may or may not be clinically relevant.

In an attempt to quantify the accuracy of *in vitro* tooth volumetric measurements from CBCTs, Ye et al., compared segmentations of extracted premolars from different voxel size CBCT images with a laser-scan generated segmentations with an accuracy of 20μm.[70] The latter were used as a reference standard. The roots and the crowns of the premolars were measured separately. They noted that with increased voxel sizes, the CBCT generated models were larger than the reference standard. All the differences were statistically significant. In the case of the same voxel size that was used in our study, 0.3mm FOV 85x85, and scan time of 8.9 sec., the crowns were around 40% bigger than the reference and the roots, around 35% larger than the reference; precisely, those values were +39.76% and +34.82% respectively. The authors attributed the larger volumes to surface surrounding artifacts. Thirty-five to 40% increase of the actual volume of the tooth is not a neglectable inaccuracy that again, may lead to wrong conclusions.

One of the explanations of this inaccuracy and increase of volumetric measurements in the digital images generated by CBCTs is the partial-volume effect. The partial-volume effect is present at sharp edges with high contrast to neighboring structures. A voxel can show only one kind of density. If that voxel fully lies within a structure, it will reflect that structure's density. However, if that voxel lies at the junction of two different structures of different levels of density, i.e. enamel and air, the voxel will reflect an average value between the true densities of the neighboring structures. This increase in the surface is difficult to eliminate in the segmentation process and three-dimensional labeling, and it leads to an artificial increase in the resultant volume,[70,82] as seen in the previously described studies. This phenomenon was also experienced by the main and the secondary researchers of this master's thesis (KC and GCM).

This effect can be observed in one of the images from the Ye *et al.*[70] study (Fig. 5.8). In the left image, a 0.125mm voxel CBCT can be observed; whereas in the right image, a 0.4mm voxel CBCT scan of the same tooth appears. Not only the partial-volume effect can be observed, but also the difference in the quality and accuracy of the two scans. As the reader can imagine, the images of our study were closer to "B" given the 0.3mm voxel size.

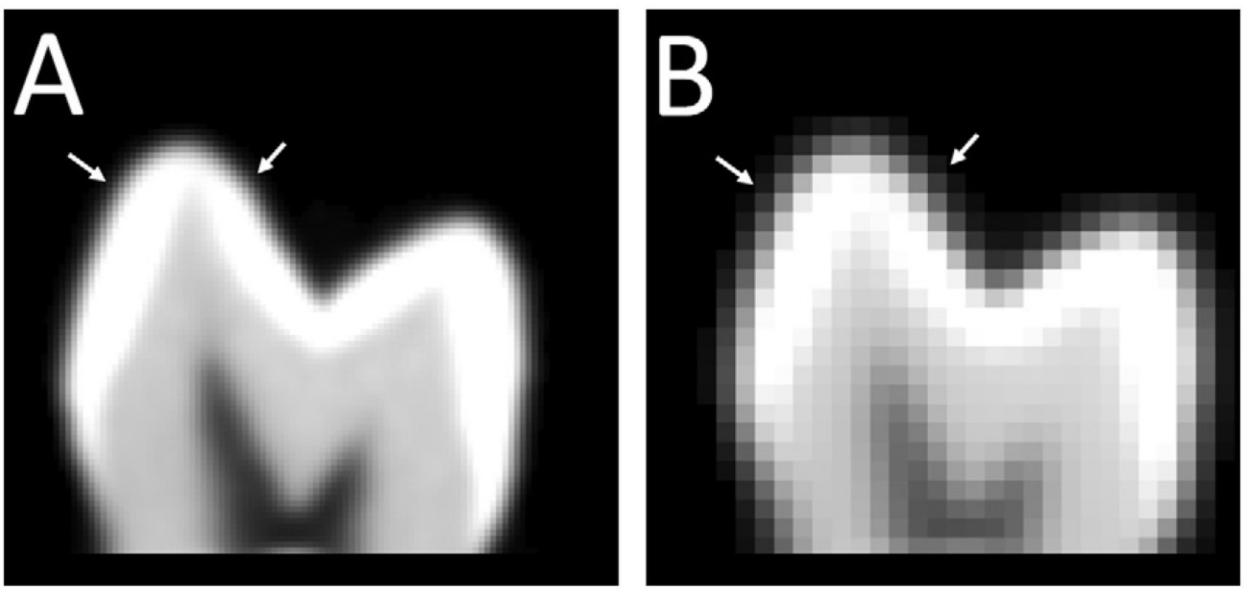


Figure 5.8: In the left image, a 0.125mm voxel CBCT can be observed; whereas in the right image, a 0.4mm voxel CBCT scan of the same tooth.

From the same study, another image that reflects this issue is the following. The real physical space between two of the crowns was two mm (Image A). However, this distance was reduced to 1.6mm in the 0.125mm CBCT scan (Image B) and to 0.9mm in the 0.4mm CBCT scan (Image C) segmentations. The authors attributed this phenomenon, again, to the partial-volume effect (Fig. 5.9).

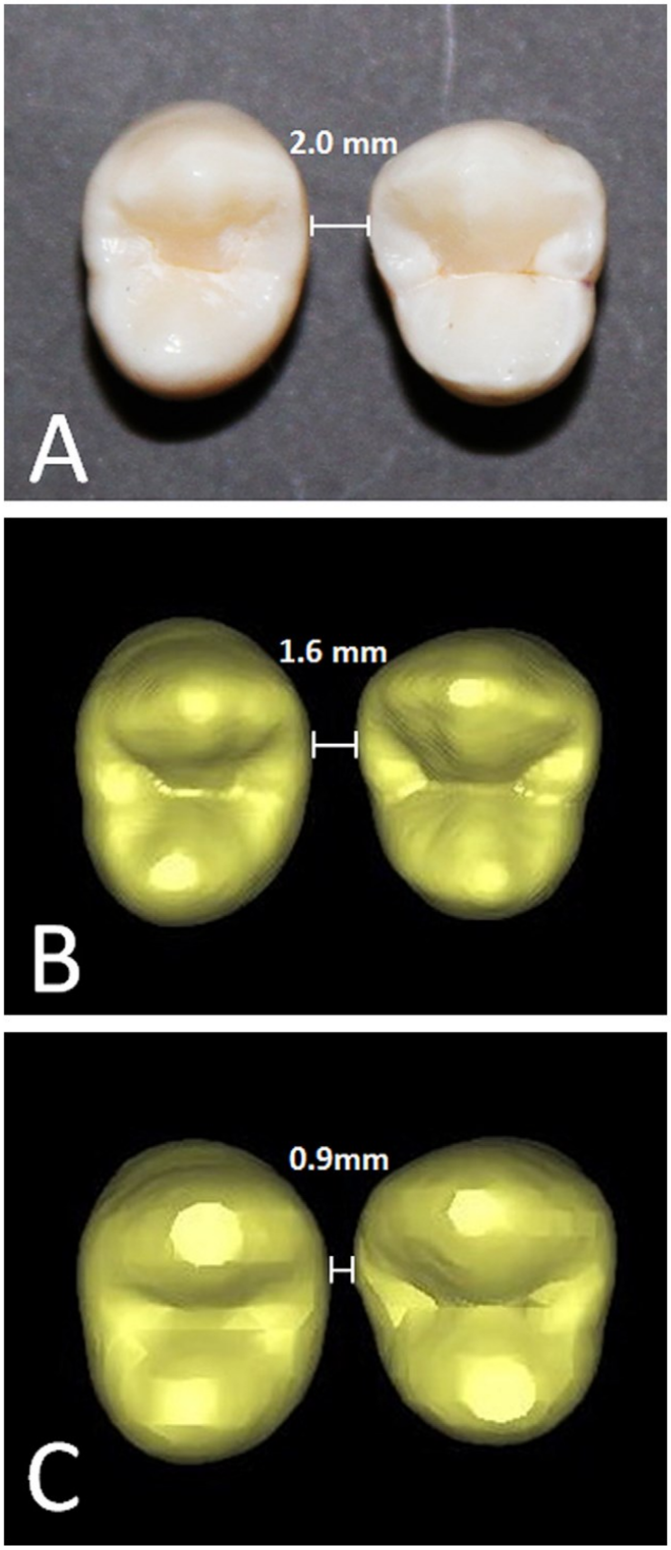


Figure 5.9: Different space measurements.

In another investigation developed by Ponder *et al.*[83] the authors set a goal to determine whether CBCT scans with resolutions similar to those produced in orthodontic offices have accuracy to quantify root resorption defects. In order to do that, they simulated root defects with burs, as it can be observed in Fig.5.10. Then the teeth were scanned with a micro-CT, with a voxel size of 0.018mm, which was the gold standard for that study and with CBCT using 0.2mm and 0.4mm voxel sizes. After the micro-CT scans, the teeth were put back into the alveolar socket of the skull and only then, the CBCT scans were taken.

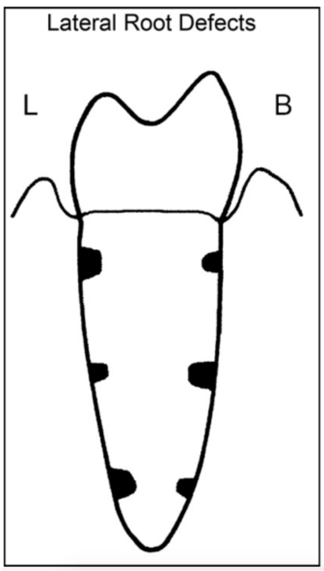


Figure 5.10: Schematization of the simulated root defects

After measuring the volume of the defects, the authors concluded that even if all the methods could accurately detect them, the high-resolution CBCT imaging is significantly more accurate than the low-resolution one when both were compared to the gold standard, the micro-CT images. The high-resolution CBCT images were also significantly more accurate when compared to the low-resolution images.

It seems that the volumetric quantification was influenced by the vertical position of the defect in the low-resolution CBCT images. The defects in the middle vertical root position are more difficult to quantify or were measured less accurately by the low-resolution CBCT scan than the defects in the coronal third of the root. They concluded that "the low-resolution CBCT images, such as those used for routine orthodontic patients, might not be adequate when a need for highly accurate quantification of lateral root resorption defect is required. Therefore, the use of low-resolution CBCT images for measuring root resorption defects might lead to inaccurate diagnosis in terms of the severity of the actual resorption."

The systematic review developed by Samandara *et al.* has been cited several times during this thesis project.[26] The authors stated that the sensitivity analysis on the basis of CBCT voxel size indicated that studies using a small (≤0.2mm) voxel size reported significantly greater OIEARR than those using a larger (>0.2mm) voxel size (1.2 and 0.6 mm, respectively). This might indicate that the latter studies had too large voxel sizes to accurately identify areas of OIERR, and therefore, small voxel sizes might be preferable to accurately diagnose OIERR. Nonetheless, even CBCT images with a voxel size of 0.20mm might be unable to identify OIERR of small magnitudes. It has to be kept in mind that most of the studies included in this review, analyzed OIERR on a two-dimensional basis, therefore, OIERR quantification was a linear measurement.

A study developed by Maret *et al.* had as main aim to assess the effect of voxel size on three-dimensional reconstruction accuracy and reproducibility of CBCT data.[71] Seventy developing tooth germs in mandibles of dead adolescent bodies were scanned with a CBCT voxel size of 0.2mm and 0.3mm, with two FOVs: 90 x 150, and 180 x 200 mm; also with a 0.076 and 0.041mm micro-CT. The last two were the reference standards (Fig. 5.11). The authors proceeded with a semi-automatic segmentation. Then, the volume of each tooth was calculated. They found that there was no difference in tooth volumes despite a slight underestimation for the CBCTs 0.2 and 0.3mm, compared to the reference groups. The underestimation was statistically significant for the CBCT 0.3mm when compared to the reference groups. They concluded that the accuracy of the CBCT as a measuring instrument is connected to the size of the voxels.

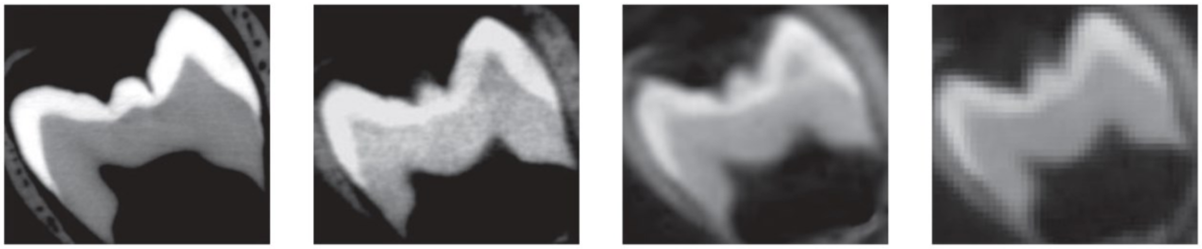


Figure 5.11: Visualization of images relative to voxel size. The same tooth is shown with a voxel size of a) 0.041mm; b) 0.076mm; c) 0.2mm; d) 0.3mm

The authors explained the underestimation by the partial volume effect, which affects the spatial resolution. According to the authors, the partial volume effect has repercussions on the image quality. It seems that CBCTs with a high spatial resolution are less affected by the partial volume effect because their voxel sizes are smaller. Moreover, the images become less sharp as the voxel size increases and certain features, like tooth fissures, connected with the post-mortem dehydration process, are less visible on images obtained with the CBCT at 0.3mm.

Another possible source of artificial increase in volumetric measurements could be scatter x-rays caused by photons. The photons that are diffracted from their original path after interaction with matter can cause scatter. Scatter could affect the density values of tissues, leading to larger tooth volumes.[70,84] The smaller the voxel size, the higher the resolution, and the smaller the field of view, the less noise from scatter radiation.[85]

In a review about the state of the art of CBCT technology in dentistry, Pauwels *et al*. summarized all these previously discussed interconnected aspects in Table 5.2:[86]

Imaging parameter	*Spatial resolution*	*Contrast*	*Noise*	*Artefacts*	*Radiation dose*
FOV size ↑[a]	–	↓	↑	↑	↑
kV ↑	–	↓	↓	–[b]	↑
mAs ↑	–	–	↓	–	↑
Voxel size ↑	↓	–	↓	–	–

↓, decrease; ↑, increase; FOV, field of view; kV, tube voltage; mAs, tube current-exposure time product.
[a]Minor image quality effects due to factors like beam divergence and truncation of the FOV not being taken into account.
[b]Beam hardening is somewhat reduced at higher tube potential values

Table 5.2: Effect of imaging parameters on image quality and radiation

b) "Increase in volume of the teeth" – Real or fake?

The low definition CBCT images like the ones employed in this RCT can lead to volumetric results that may be even bigger than the actual tooth dimensions, up to 35% to 40%,[70] as it has been seen in the previous section. The causes of that inaccuracy have been hypothesized to be surrounding artifacts, the partial-volume effect or the scatter x-rays.

In the study published by Liu *et al.*,[73] among others, the CBCT measures were sometimes larger than the gold standard. In this Master's Thesis project, some "growth" of certain roots was also noticed. The author of this Master's Thesis project attributes this fake increase in the root volumes to the lack of definition of the CBCT images used that lead to inaccuracy and imprecision of the segmentations and the final volume values. As expected, the variations would go in both directions (over- and underestimation values)

Nonetheless, some actual growth of the roots exists. According to several studies that employed cementum as an indicator of the age of the patient,[87-89] especially for forensic purposes, cementum increases with age. Indeed, new layers of cementum are deposited on the outside of the dentin throughout the life of the individual. Gupta et al. discovered a strong positive correlation between the estimated age, which was calculated by using cemental lines and the actual age.[90] It seems that each pair of lines corresponds to one year of life. The following formula for age estimation was developed: E = n + t, where estimated age (E) = number of incremental lines (n) + eruption age of tooth (t). In that study, the ages of the individuals at the time of tooth extractions ranged from 25-60. This is crucial, because cementum apposition diminished by one-third after the age of 60 years. This would not be applied to the sample of our study due to the range of age of the participants. The two following images presented belong to the previously mentioned study, figures 5.12 and 5.13.

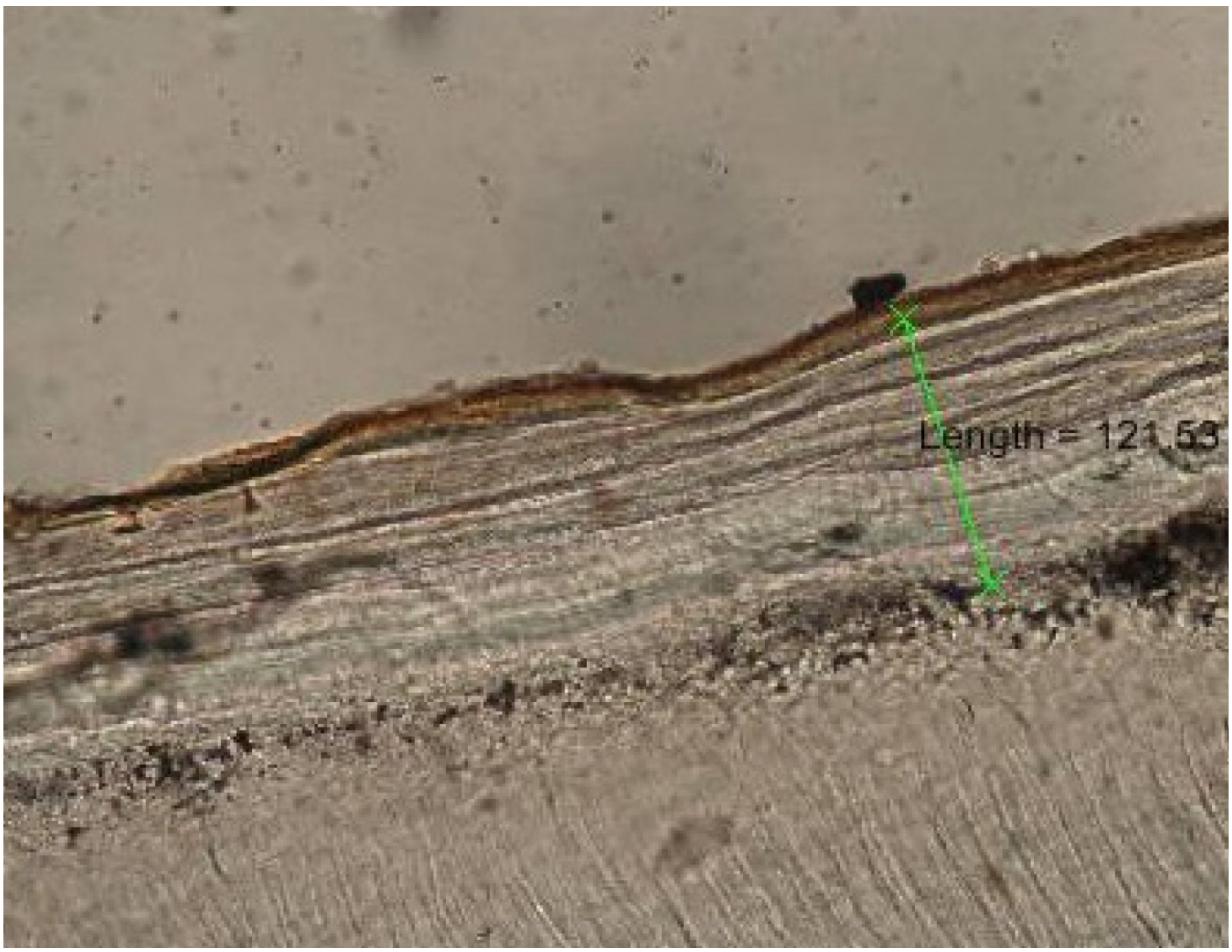
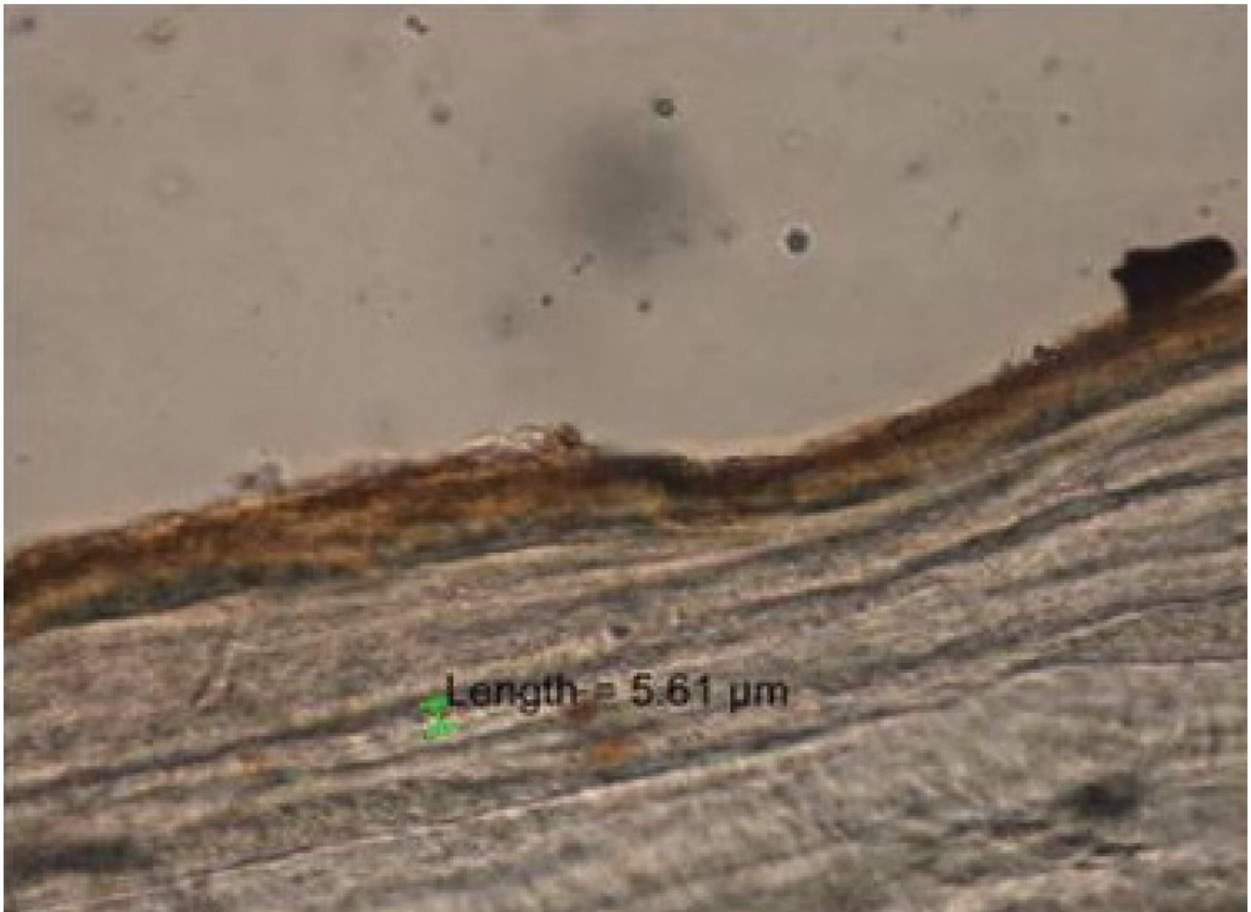


Figure 5.12: Length of the cementum layer



[Table/Fig-2]: Ground section of the tooth showing the width occupied by the two adjacent incremental lines of the cementum

Figure 5.13: Width occupied by the two adjacent incremental lines of the cementum

Even if the author of this Master's Thesis project found an increase in volume of an important number of teeth included in the study, this could not be due to the increase in the enamel because as stated in previous chapters, the enamel tends to decrease due to wear instead of increase. However, a possible explanation could be linked to the fact that the cementum increases in width with age. Nonetheless, if, for example, the length of a layer is 5.61 µm as it can be seen in the picture, the number of new layers is around two per year of life, and the average treatment time for all the patients of this study was around two years, that would result in an increase of 5.61 x 4 = 22.44 µm, which would be around 0.02 mm. This amount is way inferior to the voxel size used in our study and impossible to distinguish with the segmentation processes employed.

b) Field of view

The smaller the field of view, the less noise from scatter radiation will be generated. To measure OIEARR more accurately, a small FOV instead of a full FOV would have been preferred because of its lower scatter radiation which generates less noise and a higher signal-to-noise ratio. Nevertheless, it is highly unlikely that multiple small FOV CBCT images will be used in a clinical setting to increase the level of certainty in determining root volume loss. Most likely, such an image would only be used after previous imaging if strongly suggestive of potential OIEARR detected.

This was also the conclusion of the study by Lund *et al.,*[85] where the large FOV CBCT is the one typically used in orthodontics. It has relatively lower contrast and a lower signal-to-noise ratio, which generates challenging situations for image segmentation process[73]

Even if its quality is not the ideal for all types of measurements, including OIEARR, it seems that when taken prior to orthodontic treatment, CBCTs' voxel sizes usually range between 0.3 mm and 0.4 mm.[72] This fact has logical reasons, including the need for a comprehensive orthodontic diagnostic at the lowest possible ionizing radiation levels.

c) Subjectivity in the segmentation process

There is a certain degree of subjectivity inherent to the manual parts of the segmentation process. This has already been noticed by Liu *et al.*[73] When the authors compared the results, they realized that one observer's measurements were generally larger than the physical volume and the other observer's measurements were generally smaller; 2.65% +/-6.74% and -4.13% +/-3.15% respectively. The authors argued that these differences were small and that the clinical significance was not established. However, this suggests that the observer's eye and perception can consistently change the measurements are affected by subjectivity, and, thus, they could not be accurate in detecting OIEARR. The main and secondary researchers involved in this Master's Thesis project noticed this degree of subjectivity while performing the segmentations, although, they are difficult to be quantified.

In a different study by Maret *et al.*,[71] the subjectivity involved in the segmentation method led to different results being found by two users or by a single user between two segmentations of the same tooth.

Other studies also recognized the difficulty of segmentation and three-dimensional registration. Both processes were limited by the difficulty of defining the borders between the root surface, cementum, and alveolar bone.[43]

d) Surrounding structures

There is an overall difficulty in distinguishing between root and bone while doing segmentations. In a study published by Gateno et al., it was reported that the mandibles show a better CBCT image quality than maxilla. The authors hypothesised that this difference could be due to a greater contrast between the dental alveolus and the cortex surrounding it, resulting in a better visualization.[91] However, Liu *et al.* observed a problematic situation when the roots were adjacent to cortical bone in the mandible, which made segmentation relatively more difficult.[73] Cui *et al.* also found that it is hard to separate a tooth from its surrounding alveolar bone due to their highly similar densities, but also adjacent teeth with similar shape appearance are likely to hinder the identification of different tooth instances.[92] The main researcher of this Master's Thesis project also found an overall difficulty in distinguishing between root and bone while doing segmentations of the CBCTs of the patients of all the studies.

e) Movement

Movement during CBCT acquisition can be another source of deficient images. Ponder *et al.* found that even a small amount of patient movement such as that from respiration, can cause blurring of the three-dimensional image that will most likely lead to diminished quantification accuracy.[83] The acquisition time of the CBCTs in this RCT was 8.9 secs. Probably, during that time, the patient keeps breathing. Similar conclusion was reached by Liu *et al.* that stated that motion-related artifacts could also influence the accuracy of the segmentation.[73] However, this is an error-source aspect that could not be quantified in our study. Only one of the patients had to be ruled out because the T1 CBCT was really blurry due to clear motion of the patient during the imaging acquisition.

f) How much radiation does a CBCT represent?

A review by Ludlow et al. aimed to analyze the dose measurement and effective dose estimation of dental CBCT examinations.[93] From this review, the reader can have an idea of the differences in terms of levels of radiation generated by different CBCT FOVs. Their results showed that the reported adult effective doses for any protocol ranged from 46 to 1073 mSv for large FOVs, 9–560 mSv for medium FOVs, and 5–652 mSv for small FOVs. Child effective doses from any protocol ranged from 13-769 mSv for large or medium FOVs, and 7–521 mSv for small FOVs. Mean adult effective doses grouped by FOV size were 212 mSv (large), 177 mSv (medium) and 84 mSv (small). Mean child doses were 175 mSv (combined large and medium), and 103 mSv (small).

In addition, large discrepancies were observed between different CBCT units. It has been published that there is a linear extrapolation of higher dose-associated cancer risk to lower levels of exposure. An increased risk of cancer is produced by an acute exposure in a range of 10–50 mSv and a chronic exposure in a range of 50–100 mSv. The authors concluded that while the risk from dentomaxillo-facial imaging is small for an individual, when multiplied by the large population of patients who are exposed to diagnostic imaging, radiation risk becomes a significant public health issue. This is something to take into consideration by the orthodontist when she/he chooses his diagnostic imaging tools.

5.17 The future, where are we aiming?

Cui *et al*. presented a novel learning-based method for automatic tooth instance segmentation and identification.[92] They aimed to segment all the teeth from the surrounding issues, separate the teeth from each other, and identify each tooth by assigning to it a correct label. This is the first method to apply deep neural networks to automatic tooth instance segmentation and identification from CBCT images (Fig. 5.14).

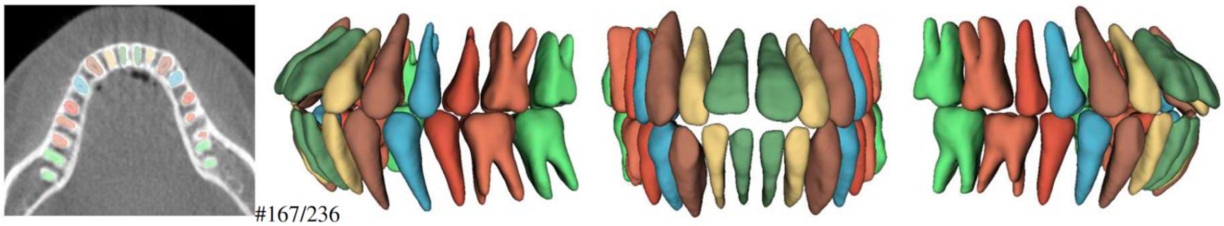


Figure 5.14: Teeth automatically segmented

The authors concluded that their method is fully automatic without any user annotation and post-processing step. It produces superior results by exploiting the novel learned edge map, similarity matrix and the spatial relations between different teeth.

Even if the author of this Master's Thesis project predicts a future in which all the segmentations of all the structures, not only the teeth, of the CBCTs will be automatically done and used for orthodontic diagnosis and treatment planning, this method has not been compared to a gold standard yet.

Probably, what the clinical and the researcher orthodontist would like to have in the future is a system that recognizes, separates and labels not only the teeth, but also all the craniofacial bones (and the craniofacial structures if an IRM is added). Ideally, this process should be performed fully automatically, with a high level of accuracy and precision from a medical imaging causing the lowest possible level of radiation for the patient.

5.18 Conclusions

OIERR is a problem in orthodontically treated patients that may lead to significant consequences in a relatively small number of cases. Class II malocclusion is a common malocclusion and one of the usually employed methods to treat them consists in the differential dentoalveolar movement of the upper and lower teeth. Among the treatment philosophies to achieve that, the Forsus® and the Crossbow® are found. Both push the lower anterior teeth with significant amounts of force. Forces generated by orthodontic appliances cause different degrees of OIERR.

Thus, the main purpose of this Master's thesis project was to determine the root resorption in the lower anterior teeth of the patients participating in a RCT which groups were Crossbow® and Forsus®. The secondary objectives were as follows: determine if there is a difference in the percentage of OIERR when gender, total treatment time, time in brackets, and amount of apical displacement were considered.

As far as we know, this is the first study that assessed the amount of OIERR using 3D technology after the use of the Forsus® spring as part of the Crossbow® appliance or as conventionally used over archwires.

The new methods proposed in the previous chapters may represent an alternative to assess changes in tooth volume of lower anterior teeth and apical displacement based on CBCT imaging. Both techniques, overall, present good to excellent reliability and are in agreement (only for volume) with other similar studies. However, the 5.64% and 8.62%, respectively, overall measurement errors may be relevant because treatment changes were clearly smaller than those values and as such actual changes may not be possible to be detected by using this technique. Hence, the measurement errors, which were close to what was obtained in previous studies (only for volume), should be taken into consideration when interpreting the results.

A comparison with a gold standard like the ones mentioned in the discussion (laser scan [70] or water displacement technique[73] applied to extracted teeth), could not be applied nor used to validate these techniques since the analyzed teeth were not extracted after treatment.

The definition of the images generated by the CBCT with the voxel size used in our study, 0.3mm, may not be accurate or precise enough to detect minor amounts of volume change in the root. Thus, this can lead to wrong diagnostic conclusions. This low definition CBCT images can lead to volumetric results that are even larger than the actual tooth volumes (from 35% to 40%). The causes of that inaccuracy have been hypothesized to be surrounding artifacts, the partial-volume effect, or the scatter x-rays. The problem with smaller voxels, which would provide higher definition and more accurate images, is that longer scanning times and a greater patient exposure to radiation are required. The smaller the field of view, the less noise from scatter radiation will be generated. To measure OIERR more accurately, a small FOV instead of a full FOV would have been preferred because of its lower scatter radiation which generates less noise and a higher lower signal-to-noise ratio.

Another possible sources of error might be the subjectivity in the manual segmentation process; an overall difficulty in distinguishing between root and bone while doing segmentations; and the movement during CBCT acquisition. All the above-mentioned sources of error lead to an increased measurement error, which was at 5.64% in this study. This variability indicates that changes of that amount or less in the root volume could be explained either by measurement error or by an actual change in the outcome.

When the developed and analyzed methods were applied to the RCT, no statistically significant difference in volume percentage change of all the teeth included was found regardless of the treatment approaches, even when the previously listed co-variables were considered. Thus, both treatment modalities seem to produce similar amounts of OIERR, if any, without a statistically or clinically significant difference. From this, we can also conclude that none of the variables played a role in the changes in root volume changes. Even if the result had been statistically significant, the amount of -0.55% overall reduction in volume, is likely not clinically relevant. As the data collected was from a properly conducted RCT with randomization and blinded applied to its maximum possible extent, any difference in the measured outcomes should likely only be attributed to the intervention.

The OIERR detected through CBCT, even if accurately and precisely quantified through the right methods, probably has little clinical relevance, which makes the added exposure to ionizing radiation through high-resolution CBCT protocols questionable in terms of risk to benefit ratio. Even more questionable if the radiation has to be increased much more to obtain a smaller voxel size and a smaller FOV that would help with the accuracy and precision of the OIERR assessment.

The lower anterior teeth are among the groups of teeth that present the most OIERR. However, an important question arises: how much is a percentage of volume decrease that triggers clinically significance? Even if scales have been presented, they are arbitrary, and studies should be developed in order to match them with levels of clinical significance.

Although the author of this Master's Thesis project suggests a future in which almost all the segmentations of all the structures, not only the teeth, of the CBCTs will be automatically done and used for orthodontic diagnosis and treatment planning; the reality is that several identified methodological barriers will have to be overcome.

APPENDIX

Table 5.3: Calculation of the measurement error from the data provided in the study published by Liu *et al.* [73]

Observer 1	Observer 2	Difference	Mean of total	% of error
0.63	0.64	0.012	0.63	1.89
0.61	0.57	0.031	0.59	5.26
0.63	0.69	0.065	0.66	9.87
0.61	0.70	0.082	0.65	12.54
0.49	0.57	0.082	0.53	15.53
0.48	0.58	0.103	0.53	19.49
0.55	0.57	0.022	0.56	3.92
0.45	0.52	0.073	0.48	15.07
0.43	0.41	0.026	0.42	6.19
0.41	0.42	0.012	0.41	2.90
0.65	0.65	0.002	0.65	0.31
0.62	0.60	0.017	0.61	2.79
0.48	0.53	0.046	0.50	9.15
0.47	0.50	0.038	0.49	7.84
0.45	0.54	0.089	0.50	17.85
0.43	0.47	0.04	0.45	8.93
0.62	0.64	0.021	0.63	3.31
0.59	0.57	0.014	0.58	2.41
0.52	0.56	0.038	0.54	7.09
0.53	0.57	0.047	0.55	8.54
0.45	0.46	0.01	0.45	2.21
0.46	0.47	0.006	0.47	1.28
0.58	0.72	0.136	0.65	20.92
0.56	0.64	0.075	0.60	12.49
			AVERAGE	8.24

5.19 References

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