External Root Resorption Associated with Maxillary Expansion Therapies as Evaluated *via* Cone Beam Computed Tomography: A Retrospective Randomized Clinical Trial

by

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ABSTRACT

Objective: To investigate and develop an appropriate measurement protocol possessing adequate precision in both intra- and inter-rater reliability for *in vivo* maxillary first molar volume measurements using cone beam computed tomography (CBCT) images. To assess *in vivo* through the use of CBCT imaging whether the type of maxillary expansion appliance [BAME versus tooth-anchored maxillary expander (TAME)] impacts the amount of external root resorption in maxillary first molars as compared to a no treatment control group.

Methods: 62 adolescents requiring maxillary expansion were randomly allocated to groups: TAME, BAME, and control. CBCT images were acquired at baseline and approximately 12-months. Segmentation procedures were investigated and developed to quantify maxillary first molar ERR. Dental volumes were measured on the CBCT images at both time points to assess maxillary first molar dental volume changes.

Results: Excellent intra- and inter-rater agreement for segmentation. Automated thresholding with manual refinements on a 2D slice-by-slice basis, yielded the highest intra- and inter-rater reliability statistics. There lacked statistically significant evidence (p>0.05) of differences in external root resorption (both percentage and absolute volume) between TAME, BAME, and control groups.

Conclusion: Whole tooth CBCT segmentation employing grayscale thresholding with 2D slice-by-slice manual refinements possesses excellent intra- and inter-rater reliability. There is no statistically significant evidence supporting increased

ERR with TAME or BAME versus control.

PREFACE

This thesis is an original work by Darren Forst. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "External root resorption associated with bone-anchored maxillary expansion and traditional rapid maxillary expansion as measured through cone beam computed tomography: a retrospective study", No. Pro00042519, October 18, 2013.

The data collection and statistical analysis in chapters 2 and 3 are my original collaborative work, as well as the systematic review in chapter 1 and the concluding analysis in chapter 4.

Chapter 1 of the thesis has been published as Forst D, Nijjar S, Khaled Y, Lagravere M, Flores-Mir C. Radiographic assessment of external root resorption associated with jackscrew-based maxillary expansion therapies: a systematic review. *Eur J Orthod* 2014 Oct;36(5):576-585. I was responsible for the article collection and analysis along with the manuscript composition. Y. Khaled assisted with the article review as the second reviewer and contributed to manuscript edits. S. Nijjar assisted with manuscript composition and edits. M. Lagravere assisted with manuscript edits and concept formation. C. Flores-Mir was the supervisory author and was involved with concept formation and manuscript composition.

Chapter 2 of the thesis has been published as Forst D, Nijjar S, Flores-Mir C, Carey J, Secanell M, Lagravere M. Comparison of in vivo 3D cone-beam computed tomography tooth volume measurement protocols. Progress in Orthodontics 2014;15:69. I was responsible for the conception, design, data acquisition, analysis, and interpretation of data. Simrit Nijjar assisted in the design, data acquisition (inter-examiner reliability readings), analysis, and interpretation of data. Carlos Flores-Mir, Jason Carey, Marc Secanell, and Manuel Lagravere assisted in the conception, design and interpretation of data and critical revision of the written work.

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LIST OF ABBREVIATIONS

ERR: External Root Resorption

BAME: Bone-Anchored Maxillary Expander

TAME: Tooth-Anchored Maxillary Expander

RME: Rapid Maxillary Expansion

RoB: Risk of Bias

CBCT: Cone beam Computed Tomography

CEJ: Cemento-Enamel Junction

PDL: Periodontal Ligament

2D: Two-dimensional

3D: Three-dimensional

CT: Computed tomography

DICOM: Digital Imaging and Communications in Medicine

ICC: Intraclass Correlation Coefficient

ANOVA: Analysis of Variance

mm: millimeter

RME: Rapid Maxillary Expander

MSCT: Multi-Slice Computed Tomography

STATEMENT OF PROBLEM

Maxillary deficiency is a common pre-treatment issue in orthodontic patients and is usually accompanied by unilateral or bilateral posterior crossbite, narrow nasal cavity, and crowding (1,2). The most common, standard of care, treatment modality in transverse maxillary deficient adolescents is rapid maxillary expansion (RME) performed with a tooth-anchored expander (Hyrax type) (3-6). There are disadvantages that have been identified with this approach as direct tooth-anchored appliances can, in some instances, result in root volume loss (5,7) and have the added potential for undesirable tooth movement (4). An alternative approach to attempt mitigation of the adverse dental effects is the use of a bone-anchored maxillary expander (BAME). BAME move the point of force application away from the teeth, with the goal of reducing unwanted dental effects associated with direct, heavy force application delivered through the teeth.

Topics such as the external root resorption (ERR) associated with various appliances and stages of orthodontic treatment have yet to be fully investigated. Historically, the *in vivo* detection of changes to dental root morphology and ERR during the course of orthodontic treatment has been mainly through use of 2D radiographs, most notably periapical radiographs (8-10). Conventional 2D radiographs have in general proven inaccurate for the reliable detection of small ERR defects (11). The essence of accurate *in vivo* detection of ERR is based upon accurate 3D dental volume measurements.

Advances in 3D medical imaging technologies, particularly the introduction of CBCT in the late 1990's, have equipped the medical and dental community with improvements in visualization, diagnosis, and treatment planning for their patients. The improvement in certain diagnostic abilities is difficult to quantify given the unfamiliar accuracy with which volumes in a CBCT image may be computed due to the challenges associated with image segmentation techniques.

Investigation into the adverse effects, particularly ERR, that bone-borne and tooth-borne expanders may have on the teeth due to the differences in the point of application of the lateral expansion force seem warranted. Establishing precise and repeatable dental volume measurement protocols for CBCT imaging to assess the appliance related effect of maxillary expansion on ERR will enable clinicians to confidently monitor ERR and adapt treatment plans to minimize the negative effects associated with ERR.

STUDY OBJECTIVES

The objectives of this study are twofold. The first objective is to investigate and develop an appropriate measurement protocol possessing adequate precision in both intra- and inter-rater reliability for *in vivo* maxillary first molar volume measurements using CBCT images. The second objective is to assess *in vivo* through the use of CBCT imaging whether the type of maxillary expansion appliance [BAME versus tooth-anchored maxillary expander (TAME)] impacts the amount of external root resorption in maxillary first molars as compared to a no treatment control group.

Chapter 1 - Radiographic Assessment of External Root Resorption Associated with Jackscrew-Based Maxillary Expansion Therapies: A Systematic Review

1.1 INTRODUCTION

External root resorption (ERR) can be considered to be an important negative sequelae of orthodontic treatment as in severe cases it can have an impact on the long-term viability of the affected dentition. ERR is defined as either a physiologic or a pathologic process resulting in the loss of cementum and dentin in the dental roots. (12) The etiology of ERR appears multifactorial in nature with numerous potential elements at play including, but not limited to, individual genetic factors and orthodontic mechanical or iatrogenic factors. (13) The orthodontic factors that are associated with ERR are complex and not fully understood.

There exists a lack of agreement in the literature regarding the specific incidence of ERR. (14) There is evidence that heavy forces are particularly harmful. (14) Numerous studies have displayed a correlation between increased ERR and heavy orthodontic forces as compared to light forces or controls. (15-18) In both tension and compression force areas, direct heavy orthodontic forces have been shown to produce significantly more ERR than in regions under light compression and light tension forces. (18) However, there is a need for more evidence to identify those teeth/individuals at higher risk for ERR and to determine ways to manage its severity and prevalence in orthodontic patients. (14)

Historically, the *in vivo* detection of ERR has been mainly through use of 2-dimensional (2D) radiographs. There are geometric limitations associated with 2D imaging of a 3-dimensional (3D) phenomenon; therefore, the quantitative value of 2D radiographs to measure ERR is questionable. (17,19,20) Given that the lateral pressures created on the dentition during rapid maxillary expansion (RME) create hyalinization and an associated necrotic periodontal ligament, (21,22) buccal resorption is intuitively expected to be the predominant site of root resorption, an area not directly visible in conventional 2D radiographs. The distortion in both tooth position and angulation in a panoramic film combined with varying magnification in different parts of the image (23) leads to limitations in the use of panoramic films to assess ERR (24-26). Consequently, although 2D radiography may be a good diagnostic tool, its use in the quantification of ERR should be avoided. (17) The quantification and measurement of ERR using 3D volumetric imaging as compared to periapical radiographs has been found to be a method with a high level of accuracy and repeatability (17,27,28); however, patient movement during scans can reduce the accuracy of measurements (28).

Maxillary deficiency is a common pre-treatment condition in orthodontic patients and is usually accompanied by unilateral or bilateral posterior crossbite, narrow nasal cavity, and crowding. (1,2) The most common, standard of care, treatment modality in transverse maxillary deficient adolescents is rapid maxillary expansion performed with a tooth-anchored expander (Hyrax type). (3-6) There are disadvantages that have been identified with this approach as direct tooth-anchored appliances can, in some instances, result in root volume loss (5,7) and have the added potential for undesirable tooth movements (4).

Therefore, the objective of this study is to critically analyze the literature to evaluate in adolescents and young adults if jackscrew-based maxillary expansion therapies result in ERR as measured *in vivo via* any radiological method.

1.2 METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist (29) was used as a template.

Protocol and Registration

Neither a protocol nor review registration was completed.

1.2.1 Eligibility Criteria

The PICOS (population, intervention, comparison, outcome, study design) format was used to formulate a clinical question with defined inclusion criteria.

- *Population*. Adolescents or young adults with transverse maxillary deficiency.
- *Intervention.* Non-surgical maxillary expansion therapy through use of a jackscrew-based maxillary expander.
- *Comparison.* Pre-treatment permanent tooth root length or volume measurements.
- *Outcome.* Post-treatment permanent tooth ERR as measured *in vivo* by any method of radiological evaluation.
- *Study Design.* Randomized or non-randomized clinical trials, cohort studies, case control studies or consecutively-treated series of cases.

- *Exclusions.* Animal studies, individuals with craniofacial syndromes, individual case reports or consecutively-finished series of cases, histological evaluations of external root resorption, studies that evaluate internal root resorption. Studies evaluating teeth with anomalies in form, shape or structure. Studies evaluating transplanted or re-implanted teeth. Studies with orthodontic appliances in place in addition to the jack-screw based maxillary expander.

1.2.2 Information Sources and Search

With the assistance of a senior health-sciences librarian, a computerized search was conducted of numerous electronic databases. Searches were conducted through use of Medical Subject Headings (MeSH), series of key words, and key word combinations with appropriate truncations and word combinations to account for differences in controlled terminology in different databases. The investigated databases were MEDLINE (OvidSP), EMBASE (OvidSP), PubMed, Scopus (Elsevier), CINAHL (EBSCO), Evidence Based Medicine Reviews *via* OvidSP (includes Cochrane Database of Systematic Reviews, The Database of Abstracts of Reviews of Effectiveness, Health Technology Assessments, NHS Economic Evaluation Database, ACP Journal Club, and Definitive Controlled Trials), and LILACS (IAH) (Latin American and Caribbean Health Sciences Literature) database from their earliest records to August 25th, 2013.

Manual searches of reference lists of the relevant articles were also completed to identify additional publications. In addition, limited grey literature searches were conducted along with Google Scholar searches to identify any relevant publications that may have been missed by the electronic database searches.

The specific search strategies used for each database are outlined in Table 1.1. No limits were applied to any of the search strategies.

1.2.3 Study Selection

Given the previously defined study inclusion and exclusion criteria, a two-phase search of the articles was conducted. In the first phase, two reviewers (D.F., Y.K.) independently reviewed the article titles and available abstracts of the electronic search results with full articles obtained for those without available abstracts or inadequate information in the abstract. Any articles, except for individual case reports, that radiographically assessed ERR in humans *in vivo* as a consequence of maxillary expansion therapy were considered for phase 1 inclusion. Discrepancies in the selection of the articles were discussed between the reviewers until consensus was reached prior to progressing to phase 2. In the second phase, the same reviewers evaluated the full text articles selected from phase 1 independently by critically applying the remaining inclusion/exclusion criteria. Again, discrepancies in article choices were resolved *via* discussion until a consensus was achieved. In addition, the reference lists of the selected articles were screened for any articles that may have been omitted. If any article information was deemed to be unclear following full evaluation the authors were contacted for clarification.

1.2.4 Data Items

The data extracted from the studies that met the inclusion criteria included study design, sample size, teeth evaluated, mean (range) age in years, type of maxillary expander, expander activation protocol, type of radiographic image used for analysis, method used to measure ERR *in vivo*, and related results.

1.2.5 Data Collection Process

The same two reviewers extracted data independently, in duplicate. The extracted data were combined and compared for accuracy with discrepancies resolved by re-examination of the literature until consensus was achieved.

1.2.6 Risk of Bias in Individual Studies

Both reviewers methodologically appraised all the selected studies according to The Cochrane Risk of Bias criteria (RoB) (30) for assessing individual studies.

1.2.7 Data Synthesis

If the available collected information was found to be adequate, a meta-analysis was considered.

1.3 RESULTS

1.3.1 Study Selection

Searches of electronic databases, Google Scholar and limited grey literature yielded 83 original articles (189 before removal of duplicates). After review of the titles and available abstracts, 11 satisfied the phase 1 inclusion criteria and were retrieved in full for further article review. Hand searching of their bibliographies was performed, however no additional articles were identified.

The application of the aforementioned inclusion/exclusion criteria as a phase 2 review process resulted in the rejection of 8 articles as either the articles involved a surgically assisted rapid palatal expansion (SARPE) approach (31,32), utilized a quad-helix rather than a jackscrew-based maxillary expander (33,34), studied an adult patient population (32,35), involved premolar extraction and histological, with no radiographic evaluation of root resorption (33,36,37), or assessed ERR on deciduous rather than permanent teeth (38). After the phase 2 review process, only three articles (7,39,40) fully satisfied the selection criteria. Figure 1.1 details the methodological flowchart for both the phase 1 and phase 2 selection process.

1.3.2 Study Characteristics

A summary of key methodological data and results of the studies can be found in Table 1.2.

1.3.3 *Risk of Bias*

Methodological appraisal of selected studies according to the RoB criteria for assessing individual studies (30) is outlined in Table 1.3 and in an abbreviated form in Table 1.4. We found the quality of reported methodology to range from moderate to high bias. Common weaknesses identified in all studies (7,39,40) were: failure to justify or calculate sample sizes, failure to report inter-rater or intra-rater reliability, failure to identify limitations in study design, failure to implement allocation concealment and blinding of both the assessors and the particular outcome assessment.

1.3.4 *Synthesis of Results*

A meta-analysis was not possible owing to the heterogeneity in study designs and collected information (qualitative radiographic results in the 2D studies (39,40) and quantitative results in the 3D study (7)). Therefore, assessment of the risk of bias across the studies was not feasible, and the reported results of this review are descriptive in nature.

1.4 DISCUSSION

1.4.1 Summary of Evidence

This systematic review sought to critically analyze the literature to evaluate in adolescents and young adults if jackscrew-based maxillary expansion therapies result in ERR as measured *in vivo via* any radiological method. Following rigorous database searches it was determined that the available literature, which radiographically assessed ERR associated with jackscrew-based maxillary expansion therapy, *in vivo,* is scarce. The results of this review suggest inconsistencies regarding the radiographic detection of ERR associated with RME therapy, mainly correlated with the imaging techniques of 2D versus 3D radiography. The 2D radiographic studies reported no radiographic signs of ERR (39) or isolated buccal root resorption (40), with Barber *et al* stating "the clinician has no way of accurately estimating the full extent of *in situ* root surface resorption caused by expansion treatment.". The only 3D radiographic study (7) reported statistically significant mean root volume loss following maxillary expansion.

It is of value to note that Barber *et al* (40) visualized frank apical root resorption of approximately 4mm on one anchor premolar in his study. The significance of this was not emphasized and the radiographic results were qualitatively summarized from only the perspective of buccal root resorption. This possibly suggests the exclusion of the significance of the apical root resorption that is readily visible on 2D radiography if of sufficient magnitude.

Both 2D studies (39,40) evaluated radiographic ERR only as a secondary assessment, as both were primarily premolar extraction studies, which investigated topographic and histologic findings utilizing scanning electron microscopy (SEM) (40) or light microscopy (39). One study (40) in regards to ERR evident on the extracted maxillary premolars suggested all anchored premolars exhibited ERR, mostly confined to the buccal surface, but also to some extent on the mesial, distal, and apical portions of the roots. The largest resorptive areas were noted on the premolars extracted shortly after the end of expansion (39) as detected *via* light microscopy. These findings display disagreement with the 2D radiographic findings in the studies. In one study (40) no evidence of ERR was reported on unattached premolars. There are potential limitations as the quantitative value of histological evaluation of ERR has been reported as questionable (17) and can be subject to limitations due to the destruction and loss of material during preparation (41). However, given the frank differences in the histological findings between anchored and non-anchored premolars (40) it appears likely a valid qualitative outcome more so than a quantitative outcome given the limitations within the technique. Therefore, ERR likely was partially undetected or underestimated in the 2D radiographic studies.

It has been hypothesized that moving the point to force application away from the teeth for rapid maxillary expansion therapy leads to a reduction of ERR. Odenrick *et al* (39) concluded the maximum anchorage of the expansion device (tissue-borne acrylic appliance) appeared preferable as it produced smaller and more shallow resorption lacunae as compared to the all wire framework alternative with solely dental anchorage. This finding is interesting in comparison to the study by Baysal *et al* (7) who determined that it was not possible to say the anchor teeth were more severely affected from RME. In addition, an animal study (42) that histologically assessed ERR at teeth distant from the expansion apparatus (maxillary incisors), noted a 750-fold increase of ERR in the incisors of treated versus non-treated groups. This perhaps lends support to findings (7,39,40) of ERR evident on teeth not directly attached to the expansion apparatus. Post-expansion records were taken immediately after completing the active expansion phase. Therefore those records will not account for additional post-expansion resorptive processes that may happen. It has also to be considered that the metallic components of the expansion appliance will generate imaging artifacts in their surroundings. These artifacts were reportedly 'clipped manually with great caution' by the study authors. (7)

The patient ages investigated in all three of the included studies ranged from 9.9 to 15.3 years. Given the stage of maxillary premolar root development, it is expected in some of the younger patients that the roots are not fully formed, especially in the maxillary second premolars. Given the findings by Baysal *et al* (7) that all roots displayed a decrease in mean root volume, there may be the consideration that root development may be disrupted by the applied force. It would be beneficial for further 3D studies to address whether RME results in shorter/decreased volumes of roots on average as compared to a control group being subjected to no active treatment.

Retention periods and timing of radiographic assessment are another variable that potentially has an effect on the extent of ERR and associated repair processes. Barber *et al* (40) established that iatrogenic ERR is sustained long after termination of the active phase of RME with residual loads stored in the appliance contributing to continuing resorption. They found (40) anchor premolars that were extracted either after RME alone, or RME and a short retention period, revealed small areas of active ERR confined mainly to the cervical regions of their buccal root surfaces as opposed to large resorption bays scattered along their entire buccal surface for anchor premolars held in longer retention periods. Significant relapse forces extending later into treatment (up to 9 months) may additionally contribute to forces on the dentition with the expansion devices operating as retainers. Alternatively, the reparative processes can also have an effect on the visualized extent of ERR as in the other included study (39), where the size of ERR lacunae was instead found to decrease with increasing retention periods due to repair. Additional literature on the subject is similarly divided as one study (43) found no direct relationship between total area of resorption and the retention period, but found repair to advance with longer retention periods. The discrepancies reported could be due to a variety of factors including patient age and the force required for midpalatal suture separation, as well as the degree of lateral expansion required, both of which could result in variations in the relapse forces experienced. The amount of time that relapse forces are sufficient to cause ERR are similarly variable with one study reporting strong relapse forces causing significant ERR up until 3 months after RME (44), while another reported 5-7 weeks before relapse forces decayed (45). It is therefore both case and patient dependent and hence difficult to determine the timing of the most significant ERR to accurately assess the extent of ERR associated with expansion. The temporal balance between resorptive and reparative processes in various patients can lead to difficulties in assessing the true extent of ERR.

A potential alternative approach to attempt mitigation of the adverse dental effects is the use of bone-anchored maxillary expanders (BAME), which move the point of force application away from the teeth, with the goal of reducing unwanted dental effects associated with direct, heavy force application delivered through the teeth. This approach does however present its own potential adverse outcomes of increased risk of infection due to its invasiveness. (46,47) A randomized clinical trial (48) reported similar results between tooth-borne and bone-borne expanders in the assessment of dental and skeletal transverse, vertical, and anteroposterior changes as evaluated through cone beam computed tomography (CBCT) and reported dental expansion to be greater than skeletal expansion for both appliances.

Another potentially significant issue identified in the histologic assessment portions of both non-randomized clinical trials (39,40) is the reparative process and subsequent deposition of hard tissue within the resorption lacunae and its effects on periodontal fiber attachment in the area. Both studies failed to show periodontal fiber reattachment in the areas of reparative cementum deposition. Similarly, a study (43) investigating anchor teeth during retention periods of 14 to 53 weeks revealed sparse and inconsistent Sharpey's fibers depression into the cellular cementum that was different from that of normal cellular cementum. This perhaps can lead to an underestimation of the detrimental effects associated with ERR as repair of a root defect by cellular cementum is not necessarily synonymous with principal periodontal fiber reattachment in those areas. Simply visualizing the surface area or volume of hard tissue in the root may not provide a corresponding accurate estimation of viable surface area with periodontal fiber attachment. Hence, although the root volume may not decrease significantly, the resorptive and subsequent reparative processes may have a more substantial and detrimental effect on the surface area for periodontal ligament support. Perhaps the most accurate indication of the long-term support and viability of teeth having undergone resorption is the determination of the resorptive process at its most progressive with the assumption of a loss of periodontal attachment fibers in these areas. Further investigation is warranted both on a histological and an *in vivo* 3D radiographic approach.

In addition, there were limited sample sizes of nine as part of the two included non-randomized clinical trials (39,40). When these limited samples were further subdivided into two different appliance groups, the results were sample groups of four or five for each appliance. This has potential to limit the information that may be drawn statistically from the studies and the results of this review are likely restricted due to the limited sample sizes in the 2D radiographic detection studies (39,40). In addition, due to the prime focus of the 2D studies to be on histologic detection of ERR, the majority of the 2D radiographic findings were simply glossed over with lack of detailed descriptions.

In summary, the literature is inconclusive in the broad sense regarding the radiographic *in vivo* effects of jackscrew-based maxillary expansion therapy on ERR. The conclusions appear to indicate the limitations of 2D radiographs in assessing the full extent of *in vivo* ERR. However, frank apical resorption appears to be in the realm of identification by 2D radiographs. In interpreting the significance of the non-randomized clinical trials that utilized 2D radiography in this review (39,40), it is of value to note that Chan *et al* (17) stated the use of 2D radiographic evaluation of ERR to have quantitative limitations and suggested its use only as a diagnostic screening tool. Severe ERR can be detected using conventional 2D radiographs (49-52), however, ERR at the mesial, distal, mid-apical, or buccal aspects is hardly visible (39,40,53). The limited 3D evidence presented by Baysal *et al* (7) represents the first documented attempt at the 3D visualization of external root resorption with maxillary expansion, as it displays the *in vivo* detection capabilities of a previously limited diagnostic process.

Further studies employing 3D evaluation of root resorption with control groups, various appliance designs, retention periods and timing of radiographic assessment seem indicated to further elucidate the effects. However, extreme caution should be exercised regarding an indiscriminate use of these ‘idealized’ 3D radiographs as there is an associated increase in the radiation exposure risks in young patients (54).

1.5 CONCLUSION

- 2D periapical radiographs do not reveal external root resorption associated with maxillary expansion therapy, except for frank apical root resorption.
- 3D CBCT radiography displays statistically significant root volume loss associated with maxillary expansion therapy. However, when considering volume loss percentages, no statistical significance was found.

Table 1.1 Systematic review literature search strategies

Search Strategy for MEDLINE via OvidSP.*	
SEARCH GROUP	**KEY WORD OR MeSH⋆ TERM**
1	tooth resorption [MeSH] OR dental root resorption OR tooth root resorption OR "root shortening" OR orthodontically induced inflammatory root resorption OR apical root resorption OR "root resorption"
2	palatal expansion technique [MeSH] OR palatal expansion OR maxillary expansion OR maxillary transverse deficiency OR rapid maxillary expansion OR transverse maxillary expansion OR SME OR RPE OR RME OR SPE
3	1 AND 2
* Limits: None	
⋆ MeSH: Medical Subject Headings	
Medline: 1948 to August 25, 2013	

Search Strategy for EMBASE via OvidSP.*	
SEARCH GROUP	**KEY WORD**
1	tooth resorption OR dental root resorption OR tooth root resorption OR "root shortening" OR orthodontically induced inflammatory root resorption OR apical root resorption OR "root resorption"
2	palatal expansion technique OR palatal expansion OR maxillary expansion OR maxillary transverse deficiency OR rapid maxillary expansion OR transverse maxillary expansion OR SME OR RPE OR RME OR SPE
3	1 AND 2
* Limits: None	
EMBASE: 1974 to August 25, 2013	

Search Strategy for PubMed.*	
SEARCH GROUP	**KEY WORD**
1	tooth resorption OR dental root resorption OR tooth root resorption OR root shortening OR orthodontically induced inflammatory root resorption OR apical root resorption OR root resorption
2	palatal expansion technique OR palatal expansion OR maxillary expansion OR maxillary transverse deficiency OR rapid maxillary expansion OR transverse maxillary expansion OR SME OR RPE OR RME OR SPE
3	1 AND 2
* Limits: None	
PubMed: 1950 to August 25, 2013	

Search Strategy for Scopus via Elsevier.*	
SEARCH GROUP	**KEY WORD**
1	"tooth resorption" OR "dental root resorption" OR "tooth root resorption" OR "root shortening" OR "orthodontically induced inflammatory root resorption" OR "apical root resorption" OR "root resorption"
2	"palatal expansion technique" OR "palatal expansion" OR "maxillary expansion" OR "maxillary transverse deficiency" OR "rapid maxillary expansion" OR "transverse maxillary expansion" OR "SME" OR "RPE" OR "RME" OR "SPE"
3	1 AND 2
* Limits: None	
Scopus: 1960 to August 25, 2013	

Search Strategy for CINAHL via EBSCO.*	
SEARCH GROUP	**KEY WORD**
1	tooth resorption OR dental root resorption OR tooth root resorption OR root shortening OR orthodontically induced inflammatory root resorption OR apical root resorption OR root resorption
2	palatal expansion technique OR palatal expansion OR maxillary expansion OR maxillary transverse deficiency OR rapid maxillary expansion OR transverse maxillary expansion OR SME OR RPE OR RME OR SPE
3	1 AND 2
* Limits: None	
CINAHL: 1937 to August 25, 2013	

Search Strategy for Evidence Based Medicine Reviews via OvidSP.*	
SEARCH GROUP	**KEY WORD**
1	tooth resorption OR dental root resorption OR tooth root resorption OR "root shortening" OR orthodontically induced inflammatory root resorption OR apical root resorption OR "root resorption"
2	palatal expansion technique OR palatal expansion OR maxillary expansion OR maxillary transverse deficiency OR rapid maxillary expansion OR transverse maxillary expansion OR SME OR RPE OR RME OR SPE
3	1 AND 2
* Limits: None	
Cochrane Database of Systematic Reviews: 2005 to July 2013	
EBM Reviews - ACP Journal Club 1991 to July 2013	
EBM Reviews - Database of Abstracts of Reviews of Effects 3rd Quarter 2013	
EBM Reviews - Cochrane Central Register of Controlled Trials July 2013	
EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012	
EBM Reviews - Health Technology Assessment 3rd Quarter 2013	
EBM Reviews - NHS Economic Evaluation Database 3rd Quarter 2013	

Search Strategy for LILACS via IAH*	
SEARCH GROUP	**KEY WORD**
1	tooth resorption OR dental root resorption OR tooth root resorption OR "root shortening" OR orthodontically induced inflammatory root resorption OR apical root resorption OR "root resorption"
2	palatal expansion technique OR palatal expansion OR maxillary expansion OR maxillary transverse deficiency OR rapid maxillary expansion OR transverse maxillary expansion OR SME OR RPE OR RME OR SPE
3	1 AND 2
* Limits: None	
LILACS: 1982 to August 25, 2013	

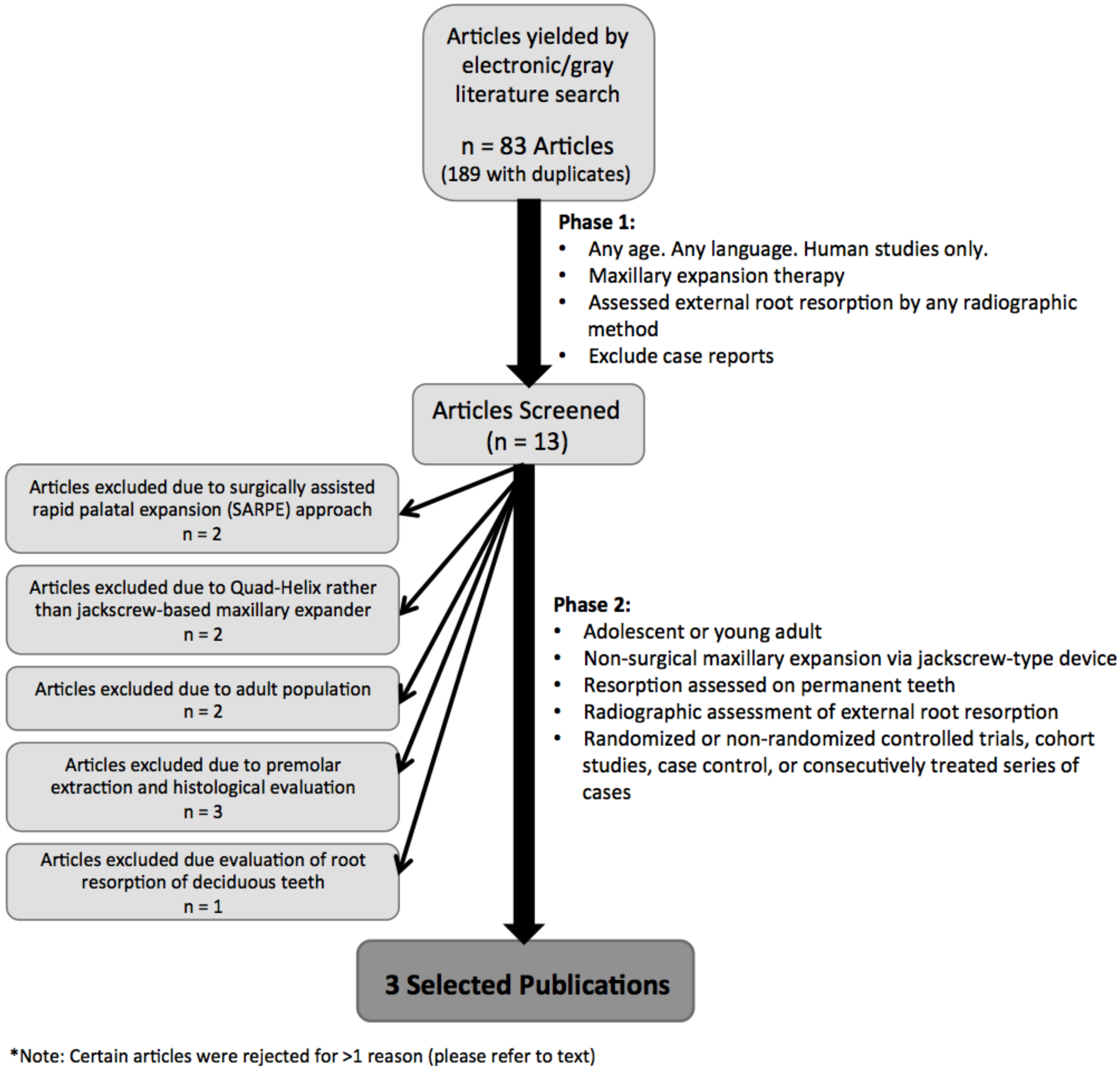

Figure 1.1 Methodology flowchart

Table 1.2 Summary of study characteristics of included articles

Study	Study Design	Sample Size	Teeth Evaluated	Mean (Range) Age in years	Type of Maxillary Expander	Expander Activation Protocol
Baysal *et al.*, 2012	Retrospective Cohort	25 (14 girls, 11 boys) (2 in mixed dentition phase)	Permanent first molars and first & second premolars (premolar teeth not evaluated in the mixed dentition patients) First molar palatal root = 47 First molar mesiobuccal root = 49 First molar distobuccal root = 47 Second premolar = 44 First premolar = 40	12.7 (11.2-14.1)	Tooth-borne banded expander (Hyrax with bands on the first premolar and first molar)	2 turns per day (0.25mm/turn) until palatal cusps of the maxillary molars were in contact with the buccal cusps of the first mandibular molars
Odenrick *et al.*, 1991	Non-randomized clinical trial	**9 Total (5 girls, 4 boys)** * 5 (3 girls, 2 boys - tissue borne appliance) *4 (2 girls, 2 boys - all wire framework appliance)	Maxillary Premolars (radiographically) *Note: In the histologic component of their study, they evaluated both maxillary and mandibular premolars)	12.0 (10.0-13.3)	**1.** Tissue-borne, fixed split acrylic (Haas) palatal expansion appliance (bands on maxillary first molar and first premolar bilaterally). - used on 5 patients. **2.** All-wire framework appliance (bands on maxillary first molar and first premolar bilaterally). - used on 4 patients. ***Note: Both expansion appliances had initial palatal contacts with the maxillary second premolars.**	One-quarter of a turn twice per day, corresponding to 0.5mm per day. The expansion screw allowed a maximum expansion of 7mm which was the objective in all patients.
Barber *et al.*, 1981	Non-randomized clinical trial	**9 Total (5 female, 4 male)** *5 (4 female, 1 male - one first premolar unattached) *4 (1 female, 3 males - both first premolars attached)	Maxillary first premolars (radiographically) *Note: In the histologic component of their study, they evaluated both maxillary and mandibular premolars)	12.6 (9.9-15.3)	Preformed bands connected via a 1.1mm diameter stainless steel wire framework to an expansion screw providing at least 7mm of total activation. *Note: Two appliance designs (one with one first premolar unattached to the RME appliance, the other with both first premolars attached to the RME appliance)	Activated 1/4 turn each morning and evening (daily screw expansion of about 0.5mm) until buccal crossbites were sufficiently overcorrected.

Study	Radiographic Image Used for Analysis	Method Used to Measure External Root Resorption *in vivo*	Study Results
Baysal *et al.*, 2012	CBCT (i-CAT, model 17-19. 5.0mA. 120kV. Exposure time 9.6 seconds. Voxel size 0.3mm.)	*Mimics* software. 3D segmentation with surface and volume rendering according to density (Hounsfield units - set individually for each patient). Molars were segmented and adjusted for 3D orientations with mesial and distal cusp tips oriented parallel to the floor and the roots separated according to a plane parallel to the CEJ and passing through the deepest point of the furcation. Each root was isolated and color coded. Premolars were assessed with the same measurement protocol, but without the separation of the roots. Two measurements: 1. Root volume loss. [difference between pre-expansion (T0) and post-expansion (T1) root volumes] 2. Percentage of root volume loss.[((pre-expansion root volume - post-expansion root volume)/pre-expansion root volume) x 100]	The mean root volumes were decreased after RME. (Statistically significant differences were found between pre-expansion and post-expansion root volumes at $P<.001$ for the buccal roots of the first molar teeth and $P=.001$ for the second and first premolars and palatal root of the first molar teeth) When the percentage of root volume loss was considered, no significant difference was found among the roots.
Odenrick *et al.*, 1991	Intraoral radiographs by 'standardized projection' technique	Radiographic examination of the premolars was performed using a 2D intraoral technique by standardized projection before the start of treatment and at the end of the transverse expansion period. ***Note: The study also histologically evaluated root resorption on extracted maxillary and mandibular premolars, but this is excluded due to lack of *in vivo* observation.**	The maxillary premolars showed a widening of the periodontal space, but there were no 2D radiographic signs of root resorption. ***Note: Systematic review results reported are limited to *in vivo* radiographic observations, not the histological outcomes reported.**
Barber *et al.*, 1981	Long-cone periapical radiographs of first premolars.	Radiographic examination of the premolars was performed using a 2D intraoral technique by long-cone periapical radiographs before and after treatments. ***Note: The study also histologically evaluated root resorption on extracted maxillary and mandibular premolars, but this is excluded due to lack of *in vivo* observation.**	No evidence of buccal resorption in any of the long-cone periapical radiographs of anchor premolars. By contrast, frank apical root loss is revealed by x-ray examination. (Authors claimed the study conclusively demonstrates that RME causes extensive buccal root resorption as assessed by scanning electron microscopy) Authors stated: "...the clinician has no way of accurately estimating the full extent of '*in situ*' root surface resorption caused by expansion treatment." ***Note: Apical root loss of approximately 4mm was identified in one anchor premolar from those examined in the present study.** ***Note: Systematic review results reported are limited to *in vivo* radiographic observations, not the histological outcomes.**

Table 1.3 Detailed risk of bias assessment

	STUDY		
CHARACTERISTIC	**Odenrick *et al.* 1991**	**Barber *et al.* 1981**	**Baysal *et al.* 2012**
Random Sequence Generation (selection Bias)	**High** - Inadequate generation of a random sequence for selection.	**High** - Inadequate generation of a random sequence for selection.	**High** - Inadequate generation of a random sequence for selection. "CBCT records of 25 patients who had undergone RME therapy by tooth-borne banded expander were selected..."
Allocation Concealment (selection bias)	**High** - Inadequate concealment of allocations.	**High** - Inadequate concealment of allocations.	**High** - Inadequate concealment of allocations. "CBCT records of 25 patients who had undergone RME therapy by tooth-borne banded expander were selected..."
Blinding of Participants and Personnel (performance bias)	**High** - Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	**High** - Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	**High** - Performance bias due to knowledge of the allocated interventions by participants and personnel during the study. Patients knew intervention type, as did researchers.
Blinding of Outcome Assessment (detection bias)	**High** - No mention of whether assessors had knowledge of the allocated interventions.	**High** - No mention of whether assessors had knowledge of the allocated interventions.	**High** - Detection bias due to the knowledge of the allocated interventions by outcome assessment. All patients received the same intervention, of which the assessors were aware.
Incomplete Outcome Data (attrition bias)	**Low** - No patient drop out during the trial.	**Low** - No patient drop out during the trial.	**Unclear** - Based on a lack of sample size calculation., effects of attrition are unclear. "Premolar teeth were not evaluated in mixed dentition patients as the apex is not completed. In addition, one first permanent molar, six first premolars, and two second premolars had been extracted before second CBCT records were taken. In one patient, bilateral fusion of the distobuccal and palatal root of the first permanent molar was observed, and these teeth were also excluded. Volumetric measurements were not performed for these teeth."
Selective Reporting (reporting bias)	**Low** - All prespecified outcomes were reported.	**Low** - All prespecified outcomes were reported.	**Low** - All prespecified outcomes were reported.
Other Sources of Bias	**Unclear** - failure to report interrater or intrarater reliability	**Unclear** - failure to report interrater or intrarater reliability	**Unclear** - failure to report interrater or intrarater reliability

Table 1.4 Abbreviated risk of bias assessment

	STUDY		
CHARACTERISTIC	**Odenrick *et al.* 1991**	**Barber *et al.* 1981**	**Baysal *et al.* 2012**
Random Sequence Generation (selection Bias)	-	-	-
Allocation Concealment (selection bias)	-	-	-
Blinding of Participants and Personnel (performance bias)	-	-	-
Blinding of Outcome Assessment (detection bias)	-	-	-
Incomplete Outcome Data (attrition bias)	+	+	?
Selective Reporting (reporting bias)	+	+	+
Other Sources of Bias	?	?	?
+	Low risk of bias		
-	High risk of bias		
?	Unclear risk of bias		

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Chapter 2 - Comparison of *in vivo* 3D Cone Beam Computed Tomography Tooth Volume Measurement Protocols

2.1 INTRODUCTION

Historically, the *in vivo* detection of changes to dental root morphology such as those associated with external root resorption (ERR) during the course of orthodontic treatment or related to trauma has been mainly through use of 2-dimensional (2D) radiographs, most notably periapical radiographs (1-3). Although histological studies have identified a relatively high incidence of apical ERR, 2D radiographic studies have been less definitive (4,5) and have in general proven inaccurate for the reliable detection of small ERR defects (6). In fact, 2D periapical radiographs do not reveal external root resorption to an appreciable extent, except for frank apical root resorption, which appears to be in their realm of identification (7). In addition, there are geometric limitations associated with 2D imaging of a 3-dimensional (3D) phenomenon; therefore, the quantitative value of 2D radiographs to measure ERR is questionable (8-10). When considering panoramic films, the distortion in both tooth position and angulation combined with varying magnification, distortion, superimposition, and imaging artifacts in different parts of the image (11,12) leads to similar limitations in the use of panoramic films to assess ERR (13-15). Therefore, although 2D radiography may be a good screening tool, its use in the quantification of ERR remains controversial (9).

Advancements into 3D imaging techniques have facilitated volumetric imaging capabilities not previously available on an *in vivo* basis; however, accurate dental volume measurement procedures are required in order to fully utilize the technology. The resulting use of 3D imaging has enabled the quantification and measurement of ERR to be completed with a high level of diagnostic accuracy and repeatability when compared to periapical radiographs (9,16-18). The strength of CBCT for accurate dental volume measurements *in vivo* has been shown not to be statistically significantly different as *in vitro* measurements in one study (19) and even when comparing its accuracy to *in vitro* micro-CT imaging methods (20); however, there may exist machine specific variations. The feasibility of *in vivo* dental volume measurements using CBCT imaging has similarily been reported by Liu *et al*; however, their use of post-processing surface smoothing has been shown to decrease 3D volume measurements. (21) Conversely, increasing the voxel size has been shown *in vitro* to actually increase volume measurements.(22) It is intuitively apparent that the accuracy of the 3D segmentation procedure is related to the voxel size during acquisition (23) with 0.25mm voxel size an appropriate compromise between diagnostic accuracy and patient radiation dose.(22) An additional factor is development of a clearly defined measurement protocol, which appears lacking in the literature as the study currently employing CBCT as a means of determining root volume loss with maxillary expansion lacks a clearly defined measurement protocol involving incorrectly utilized Hounsfield units with the teeth of interest "segmented cautiously" (24). There exists a potential limiting factor inherent in the use of CBCT scans to measure accurate volumetric information as the time period required to capture the radiograph as patient movement during scans can reduce the accuracy of measurements (15,25).

The validation of CBCT as a tool for measurement of both root lengths and volumes has been focused on in numerous studies (15-17,19,21,26-33). The investigation of *in vivo* volumetric determination utilizing CBCT images has been shown to yield slight differences from actual physical volumes within -4% to +7% (21). However, there lacks a clearly defined gold-standard 3D segmentation protocol in the literature.

Given the inconsistencies of the techniques reported in the literature, the development of an appropriate CBCT measurement protocol possessing accuracy and precision in both intra- and inter-rater reliability for *in vivo* dental volume measurements is desired. Due to the relative infancy of the area of 3D dental volume segmentation, with lack of a gold-standard technique, the need to employ and evaluate segmentation techniques to identify which measurement protocol is most superior is a necessity. Through the establishment of precise and accurate dental volume measurement protocols, clinicians can more confidently employ the available tools to monitor such phenomena as ERR during the orthodontic process and ERR related to dental trauma.

The objective of this study is therefore to analyze a set of developed and proposed image segmentation protocols for precision in both intra- and inter-rater reliability for *in vivo* tooth volume measurements using cone beam computed tomography (CBCT) images.

2.2 MATERIALS AND METHODS

2.2.1 Cone Beam CT Images

The radiographic data set used for the analysis of dental volume was previously acquired as part of a randomized clinical trial at the University of Alberta, Edmonton, Alberta, Canada. Subjects were recruited during an 18-month period. Inclusion criteria for selection included transverse maxillary deficient adolescents with no previous orthodontic treatment. The age range of patients selected for this study ranged from 11 to 17 years old. Subjects were not excluded based on the presence or absence of coronal restorations. Informed consent from the patients' parents and ethical approval from the Ethics Committee at University of Alberta was obtained.

All CBCT images were taken with the NewTom 3G (QR, Verona, Italy) device at 110 kV, 6.19 mAs, and 8-mm aluminum filtration with the patient in maximum intercuspation following common CBCT imaging protocols. Images were converted to DICOM format by using the NewTom software to a voxel size of 0.25 mm. The DICOM-formatted images were volume rendered with Avizo 3D analysis software (Visualization Sciences Group, Berlin, Germany).(34) Patient images were acquired at two timepoints during the trial: T1 (before treatment) and T2 (after treatment, approximately 12 months).

2.2.2 Tooth Volume Measurement Protocols

Three protocols for dental tooth volume determination were investigated using Avizo 3D analysis software:

1. Manual human segmentation on a repeated 2D basis.
2. Automated segmentation without human refinement.
3. Automated segmentation with manual human refinement on a repeated 2D basis.

In addition, two methods for tooth volume selection were simultaneously investigated. These involved the entire tooth structure including the crown, and only the dental root structure apical to the cemento-enamel junction (CEJ). All three protocols and two methods were applied to determine the technique producing greatest intra- and inter-rater reliability. The dental pulp chamber and canals were included in the volume measurements. The investigator was blinded to whether they were T1 (before treatment) or T2 (after treatment) radiographs. In all, a total of 6 different approaches (combination of three protocols and two tooth volumes) to tooth volume segmentation were investigated. Ten randomly selected maxillary first molars (selected from both T1 and T2 patient images) were measured *in* vivo in random order three times with 10 days separation between measurements.

The threshold value for image segmentation was set for each tooth. This same threshold value was used in all protocols to assess the particular tooth of interest to limit variability between methods. The first protocol did not require a threshold value to be explicitly set as the protocol was strictly manual human tracing of the image on a 2D slice-by-slice basis.

No image orientation adjustments were completed prior to testing of the protocols. The sagittal plane was utilized for initial evaluations for each technique, as it appeared most useful in the visualization and evaluation of the tooth structure of the crown and root simultaneously.

1. Manual human segmentation on a repeated 2D basis.

The first protocol involved manual image segmentation procedures on a 2D slice-by-slice basis through the use of Avizo's 'lasso' tool, which allows one to define an area freehand by generating a closed contour curve in 2D. The delineation of tooth structure from surrounding alveolar and cortical bone was first determined on a slice-by-slice basis in the YZ (sagittal) plane (Figure 2.1) based upon visual inspection only. Refinements in the XY (axial) plane (Figure 2.2) were then manually completed for the observation of tooth anatomy from a different perspective. An axial view enabled root structure and interproximal contact point refinements. Finally, additional refinements in the XZ (coronal) plane (Figure 2.3) were again manually completed. A coronal view enabled refinements to root structure that was in close proximity to the buccal and palatal cortical plates. The 3D resultant tooth was evaluated for approximately normal maxillary first molar dental anatomy to limit gross misidentification of dental structures (Figure 2.4). Once segmentation was completed, the software automatically computed the tooth's radiographic volume. No smoothing functions were applied to the 3D tooth structure to prevent smoothing of minor root defects/imperfections or possible resorption lacunae. Both the complete tooth volume (Figure 2.5 A), and the dental root volume, defined as the anatomical root apical to the CEJ, (Figure 2.5 B) were measured.

2. Automated segmentation without human refinement.

The second protocol involved the use of the 'magic wand' tool in Avizo 3D imaging software as a 'region-growing' tool. The 'magic wand' tool allows one to perform so-called 'region-growing' in either 2D or 3D. Selecting an individual 'seed voxel' of a tooth root or crown selects the largest connected area (either 2D or 3D) that contains the voxel itself and all voxels with gray values contained within a user-specified range. The range can be chosen to represent absolute gray values or gray values relative to that of the seed voxel. For the purposes of our investigation, absolute gray values were chosen to limit variability in selection of the seed voxel gray value. Segmentation was performed using strictly an automated approach after minor operator input to the selection of the seed voxel in the enamel of the tooth without focused manual refinements in an attempt to test an efficient measurement procedure. The user input to select the seed voxel proved to be a necessity given the software. The rest of the procedure required no operator input for the actual segmentation procedure. A visually defined optimal threshold value was set for each tooth in the YZ (sagittal) plane (Figure 2.1). The threshold level was set to most clearly show the tooth anatomy with minimal interference from the surrounding bone and adjacent structures. The 3D resultant tooth was evaluated for approximately normal maxillary first molar dental anatomy to limit gross misidentification of dental structures. Once segmentation was completed, the software automatically computed the tooth's radiographic volume. As in protocol 1, no smoothing functions were applied and both the complete tooth volume and dental root volume were measured.

3. <u>Automated segmentation with manual human refinement on a repeated 2D basis.</u>

The third protocol also involved the use of the ‘magic wand’ tool in Avizo 3D imaging software as a ‘region-growing’ tool, similar to that utilized in the second protocol; however, in this case segmentation was performed using a mixture of an automated approach with manual localized visual refinements to the tooth structure. For the purposes of our investigation, absolute gray values were chosen to limit variability in selection of the seed voxel gray value. The same absolute gray value range was selected as in the second protocol to limit variability between methods for each tooth. Segmentation was performed using a mixture of an automated approach with manual localized visual refinements to the tooth structure. A visually defined optimal threshold value was set for each tooth in the YZ (sagittal) plane (Figure 2.1). The threshold level was set to most clearly show the tooth anatomy with minimal interference from the surrounding bone and adjacent structures. Manual refinements were processed on a slice-by-slice basis to enhance accuracy by correcting for over- and under-contoured voxels in the tooth volume. Initial refinements occurred in the YZ (sagittal) plane. Secondary refinements were performed in the XY (axial) plane (Figure 2.2) to refine root structure and interproximal dental contact points. Tertiary refinements were performed in the XZ (coronal) plane (Figure 2.3) to verify tooth anatomy and focus on the delineation of dental root structure from the buccal and palatal cortical plates. The 3D resultant tooth was evaluated for approximately normal maxillary first molar dental anatomy to limit gross misidentification of dental structures. Once segmentation was completed, the software automatically computed the tooth's radiographic volume. As in protocols 1 and 2, no smoothing functions were applied and both the complete tooth volume and dental root volume were measured.

2.2.3 Statistical Analysis

The volume data was manually entered into Microsoft Excel 2011 for MAC (Microsoft, Redmond, WA). SPSS for MAC (version 21, IBM, Armonk, New York) was used to run all statistical tests. For all tests, statistical significance was set at an α value of 0.05.

Intraclass Correlation Coefficient (ICC) was used to measure agreement between the measurements for the continuous dependent variable (dental tooth volume) taken on the three separate days. A single measures with consistency under two-way mixed model was chosen, thus removing the rater's variation, and the subjects/teeth were chosen randomly with the rater fixed. The technique that produced the highest ICC value and lower bound of the 95% confidence interval was chosen as the preferred measurement protocol.

To assess inter-rater reliability for the two approaches, the second rater (S.N.) was trained directly by the initial rater step-by-step in the use of the software and chosen measurement technique as determined from the intra-examiner reliability assessment. The general use of the software, visualization of the tooth of interest in all 3 planes of space, automated segmentation procedures, manual refinements, and 3D visualization of the resultant volume were reviewed in training. The second rater (S.N.), who possessed a dental background and knowledge of normal dental anatomy, measured the same ten randomly selected maxillary first molars as measured by the principal investigator (both the whole tooth method and the dental root apical to the CEJ method). Intraclass Correlation Coefficient (ICC) was used to measure agreement between the principal investigator's second measurement, as determined randomly, and the additional investigator's single measurement. A single measures with absolute agreement under two-way mixed model was chosen to account for rater variation and the subjects/teeth were chosen randomly with the raters fixed.

2.3 RESULTS

2.3.1 Intra-Rater Reliability

2.3.1.1 Protocol 1: Manual human segmentation on a repeated 2D basis.

The ICC demonstrated agreement, ICC(Single Measures) = 0.885, 95% CI (0.707,0.967), within rater for the whole tooth measurement. The ICC demonstrated agreement, ICC (Single Measures) = 0.904, 95% CI (0.749,0.973), within rater for the root measurement apical to the CEJ.

2.3.1.2 Protocol 2: Automated segmentation without human refinement.

The ICC demonstrated agreement, ICC(Single Measures) = 0.826, 95% CI (0.697,0.952), within rater for the whole tooth measurement. The ICC demonstrated agreement, ICC (Single Measures) = 0.899, 95% CI (0.742,0.953), within rater for the root measurement apical to the CEJ.

2.3.1.3 Protocol 3: Automated segmentation with manual human refinement on a repeated 2D basis.

The ICC demonstrated excellent agreement, ICC(Single Measures) = 0.996, 95% CI (0.989,0.999), within rater for the whole tooth measurement. The ICC demonstrated agreement, ICC (Single Measures) = 0.904, 95% CI (0.751,0.973), within rater for the root measurement apical to the CEJ.

Therefore, the whole tooth measurement utilizing protocol 3 was selected as the measurement method as it possessed the highest ICC value and lower bound of the confidence interval (ICC(Single Measures) = 0.996, 95% CI (0.989,0.999)) when compared to all other measurement protocols investigated.

The summary of intra-rater reliability *via* the ICC is presented in Table 2.1. In addition, a summary of the largest volume differences for intra-rater repeated measures are presented in Table 2.2.

2.3.2 Inter-Rater Reliability

Looking strictly at the variability on an intra-rater basis was the focus of our determination of appropriate methods to be evaluated on an inter-rater basis. Therefore, the method with highest intra-rater reliability was chosen to further address inter-rater reliability. Given that protocol 3, automated segmentation with manual human refinement on a repeated 2D basis, yielded the highest intra-rater reliability statistics, the inter-rater reliability was computed utilizing measurement protocol 3. The ICC demonstrates excellent agreement, ICC (Single Measures) = 0.990, 95% CI (0.961,0.998), between raters for the whole tooth measurement. However, the ICC demonstrates less powerful agreement, ICC (Single Measures) = 0.728, 95% CI (0.198,0.926), between raters for the root measurement apical to the CEJ. The inter-rater analysis results are in agreement with the chosen measurement protocol as determined via intra-rater ICC values.

The reliability readings for protocol 3 are included in Table 2.3. It serves to display the differences in absolute volume measurements for the repeated measures and inter-rater values.

One subject had coronal restorative material present in the evaluated tooth. The presence of this restorative material did not have significant effects on the segmentation results, as it was not an outlier in the data set.

2.4 DISCUSSION

The method involving automated segmentation with manual human refinement on a repeated 2D basis for the whole tooth proved to be the most reliable measurement protocol both within and between observers. Essentially, the intra- and inter-rater analysis results are in agreement with measurement protocol 3 as determined via ICC values. For excellent agreement, the ICC 95% confidence interval should be above 0.750 (35,36), which is the case for the results obtained for protocol 3 using the entire tooth volume. It is of value to note that the protocol developed possesses similarities to studies investigating the accuracy of dental volume measurement *in vivo* using CBCT (21) and condylar head volume measurement (37) and hence lends to our segmentation technique's credibility.

The greatest difference across intra-rater repeated measures for the whole tooth approach utilizing protocol 3 was 17.76 mm^3 (approximately 1.50% of the average whole tooth volume measured), whereas for the roots only approach utilizing protocol 3 was 64.79 mm^3 (approximately 11.45% of the average root volume apical to the CEJ measured). The intra-rater variability was thus approximately 3.6 times greater in absolute volume (64.79 mm^3 versus 17.76 mm^3) and 7.6 times greater in proportion of structure measured (11.45% versus 1.50%) when measuring roots only as compared to measuring the entire tooth volume.

Visualization of the respective maximum volume difference as displayed in Table 2.3 applied to a single tooth in various scenarios is displayed in Figure 2.6. The maximum volumetric discrepancy between repeated intra-observer measurements for the whole tooth was 17.76 mm^3. The maximum volumetric discrepancy for inter-observer measurements for the whole tooth was 30.39 mm^3. The effects of these measurement variations can be shown visually in a number of ways as displayed in Figure 2.6. Removal of the maximum inter-observer volume difference (30.39 mm^3) strictly from the most apical portion of the palatal root (Figure 2.6B), from the apical portions of all 3 roots (Figure 2.6C), and from the buccal surfaces of the mesiobuccal and distobuccal roots are displayed (Figure 2.6D). Nearly imperceptible changes when differences are distributed across all roots and on the buccal surfaces of the mesiobuccal and distobuccal roots visually display the inter-observer errors with which tooth volumes may be determined. Visualizing the maximum volumetric discrepancy between repeated intra-observer measurements for the whole tooth of 17.76 mm^3 is displayed visually in Figure 2.7. The volume displayed is the mesiobuccal cusp tip of the maxillary right first molar. The occlusal-apical dimension of the cusp tip volume measures only 1.2mm, thus providing an approximate clinical interpretation and visualization of the volume differences. In addition, when considering the measurements of ERR with tooth-anchored maxillary expander (TAME) for the maxillary first molars completed by one rater, average maxillary first molar ERR volume changes of 42.67mm^3 have been previously reported in the literature (24), which is approximately 2.4 times greater than the intra-rater reliability protocol established for this technique.

The method resulting in the worst reliability was automated segmentation without human refinement. There are numerous reasons why this protocol was flawed. The determination of the boundaries between the tooth roots and the buccal and palatal cortical plates is sometimes indistinct given the very close proximity of the roots. The furcation area of the tooth possesses a large surface area of lamina dura, the dense surrounding cortical bone, which can lead to unclear tooth furcation anatomy. The proximity of the erupting second molar in some patients, as well as the interproximal contacts with adjacent teeth, often led to over-contouring of the volume of the crown of the maxillary first molar. In addition, the presence of dense bone islands of increased radiopacity can also result in misidentification of the proper root morphology. Given the limitations associated with a strictly automated method, it is still not possible, at least at a 0.25 mm voxel size, to automate the segmentation procedure. To be precise, the process must still involve manual human refinements with proper knowledge and interpretation of the 3D anatomy. As such, the process is extremely labor intensive given the slice-by-slice refinements that are required in all 3 planes of space.

In the approaches investigated, the pulpal tissue was included in the volumes as additional errors in delineating dentin from pulpal tissue would be an added source of variation. The additional dentin/soft tissue border, which is likely more challenging anatomy than the tooth to surrounding bony support to identify, due to intricate pulpal canal architecture of small dimension, would require identification. Therefore, since our area of interest is only ERR, internal pulpal changes are irrelevant. Consequently, both the hard and soft tissues within the cementum of the tooth were calculated as a part of the total tooth volume.

Due to the retrospective nature of the study, certain limitations were imposed on our ability to verify the accuracy of the volume measurements. To address this concern, focus was turned to the precision of volume measurements from both an intra- and inter-examiner perspective. The limitations from the retrospective nature of the study are two-fold. Firstly, the CBCT machine used to capture the initial images was no longer functional or available for additional measurements such as *in vitro* dental volume comparisons. Secondly, due to the non-extraction orthodontic treatment of these patients, and that investigation of maxillary first molar volume was desired, the true value of the molar volumes is unknown and is unlikely to be known in future studies as maxillary first molars are not commonly extracted for orthodontic purposes except in rare circumstances. However, there appears no obvious reason for not being able to extrapolate the measurement protocol identified to other teeth. Therefore, with the inability to focus on the validity of the data, the approach was chosen to identify a measurement protocol to give highly precise results, both in intra- and inter-rater conditions.

The desire and ability to verify the true volumes or accuracy for this particular CBCT machine brings into question the capability to replicate an *in vivo* scenario. Numerous factors could not be addressed in a *post hoc* replicated model including the lack of a periodontal ligament, cortical bone, soft tissues, and patient movement to name a few. In addition, the imaging of a model as opposed to an *in vivo* dental volume followed by extraction and *in vitro* dental volume measurement would lead to the introduction of several errors and inaccuracies.

The validation of CBCT as a tool for measurement of both root lengths and volumes has been addressed in a number of studies with a multitude of image segmentation techniques. (16,17,19-21,27-33) The weaknesses of the studies include the lack of investigation into more than one image segmentation protocol to provide the most precise experimental data. As an example, the study assessing ERR with maxillary expansion using 3D CBCT images (24) utilizes a segmentation procedure employing a root only approach (apical to the CEJ for maxillary premolars and apical to the deepest point of the furcation for maxillary molars). The results of our study yielded the greatest intra-rater variability when using a similar method. Therefore, assessment of the root volume only appears to be wrought with errors in identification of the desired volume. Although an identical CBCT machine was not utilized in our own study, the voxel size and imaging parameters were similar to that of another (21). In general, a change of software or CBCT machine appears to not be significantly clinically important given voxel sizes are held constant. There exist other 3D software programs for analyzing CBCT data with similar functions as the software is being utilized only as a tool to compute a volume. What does appear important however is voxel size and segmentation protocol, not the particular software used, as long as there is segmentation functionality.

Due to the uniqueness of our data set and limited access to the original CBCT machine because of the retrospective nature of the study, validation of our method, was sought in the literature. After the independent development, reliability testing, and subsequent comparison with existing published literature employing image segmentation protocols for dental volumes, some conclusions were reached. With numerous segmentation protocols in the literature, the volume measurement techniques in one CBCT volume validation study (21) were identical (in so far as can be determined from their reported methods) to our Protocol 3 (whole tooth), which possessed the most precise volume segmentation results. Given the similarity of our measurement protocols, we feel confident in the validity of our results obtained to the study that verified the accuracy and validity of the dental tooth volume to within -4% to 7% (21).

Traditionally, as reported in the literature, bicuspids were routinely measured *in vivo* and subsequently extracted for physical volumetric determination (21). There is an inherent tooth type limitation likely to be present in all studies due to the rarity of maxillary first molar extractions associated with orthodontic treatment. In our study, investigation of the maxillary first molar was chosen for a number of reasons including its complex root anatomy, early eruption and completion of root development in orthodontic aged adolescent patients, and its use as an anchorage unit for initial phase orthodontic care. The potential for incomplete root development would be a limitation in evaluating any permanent tooth in adolescents, but given the comparatively early eruption of the permanent first molars, this limitation is mitigated as much as possible. An additional reason for this decision is because utilizing CBCT to assess ERR associated with maxillary expansion appliances is the ultimate goal. With maxillary first molars being the most commonly banded teeth that are attached to a maxillary expansion appliance, it makes inherent sense to assess the resorptive changes occurring within the anchor teeth themselves.

A strength of our reliability investigation lies not only in the numerous image measurement protocols investigated, but also in the investigation of the entire maxillary first molar tooth volume versus the volume of the roots apical to the CEJ for each protocol as different segmentation cutoff points have been reported in the literature with no justification (24) or mention of technique accuracy or reproducibility. The reason two volumes were investigated is numerous. If the entire tooth volume was used, this adds the potential for patient coronal tooth volume variability between time points due to possible attrition, decay, loss of coronal tooth structure, and the placement or adjustment of new fillings or occlusion, in addition to other unidentified sources. This coronal tooth structure variability was not directly investigated in this particular paper, as the volume measurements for reliability were repeated measures on the same teeth at the same point in time. However, the identification and attention to the possible sources of variability aids in deciding whether the variability present in the root volume only measurements apical to the CEJ approach is more favorable due to the absence of the coronal variability. To address this from a visual perspective, Figure 2.8 displays the coronal changes that would have to be present on the cusp tips of the maxillary first molars to represent the maximum difference in additional variability of the root versus whole tooth (64.79 mm^3 – 30.39 mm^3 = 34.40 mm^3) in the repeated measures. With visualization of the hypothetical coronal changes, it appears clear that measuring the whole tooth appears superior when compared to the roots only given the additional variability associated with measuring the roots only is more than can be expected from coronal changes over the short term (1-2 years). Support for the use of the whole tooth measurement protocol comes from a study exploring crown and root length of teeth using CBCT images. The study found a wider range of limits, and hence more variability, in measuring root lengths as opposed to crown lengths (26). This increased error can perhaps be extended to root volumes due to difficulties in determining the CEJ location as the enamel is at its thinnest in this area. The CEJ is anatomically not a straight line; however, in many images, the lack of definition of the apical extent of the enamel resulted in a nearly straight-line resultant 3D segmentation. The best suggested method considers all the tooth structure not just the root in order to eliminate CEJ identification. For instance, an error in identification of one axial 2D slice was found to introduce root volume changes between 40-65mm^3 depending on tooth size. The increased variability appears to occur due to the fact that the CEJ represents quite a large 2D axial volume. In contrast, attrition at the molar cusp tips leads to almost imperceptible changes in tooth volume. The differences between a cusp tip axial slice area versus a CEJ slice area are displayed in Figure 2.9. Therefore, due to the increased difficulties in CEJ identification, the role of external coronal volume changes from T1 to T2 were judged to be minimal compared to the effects of an error in CEJ identification.

In general, the presence of radiodense restorative materials, such as amalgam and some highly filled composites, which greatly inhibit the passage of electromagnetic radiation, has the potential to introduce further variability into dental volume determination and result in imaging artifacts. These artifacts can result in the inability to predictably identify the true extent of the radiodense material or adjacent structures and thus affect volume segmentation.

There exists the obvious issue of resolution of a CBCT image in determining the volume of a tooth. Given the voxel size of 0.25 mm in each dimension, there are concerns regarding the potential that the border of a tooth versus bone could be contained within a voxel. A limitation in computed tomography imaging is the so called ‘partial volume effect’. In essence, this phenomenon can present issues in the differentiation of different tissue types. For example, a large amount of periodontal ligament (PDL) space and a thin layer of compact bone such as the lamina dura can cause the same attenuation in a voxel as the dentin of a tooth alone. The issue of resolution is complex as improved resolution can be acquired, but at the expense of increased patient radiation dose (30). Although improved volumetric determination and ERR detection can be obtained with smaller voxel sizes and increased scan times (28), there exists a limit, which has to be established between patient radiation dose and resolution required for appropriate diagnostics. However, early detection of root changes may modify treatment mechanics and thus limit the progression of ERR and the long-term impact on the affected teeth. Using a voxel size of 0.125 mm has the potential to yield *in vivo* volume measurement of teeth comparable to Micro-CT *in vitro* analysis (20), but understandably has the disadvantage of increased patient radiation dose. A study, which investigated the influence of voxel size on the diagnostic ability of CBCT to evaluate ERR, concluded CBCT to be a reliable method of ERR detection with a voxel size of 0.3mm as the 'best protocol' when balancing patient dose and diagnostic performance. (38) Given the voxel size of 0.25mm used in this study, there appears to be more than adequate resolution required to measure dental tooth volumes while balancing patient radiation dose.

A limitation of the study involves the use of only one CBCT model to capture the patient images. There exists the potential issue of variation between different CBCT models that may possibly possess varying image quality and grey value distributions for the aforementioned segmentation methods.

Through the establishment of precise and accurate dental volume measurement protocols, clinicians can more confidently employ the available tools to monitor such phenomena as external root resorption (ERR) at various stages throughout the orthodontic process and ERR related to dental trauma. However, patient radiation exposure and diagnostic imaging needs require a careful balance to be established. The uses of CBCT imaging are to maximize the diagnostic information available to the clinician while limiting patient radiation exposure to make individualized treatment decisions while considering as many patient specific factors as possible.

2.5 CONCLUSION

- The proposed maxillary first molar dental volume measurement protocol for CBCT images employing automated segmentation with manual human refinement on a repeated 2D slice-by-slice basis in all 3 planes of space possesses excellent intra- and inter-rater reliability and precision.
- Maxillary first molar 3D volume measurements of the entire tooth structure are more precise than 3D volume measurements of only the dental roots apical to the CEJ.

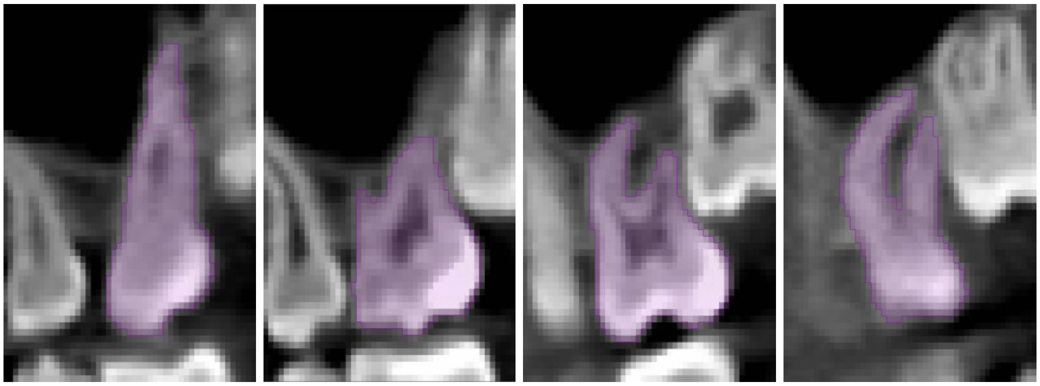


Figure 2.1 YZ (sagittal) plane

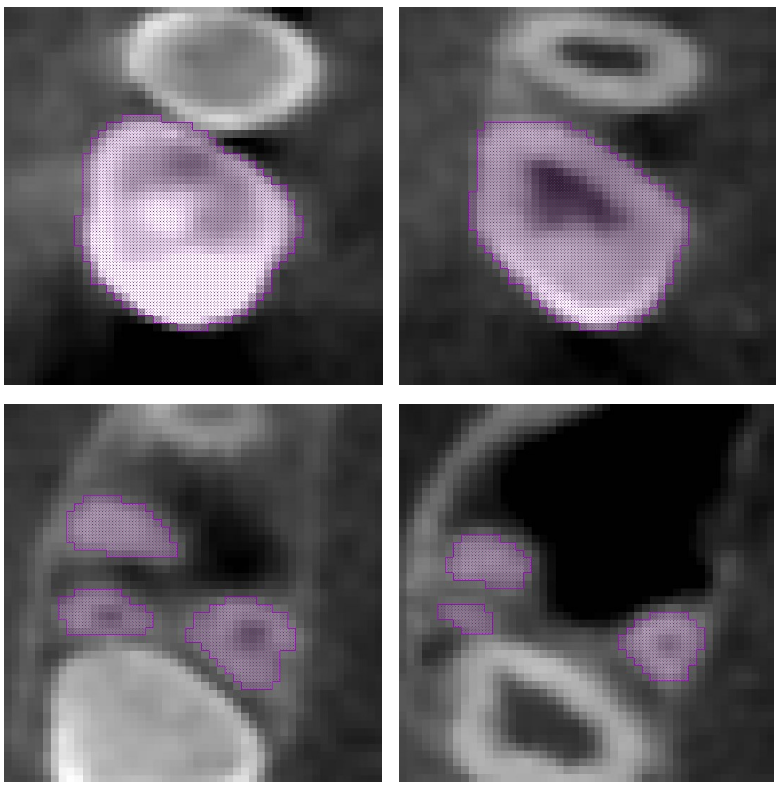


Figure 2.2 XY (axial) plane

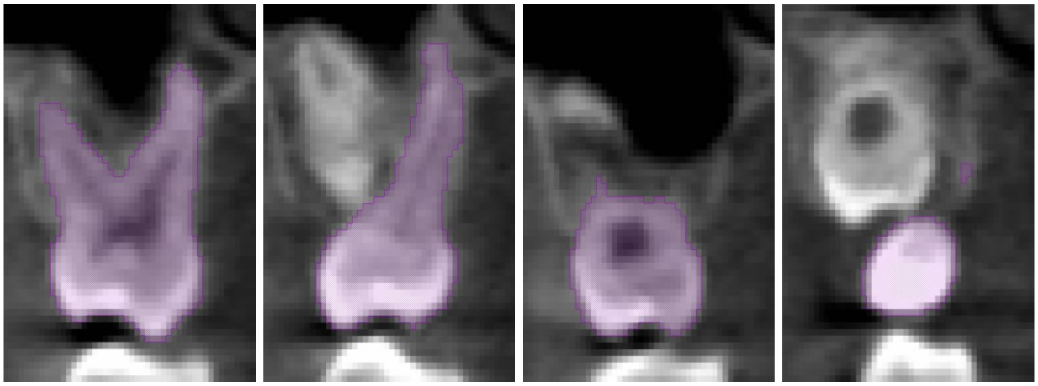


Figure 2.3 XZ (coronal) plane

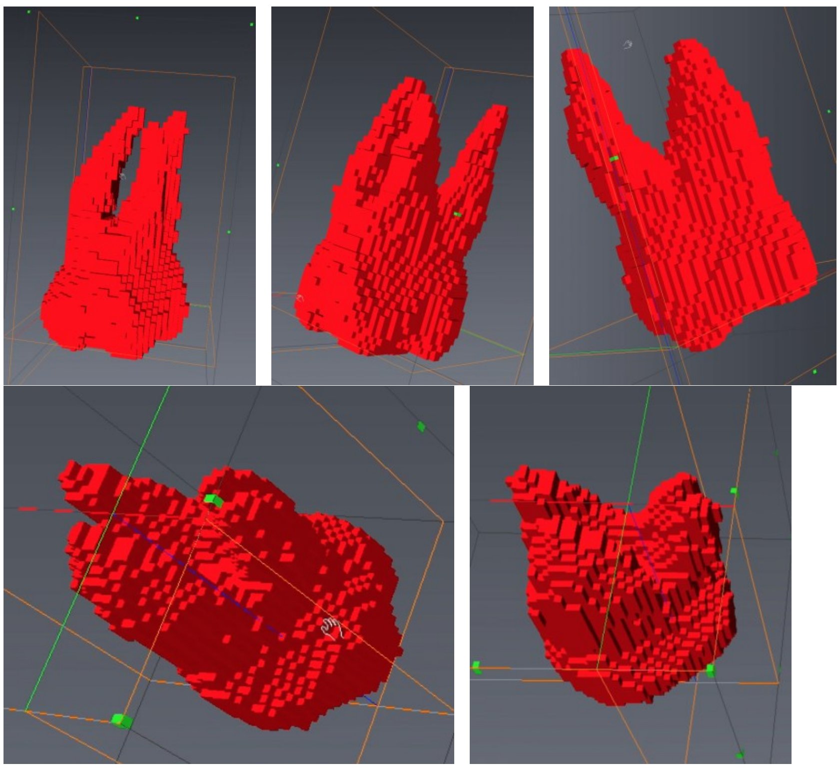
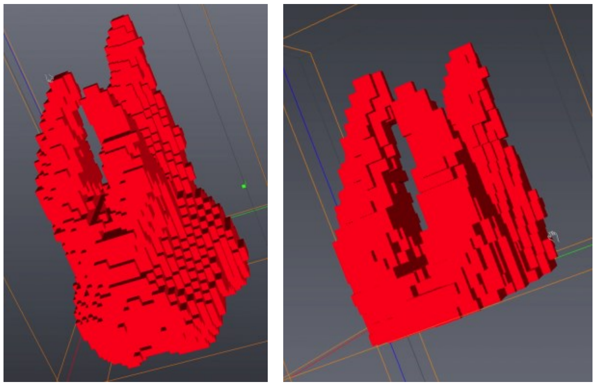


Figure 2.4 3D sample view of maxillary first molar volume without smoothing



A. **B.**

Figure 2.5 Tooth Volumes A. Three-dimensional complete tooth volume. B. Three-dimensional tooth volume apical to the cemento-enamel junction.

Table 2.1 Intra-Rater Intraclass Correlation Coefficient Values

Measurement Protocol	Volume Measured	ICC	CI (lower bound)	CI (upper bound)	F-test, p-values
Protocol 1: Manual	Whole Tooth	0.885	0.707	0.967	$F(9,18) = 24.158$, $p < .0005$
Protocol 1: Manual	Roots Apical to CEJ	0.904	0.749	0.973	$F(9,18) = 29.406$, $p < .0005$
Protocol 2: Automated	Whole Tooth	0.826	0.697	0.952	$F(9,18) = 12.215$, $p < .0005$
Protocol 2: Automated	Roots Apical to CEJ	0.899	0.742	0.953	$F(9,18) = 27.512$, $p < .0005$
Protocol 3: Automated with Refinements	Whole Tooth	**0.996**	**0.989**	**0.999**	**$F(9,18) = 767.557$, $p < .0005$**
Protocol 3: Automated with Refinements	Roots Apical to CEJ	0.904	0.751	0.973	$F(9,18) = 29.406$, $p < .0005$

*CEJ = Cemento-Enamel Junction
*CI = Confidence Interval
*ICC = Intraclass Correlation Coefficient

Table 2.2 Largest volume differences for intra-rater repeated measures

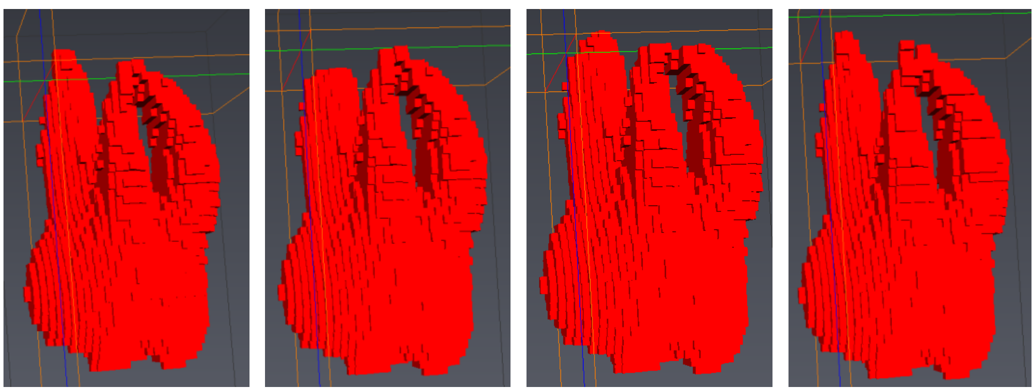
		Largest Difference (Single Rater)
Protocol 1:	**Whole Tooth**	49.15 mm3
	Roots Apical to CEJ	76.21 mm3
Protocol 2:	**Whole Tooth**	52.51 mm3
	Roots Apical to CEJ	75.15 mm3
Protocol 3:	**Whole Tooth**	17.76 mm3
	Roots Apical to CEJ	64.79 mm3

*CEJ = Cemento-Enamel Junction

Table 2.3 Reliability readings for protocol 3. (All units in mm^3)

	Rater 1 - 1st Measurement	Rater 1 - 2nd Measurement	Rater 1 - 3rd Measurement	Rater 1 - Average Measurement	Rater 1 Largest Volume Difference	Rater 2 - Measurement	Rater 1 Average vs Rater 2 Difference	Rater 1 (2nd Measurement) vs Rater 2 Difference
Whole Tooth	1072.26	1058	1063.25	1064.50	14.26	1056.25	8.25	1.75
	1054.7	1066.26	1060.58	1060.51	11.56	1077.73	17.22	11.47
	1019.74	1030.25	1033.55	1027.85	13.81	1039.89	12.04	9.64
	1017.71	1020	1021.32	1019.68	3.61	1006.65	13.03	13.35
	990.74	992.42	993.24	992.13	2.5	1005.58	13.45	13.16
	1195.89	1178.13	1170.26	1181.43	**17.76**	1160.21	21.22	17.92
	972.53	968.71	965.85	969.03	6.68	995.22	26.19	**26.51**
	859.34	851.43	853.25	854.67	7.91	838.88	15.79	12.55
	1229.75	1219.06	1221.39	1223.40	10.69	1242.85	19.45	23.79
	1251.74	1238.41	1249.85	1246.67	13.33	1216.28	**30.39**	22.13
Roots Apical to CEJ	589.15	552.04	542.03	561.07	47.12	601.54	40.47	49.5
	499.17	505.27	489.25	497.90	16.02	546.83	48.93	41.56
	546.6	532.21	525.24	534.68	21.36	500.24	34.44	31.97
	452.29	487.68	442.88	460.95	44.8	402.86	58.09	**84.82**
	607.23	607.89	615.25	610.12	8.02	548.95	**61.17**	58.94
	610.79	657.77	662.66	643.74	51.87	630.84	12.90	26.93
	504.22	533	492.02	509.75	40.98	552.21	42.46	19.21
	403.67	445.49	394.12	414.43	51.37	459.21	44.78	13.72
	498.52	490.25	483.66	490.81	14.86	480.65	10.16	9.6
	578.15	527.26	592.05	565.82	**64.79**	607.54	41.72	80.28

*CEJ = Cemento-Enamel Junction



A. B. C. D.

Figure 2.6 Three-dimensional visualization of inter-observer volume differences for the whole tooth measurement.

A. Entire tooth volume. B. Entire tooth volume with maximum inter-observer variability removed from palatal root. C. Entire tooth volume with maximum inter-observer variability removed from apical portion of all three roots. D. Entire tooth volume with maximum inter-observer variability removed from buccal surfaces of the mesiobuccal and distobuccal roots.

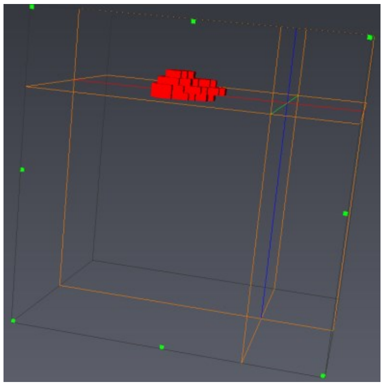
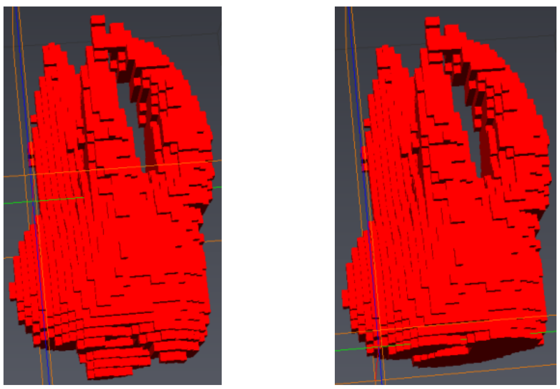
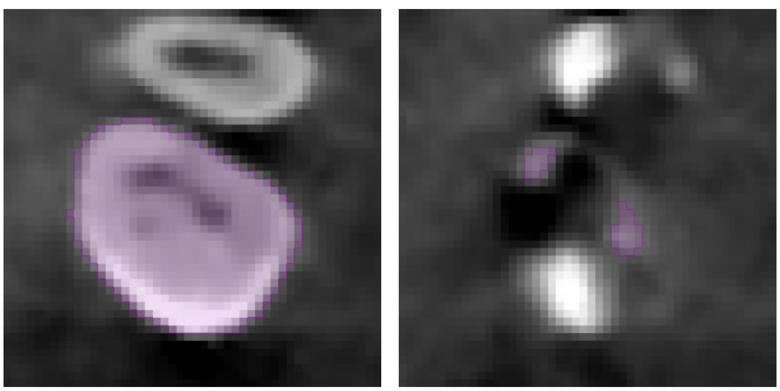


Figure 2.7 Three-dimensional visualization of the intra-observer volume difference for the maxillary right first molar mesio-buccal cusp tip



A. B.

Figure 2.8 Cusp tip attrition that would have to be present to represent the maximum difference in additional variability between roots only and whole tooth in the repeated measures. A. Normal 3D volume. B. 3D volume representing maximum difference in additional variability of the roots versus the whole tooth (64.79 mm^3 – 30.39 mm^3 = 34.40 mm^3) in the repeated measures removed from cusp tips.



A. B.

Figure 2.9 Axial slice area at the cement-enamel junction (CEJ) versus cusp tip. A. Axial slice area at the molar CEJ. B. Axial slice area at the molar cusp tips.

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Chapter 3 - External Root Resorption Associated with Bone-Anchored Maxillary Expansion versus Tooth-Anchored Maxillary Expansion as Evaluated *in vivo via* Cone Beam Computed Tomography: A Retrospective Randomized Clinical Trial

3.1 INTRODUCTION

Maxillary transverse deficiency is a common pre-treatment issue faced by many orthodontic patients and is usually accompanied by unilateral or bilateral posterior crossbite, narrow nasal cavity, and crowding (1,2). The standard of care, treatment modality in maxillary transverse deficient adolescents is rapid maxillary expansion (RME) performed with a tooth-anchored expander (Hyrax type) (3-6). There are disadvantages that have been identified with this approach as direct tooth-anchored appliances can, in some instances, result in root volume loss (5,7) and have the added potential for undesirable tooth movement (4). An alternative approach to attempt mitigation of the adverse dental effects is the use of bone-anchored maxillary expanders (BAME). BAME move the point of force application away from the teeth, with the goal of reducing unwanted dental effects associated with direct, heavy force application delivered through the teeth. The BAME approach however presents its own potential adverse outcomes of increased risk of local infection due to its invasiveness(8,9) and mild bony palatal indentations assessed to be of no clinical significance(10). The clinical outcomes appear similar between tooth- and bone-anchored approaches with similar results in the assessment of the dental and skeletal changes evaluated *via* cone beam computed tomography (CBCT) images with dental expansion greater than skeletal expansion in both(11).

Orthodontically induced external root resorption (ERR) can be considered to be an important negative sequelae of orthodontic treatment as in severe cases it can impact the long-term viability of the affected dentition. ERR is defined as either a physiologic or a pathologic process resulting in the loss of cementum and dentin in the dental roots(12). The specific incidence of ERR is unknown and its etiology appears multifactorial in nature and is not fully understood with numerous potential elements at play including, but not limited to, individual genetic factors and orthodontic mechanical or iatrogenic factors(13,14). There is evidence that heavy forces are particularly harmful with numerous studies displaying a correlation between increased ERR and heavy orthodontic forces (14-18). Although, if ERR is identified in a timely manner, and the applied orthodontic forces are suspended, the extent of ERR can be reduced (19). Therefore, the early identification of resorptive defects penetrating the cementum appears crucial to minimizing the irreversible loss of external root dentin (20). Accordingly, it would be useful to identify the true amount of ERR associated with various aspects of orthodontic treatment in order to ascertain at which stages or with which mechanics a patient is most susceptible to resorptive defects. There is a need for more evidence to identify those teeth/individuals at higher risk for ERR and to determine ways to manage its severity and prevalence in orthodontic patients (14).

Historically, *in vivo* detection of changes to dental root morphology and ERR during the course of orthodontic treatment has been mainly through use of 2-dimensional (2D) radiographs, most notably periapical radiographs (19,21,22). Although histological studies have identified a relatively high incidence of apical ERR, 2D radiographic studies have been less definitive(13,23) and have in general proven inaccurate for the reliable quantitative detection of small ERR defects(17,24-26). There are geometric limitations associated with 2D imaging of a 3-dimensional (3D) phenomenon; therefore, in reference to 2D detection of ERR associated with maxillary expansion, Barber *et al* stated “the clinician has no way of accurately estimating the full extent of *in situ* root surface resorption caused by expansion treatment.” (27)

The validation of CBCT as a tool for measurement of both root lengths and volumes has been the focus of numerous studies(28-40) and found to be an effective method with a high level of diagnostic accuracy and repeatability(1,2,17,20,29,31) not significantly different from corresponding *in vitro* measurements(35). In fact, *in vivo* volumetric determination utilizing CBCT images has been shown to be accurate in the detection of resorption cavities larger than 3.47 mm^3(41). In addition, a well-defined CBCT segmentation protocol with excellent intra- and inter-rater reliability and precision has been identified in the literature(42).

Due to the additional 3D information that is available through CBCT imaging, investigation appears warranted into the adverse effects that bone-borne and tooth-anchored maxillary expanders (TAME) may have on the anchor teeth due to the differences in the point of application of the lateral expansion force. As sustained heavy forces on the dentition are noted to be particularly harmful from a root resorption perspective, (14) one would intuitively expect that moving the point of force application away from the dentition would mitigate or even eliminate the potential adverse effects of ERR. Knowing the potential side effects associated with an early phase of orthodontic treatment for a maxillary transverse deficient individual may alter treatment mechanics and goals if a second, prolonged phase of orthodontics is anticipated. However, the knowledge of the side effects and their severity are first required, on an *in vivo* basis, if possible.

The objective of this study is to assess through the use of CBCT imaging whether the type of maxillary expansion appliance (BAME versus TAME) has impact on the external root resorption of maxillary first molars.

3.2 MATERIALS AND METHODS

3.2.1 Treatment Groups

The radiographic data set used for the analysis of root volume was previously acquired as part of a randomized clinical trial at the University of Alberta. Informed consent from the patients' parents and ethical approval from the Ethics Committee at University of Alberta was obtained (Appendix A). "Subjects were recruited from the patients at the orthodontic clinic at the University of Alberta in Edmonton, Alberta, Canada, during an 18-month period. Inclusion criteria for selection included maxillary transverse deficient adolescents with no previous orthodontic treatment. A total of 62 patients needing maxillary expansion treatment were randomly allocated into one of three groups: traditional hyrax tooth-anchored maxillary expander (hyrax with bands on the first permanent molars and first premolars), bone-anchored maxillary expander (Hyrax directly attached to the palatal bone), and a delayed treatment control (NO_TX). Age and sex distributions for the three treatment groups can be seen in Table 3.1. The control group had an age approximately 1 year younger than both treatment groups. This was judged to be a coincidental finding due to the randomization procedure (a random number generated list) employed for patient assignment to the three groups. CBCT images were taken at baseline (initial records to plan an orthodontic treatment) [T1] and just before fixed bonding (12 months [T2]). The T2 imaging in the control group was collected as a 2nd set of records to plan their subsequent orthodontic treatment."(11)

"The subjects in the first group received a traditional tooth-anchored maxillary expander (TAME) (hyrax with bands on the first permanent molars and first premolars) as seen in Figure 3.1, A. The expansion screw was activated twice a day (0.25 mm per turn, 0.5 mm daily) until posterior dental crossbite overcorrection was achieved. After active expansion treatment, the screw was fixed with light-cured acrylic and kept in place passively for 6 months. The appliance was then removed and left without retention for an additional 6 months."(11)

"Subjects in the second group received a bone-anchored maxillary expander composed of 2 custom-milled stainless steel onplants (diameter, 8 mm; height 3 mm), 2 miniscrews (length, 12 mm; diameter, 1.5 mm; Straumann GBR-System, Andover, Mass) and an expansion screw (Palex II Extra-Mini Expander, Summit Orthodontic Services, Munroe Falls, Ohio), shown in Figure 3.1, B. This appliance was placed on each side between the projection of the permanent first molars and second premolar roots deep into the palatal vault and 6 mm laterally from the suture. Before appliance placement, the patient was asked to rinse for 2 minutes with chlorhexadine (0.12%). This was followed by local anesthesia infiltration of the palatal mucosa between the first molars and second premolars. An 8-mm diameter tissue punch was used to make a circular incision. Tissue including the periosteum was removed, and the appliance was seated so that the onplant would have maximum direct contact with the bone surface of the palate. Guide drills were used to perforate the cortical plate of the bone, and miniscrews were placed to secure the appliance. Acrylic resin was used to seal the head of the screw to the stainless steel disc and prevent unwinding of the screw during appliance activation. Patients were prescribed oral antibiotics and a chlorhexidine rinse for 5 days to prevent infection. A healing period of 1 week was allowed before activation of the expander. Activation consisted of 1 turn of the screw (0.25 mm per turn) every other day until overcorrection was achieved. After active expansion, the retention protocol was the same as in the TAME group."(11)

"The two treatment groups employed slightly different activation protocols due to the BAME appliance being in its trial period with lack of agreement on an activation rate. The slower rate of activation of the BAME appliance was employed to limit the possible risks of trauma to the palatal shelves. The TAME treatment group employed the traditional 2 turns per day activation protocol."(11)

"The subjects in the third group had treatment delayed for 12 months to serve as a control group. The delay of 12 months had no negative consequences regarding the patients' treatment outcome."(11)

The aforementioned detailed clinical experimental design was obtained directly from a publication by Lagravere *et al* (11).

3.2.2 Cone Beam Computed Tomography Images

All CBCT images were taken with the NewTom 3G (QR, Verona, Italy) device at 110 kV, 6.19 mAs, and 8-mm aluminum filtration in maximum intercuspation following CBCT image protocol. Images were converted to DICOM format by using the NewTom software to a voxel size of 0.25 mm. Avizo 3D analysis software (Visualization Sciences Group, Berlin, Germany) was used to render the DICOM-formatted images into volumetric images(11). All diagnostic records were coded and the principal investigator was blinded with respect to treatment group and timing of each image when analyzing the diagnostic records.

3.2.3 Tooth Volume Measurement Protocol

Avizo 3D analysis software (Visualization Sciences Group, Berlin, Germany) was used to segment the CBCT images to measure the volume of maxillary first molars. Measurements were made employing automated segmentation procedures with manual human refinement on a repeated 2D slice-by-slice basis in all three planes of space with the entire tooth volume (crown and entire root volume inclusive of the pulpal tissue and cementum) measured as per the optimal volume measurement protocol, possessing repeatability and Intraclass Correlation Coefficient (ICC) 95% confidence interval lower bounds of 0.989 for intra-rater and 0.961 for inter-rater reliability, as identified in the literature(42).

Only one investigator segmented and measured the volume of each maxillary first molar tooth in all 62 patients at T1 and T2 given the segmentation technique's excellent intra- and inter-examiner reliability(42).

Root resorption associated with the different treatment modalities, specifically the dental tooth volume of maxillary first molars, was measured for each maxillary first molar tooth and compared between groups.

The maxillary first molar was chosen because of its complex root anatomy, early eruption and completion of root development in orthodontic aged adolescent patients, and its use as an anchorage unit for the maxillary expansion process. Given the patient age range investigated, the completion of root development of the maxillary first molars was assumed as this is highly likely given its comparatively early completion of root development within the permanent dentition.

Given that patient movement during CBCT image acquisition can introduce distortion and significantly reduce the accuracy of volume measurements(38), each patient image at both T1 and T2 was visually assessed for patient movement that produced 'double-images', motion artifacts or blur in the region of interest. If patient movement was evident in the image, the images were not measured and were excluded from the analysis due to the significant limitations and inaccuracies associated with measuring the indistinct borders.

Given the two time points investigated, temporal changes to the coronal tooth structure by either the placement of restorations or fixed restorative materials or advancing dental decay required consideration. Once the image segmentation procedures were completed, the images were again reviewed and the T1 image was visually compared directly with the T2 image for any evidence of the placement of new dental restorative materials or advancing dental decay. This was performed to ensure restorations were not placed in the interim or decay did not grossly progress so as not to introduce an additional source of variability.

Patient movement in the scans was a significant factor affecting data collection. In total, 62 patients were measured for the three treatment groups at both T1 and T2. The BAME group, which originally contained 21 subjects had 2 subjects removed due to excessive patient movement during CBCT image acquisition for a total of 19 BAME subjects remaining. The TAME group, which originally contained 20 subjects, had 2 subjects removed due to excessive patient movement during CBCT image acquisition for a total of 18 TAME subjects remaining. The no treatment (NO_TX) group, which originally contained 21 subjects, had 6 subjects removed due to excessive patient movement during CBCT image acquisition for a total of 15 NO_TX subjects remaining. Overall, 10 patients out of the 62 were removed from the analysis due to excessive movement during CBCT image acquisition.

3.2.4 Statistical Analysis

The volume data was manually entered into Microsoft Excel 2011 for MAC (Microsoft, Redmond, WA, USA). SPSS for MAC (version 21, IBM, Armonk, New York, USA) was used to run all statistical tests. For all tests, statistical significance was set at an α value of 0.05.

A random selection of either the left or right maxillary first molar was completed for each patient to include in the statistical analysis so as not to artificially inflate the sample size or absolute amount of resorption as would occur by including the total resorptive volumes from both teeth together.

Statistical Approach: Analysis of the percentage change scores across the groups using one-way ANOVA.

Percentage of dental volume change [$(T2_{volume} - T1_{volume}) / T1_{volume}$] *100% is the continuous response (dependent) variable. Treatment group (BAME, TAME, or NO_TX) is the categorical independent variable.

Descriptive statistics were generated for each group of independent variables. When assessing the effect of treatment (BAME, TAME, NO_TX) on dental tooth volume, an Analysis of Variance (ANOVA) in conjunction with a post-hoc analysis as required was completed.

The ANOVA hypotheses tested were:

H_0: all group means are equal (i.e., $\mu_{BAME} = \mu_{TAME} = \mu_{NO\_TX}$)

H_A: at least one group mean is different (i.e., they are not all the same)

Prior to performing the ANOVA statistical analysis, the data was checked to ensure the statistical test model assumptions were satisfied.

- Independence of samples
- Absence of outliers

- Normal distribution
- Homogeneity of variances

Common methods of analyzing data with a pre-test/post-test design for more than 2 independent treatment groups include the following:

1. Analysis of the difference scores across the groups using one-way ANOVA.
2. Analysis of the percentage change scores across the groups using one-way ANOVA.
3. ANCOVA using the post-test score across the groups as the outcome variable and the pre-test score as the covariate.
4. A variation of a repeated measures ANOVA in which the pre-test/post-test scores are represented as two levels of a within-subjects factor and the groups as 3 levels of a between-subjects factor.

Given there is no single correct answer regarding which statistical test is better to use, (43) it may be informative to analyze the data using several different methods, while being cognizant of model assumption violations and results of each statistical method in the ultimate interpretation of the data. This was completed and will be stated in the results.

3.3 RESULTS

3.3.1 Preliminary analysis to assess left and right side for differences

A paired t-test was used to assess the similarity of the left and right molars.

The paired t-test hypotheses tested for both T1 and T2 were:

H_0: mean difference between right and left molar volume change is zero (i.e., $\mu_{Difference} = \mu_{R\ molar} - \mu_{L\ molar} = 0$)

H_A: mean difference between right and left molar volume change is not zero.

Assumption checking:

<u>Detecting Outliers</u>: There were outliers present in all groups as assessed by inspection of a boxplot (Figure 3.2) for values greater than 1.5 inter-quartile box-lengths from the edge of the box. The outliers were kept in the analysis, as they were not extreme outliers. A sensitivity analysis was conducted by running the test both with the outliers included and with the outliers removed and comparing the results for similarity. There were no differences detected, therefore the outliers were included in the statistical analysis.

<u>Testing for Normality:</u> ERR volume difference (left minus right) was approximately normally distributed for the BAME, TAME, and NO_TX groups at both T1 and T2, as assessed by visual inspection of Q-Q Plots (Figure 3.3) and boxplots (Figure 3.2).

<u>Testing left versus right for differences:</u>

There was not a statistically significant (p = 0.088) difference between the left and right maxillary first molars measured at T1 irrespective of groups (Table 3.2).

There was not a statistically significant (p > 0.05 for all three groups) difference between the left and right maxillary first molars measured at T1 for each group individually. (Table 3.2)

There was not a statistically significant difference (p = 0.065) between the left and right maxillary first molars measured at T2 irrespective of groups (Table 3.2).

There was not a statistically significant (p > 0.05 for all three groups) difference between the left and right maxillary first molars measured at T2 for each group individually (Table 3.2).

3.3.2 Exploration of data at T1 to assess for initial group differences

Computation of an ANOVA for the random assignment of maxillary first molars at T1 to assess for initial differences among the treatment groups yielded a statistically non-significant result (p = 0.207) (Table 3.3). Therefore, there appears to be no significant random tooth volume difference between groups at T1.

3.3.3 Analysis of the percentage change scores across the groups using one-way ANOVA (random assignment of maxillary first molars)

<u>Detecting Outliers</u>*:* There were outliers present in the TAME group as assessed by inspection of a boxplot (Figure 3.4) for values greater than 1.5 inter-quartile box-lengths from the edge of the box. The outliers were kept in the ANOVA analysis, as they were not extreme outliers. A sensitivity analysis was also

conducted by running a one-way ANOVA and post-hoc tests both with the outliers included and with the outliers removed and comparing the results for similarity.

Testing for Normality: Percentage of dental volume change [($T2_{volume} - T1_{volume}$) / $T1_{volume}$] *100% was normally distributed for the BAME, TAME, and NO_TX groups, as assessed by visual inspection of Q-Q Plots (Figure 3.5) and boxplots (Figure 3.4). Additionally, ANOVA is inherently robust to departures from normality. Although the data samples were not balanced, they were reasonably close to equivalent sizes (19 vs 18 vs 15).

Testing for Homogeneity of Variances: The largest standard deviation (TAME group standard deviation = 4.45) was less than twice (1.72 times) that of the smallest standard deviation (NO_TX group standard deviation = 2.58) of the factors analyzed. Given the sample sizes of each group were approximately balanced, the homogeneity of variances is judged not to be violated for the application of one-way ANOVA.

Descriptive statistics are provided in Table 3.4. Descriptive statistics for the data is presented as mean ± standard deviation in units of percent. The difference in percentage of dental ERR volume loss increased from the NO_TX (-1.07 ± 2.56), to BAME (-2.67 ± 3.28), to TAME (-4.18 ± 4.45) groups, in that order.

The dental ERR percentage volume loss as assessed by ANOVA was not statistically significantly different between different groups $F(2,49) = 3.104$, $p =$

0.054 (Table 3.5). Therefore, we fail to reject the null hypothesis (**H_0**) that all group means are equal.

For a representation of the volume changes for the corresponding percentage differences reported, descriptive statistics of the volume changes are provided in Table 3.6. Descriptive statistics for the data is presented as mean ± standard deviation in units of mm^3. The difference in dental ERR volume loss increased from the NO_TX (-13.15 ± 28.08), to BAME (-31.50 ± 37.31), to TAME (-49.32 ± 53.02) groups, in that order.

The aforementioned sensitivity analysis, which computed an ANOVA with the outliers omitted, yielded identical statistical conclusions as computing an ANOVA with outliers included. Therefore, the outliers were judged not to have an appreciable effect on the analysis and the results are reported with inclusion of the outliers in the analysis.

3.3.4 Summary of comprehensive statistical results

Method of analysis of pre-test and post-test experimental designs:

1. Analysis of the difference scores across the groups using one-way ANOVA.
2. Analysis of the percentage change scores across the groups using one-way ANOVA.
3. ANCOVA using the post-test score across the groups as the outcome variable and the pre-test score as the covariate.

4. A variation of a repeated measures ANOVA in which the pre-test/post-test scores are represented as two levels of a within-subjects factor and the groups as 3 levels of a between-subjects factor.

The statistical conclusions remain the same for each method analyzed at a significance level of $p = 0.05$. There appears to be no statistically significant difference in the volume of ERR loss in maxillary first molars among the three treatment groups (BAME, TAME, NO_TX).

3.4 DISCUSSION

Due to the relatively heavy transverse forces applied to the maxillary dentition in traditional tooth-anchored rapid maxillary expansion therapy, there has been speculation regarding the effect this may have on ERR of the anchor teeth, particularly the maxillary first molars. By moving the point of force application away from the dentition itself, through use of a BAME appliance, the detrimental effect of ERR associated with direct, heavy orthodontic force application delivered through the teeth had wished to be mitigated. This study indicates that there is not a statistically significant difference in the amount of ERR experienced in the maxillary first molar teeth between the three groups both on a percentage basis and on a volume difference. Equivalently it can be extrapolated that neither active treatment approach produced more ERR than what would be expected in a non-treatment/normal growth scenario.

The mean volume loss and corresponding standard deviation in mm^3 as a result of ERR, reported as (mean volume loss in mm^3, standard deviation in mm^3)

for the TAME, BAME, and NO_TX groups were (49.32, 53.02), (31.50, 37.31), and (13.15, 28.08) respectively. The reasons for the relatively large variability is hypothesized to be the result of many factors including individual patient susceptibility, degree of lateral expansion required, amount of force required for lateral expansion, decay of expansion forces after activation, degree of midpalatal suture interdigitation, incomplete dental root formation, imaging technology limitations, and measurement variability. In particular, with respect to measurement variability using the method defined in the literature (42), the measurement error had a range of 1.67 to 17.09 mm^3 with an average of 7.33 mm^3 based on the optimal segmentation method identified.

A comparison of the analysis of the data using ANOVA for volume difference and the percentage volume change was attempted for a few reasons. From the perspective of the size of the tooth roots, there are two potential competing hypotheses regarding the possible effects. Firstly, assuming a larger tooth root volume initially, there exists potentially more surface area available as well. This increased surface area could possibly be susceptible to more resorption on strictly an absolute volume (mm^3) basis, which could artificially increase the absolute amount of resorption experienced when compared to an initially smaller tooth root with potentially less surface area available for the resorptive process. From that perspective, a percentage volume change analysis may be more appropriate. Secondly, and conversely, looking at it from an alternative perspective that assumes a larger tooth has more surface area to resist and dissipate the heavy forces and hence potentially decrease the amount of ERR happening, absolute values may be better to analyze. Essentially, the larger volumes may also serve to dissipate the forces over a larger surface area leading to less resorption happening overall. Given the valid and competing rationalizations on both sides, a decision was made to analyze the data using both methods and assess if there was a difference. As mentioned previously, both approaches to the analysis yielded similar, non-statistically significant ($p > 0.05$) differences between the three groups.

There are a number of dental specific factors that were considered in the design of the study including the presence or placement of restorations, advancing dental decay, pulpal tissues, and tooth chosen to analyze. These will each be addressed in turn.

The presence of radiodense restorative materials, such as amalgam and some highly filled composites, which greatly inhibit the passage of electromagnetic radiation, has the potential to introduce further variability into dental volume determination. The ability of radiodense restorative materials to completely extinguish the x-rays can result in imaging artifacts. These artifacts are most commonly caused by sudden transitions between radiolucent and radiopaque materials and can result in the inability to predictably identify the true extent of the radiodense material or adjacent structures affected by the associated line-artifacts. A few patients in the study possessed restorations on their maxillary first molars, thus creating minor difficulties in identifying the true extent of the coronal tooth structure. However, the differences for these select patients were not identified as data outliers.

The potential of temporal changes to the coronal tooth structure by either the placement of restorations or fixed restorative materials or advancing dental decay was assessed. There was no indication in any of the patient CBCT images of changes in any of the maxillary first molars. Therefore, no omissions of patient data were required from this perspective and no additional variability was experienced as assessed by visual inspection.

In the approaches investigated, the pulpal tissue was included in the volumes. The reason for its inclusion is threefold. Firstly, the additional error in delineating dentin from pulpal tissue is an added source of variability, which could increase measurement variation. An additional dentin/soft tissue border, which is likely more challenging than the tooth to surrounding bony support to identify, due to intricate pulpal canal architecture of small dimension, would require identification (Figure 3.6). Secondly, since our area of interest is only ERR, internal pulpal changes are irrelevant. Thirdly, during the phases of tooth development and maturation, the deposition of secondary dentin has the ability to change the hard tissue volume of a tooth. Secondary dentin is formed after dental root formation is complete, and normally at a stage when the tooth has erupted and is functional in the occlusion. To remove inherent variability due to this phenomenon between time points T1 and T2, the pulpal tissue was included in the tooth volume measurement. If secondary dentin was deposited, or pulpal anatomy difficult to delineate, it would make no difference in our volume measurements as the pulpal tissue was not considered individually. Therefore, both the hard and soft tissues within the cementum of the tooth were calculated as the total tooth volume in agreement with published techniques(42).

The investigation of ERR was limited to maxillary first molars in this study for a number of reasons. The maxillary first molars are the most common point of force application in traditional rapid maxillary expansion techniques and hence of interest to investigate the adverse effects on the anchor teeth. The earliest imaging on any patient occurred at age 11 years 2 months. Given the usual root completion time for the maxillary first molars is age 10.5(44) it is expected that the majority of maxillary first molars are completed their root development at the time of the image acquisition. Patient variations, specifically delays, in the completion of maxillary first molars could possibly account for the few positive changes noted in ERR between time points T1 and T2 as the root could potentially still be completing its development. However, based on patient ages in the study, a very significant developmental delay for the maxillary first molars would have to be present to account for continued root elongation in the minority of patients. The potential for incomplete root development would thus be a limitation in evaluating any permanent tooth in adolescents, but given the comparatively early eruption of the permanent first molars, this limitation is mitigated as much as possible. Through visual inspection of the maxillary first molars investigated, all appeared to have normally expected root anatomy and completion of root development. The positive variation is more likely an issue of measurement variability between time points. Other studies have focused on maxillary premolar ERR associated with expansion(7,27,45). Given that maxillary first and second premolar root development is normally completed by age 13.5 and 14.5 years respectively(44), it is expected in some of the younger patients that the premolar roots are not fully formed, especially the maxillary second premolars. Given the findings by Baysal *et al*(7) that all roots displayed a decrease in mean root volume, there may be the concern that the applied force may disrupt root development; however, flaws in their segmentation procedures, specifically a lack of a clearly defined segmentation protocol and the coronal extent used for the root segmentation with questionable reproducibility, may limit conclusions. With the narrow window for non-surgical maxillary expansion therapies to be effective, it is unlikely studies will be able to rule out the variability due to premolar root formation given the typical patient ages investigated. An exception would be accomplishing maxillary expansion later in life via a surgically assisted approach.

The effects of patient movement were larger than initially anticipated, but the issue is intuitively obvious and not new to the literature(38). Movement in either of the T1 or T2 images resulted in omission of all patient data for both their maxillary first molars as there would be insufficient data to assess ERR from T1 to T2. In total, 10 patients were excluded due to movement during image acquisition. These movements occurred in only one of the two time points for each patient. Given the 124 images acquired in total (T1 and T2), only 10 images, or roughly 8%, possessed patient movement affecting accurate volume measurements of the maxillary first molars. This effect was amplified in our patient data as movement in either T1 or T2 automatically excluded the companion image at the other time point. A stricter clinical imaging protocol with patient education as well as apparatus in place to stabilize the patient's head for the scan duration seem applicable to further enhance the diagnostic strength of the images.

When considering the current literature in the area, there are a number of comparisons and critiques that may be made. The average amount of TAME ERR (-49.32 mm^3 per tooth) was found to be slightly less than a previous study, which also used CBCT to volumetrically assess ERR, when performing intrusion of maxillary molars using mini-screws (-58.39 mm^3) (35). The reasons hypothesized for this minor increase in the amount of ERR with intrusion mechanics as opposed to expansion mechanics could stem from the concentration of forces at the small root apices in intrusion, rather than on the broad buccal root surfaces as seen in transverse maxillary expansion since the concentration of heavy forces has been shown to increase resorption(14).

In general, the body of existing literature is inconclusive in the broad sense regarding the radiographic *in vivo* effects of jackscrew-based maxillary expansion therapy on ERR. Granted, most studies utilized 2D radiographs to assess ERR(27,45) and the presence of CBCT studies(7) on the subject are limited. The limited 3D evidence presented by Baysal *et al*(7) represents the first attempt at the 3D visualization of external root resorption with maxillary expansion; however, their segmentation procedure employing a root-only approach (apical to the CEJ for maxillary premolars and apical to the deepest point of the furcation for maxillary molars) yields the greatest intra-rater variability when segmentation techniques are evaluated(42), so their results may be open to debate. The contributing results of this study, with an improved segmentation approach(42) indicate the lack of statistically significant ERR in anchor maxillary first molar teeth in both traditional TAME and BAME appliances as opposed to the control group. However, the variability in the timing of the active root resorption phase and the reparative phase is unknown and therefore the greatest degree of resorption present is difficult to accurately determine. Since the lateral forces required and the decay of those expansion forces are individual to each patient, the end of the active phase of root resorption is unlikely to be known definitively. Further studies employing 3D evaluation of root resorption with control groups, various appliance designs, retention periods, activation protocols, and timing of radiographic assessment seem indicated to further elucidate the effects.

From a clinical perspective, the issue of individual patient susceptibility requires further attention as the ERR measured in the treatment groups possessed quite a degree of variability. Some experienced very little to no ERR whereas others experienced significant ERR, which was mainly seen in the TAME group due to the presence of several negative outliers in the data acquired (Figure 3.4). These results parallel literature displaying the majority of ERR occurred in a minority of patients(46). Although not statistically significant at a p value of 0.05, the p value was very close at 0.054 and the data seems to display a trend of the mean ERR increasing from the NO_TX (-13.15 mm^3) to the BAME (-31.50 mm^3), to the TAME groups (-49.32 mm^3), possibly indicating there may be an effect based on the expansion appliance used. A statistically significant difference appears to be masked by the relatively large standard deviations of the data, which may potentially be explained by differences in individual patients' physiological response to the expansion forces.

Considerations regarding the time required for segmentation of the 3D images to obtain a quantitative value require mention as a significant time investment may be needed if multiple teeth are to be assessed. In general, an average time requirement of 20 minutes was needed for a maxillary first molar with 3 roots. When applied to a tooth with a single root, an average time of 8 minutes was required for the segmentation procedure. This provides an indication of the time investment needed for accurate segmentation procedures.

The presence of ERR does not result in long-term morbidity for the majority of orthodontic patients. However, the small subset of patients who experience moderate to severe ERR encourage researchers to improve the diagnostic tests that will identify the early stages of ERR in order to alter treatment mechanics or goals. The complicated and elusive multifactorial etiology of ERR susceptibility means clinicians must still rely on radiographic screening tools available to them to detect ERR both before and during active orthodontic treatment mechanics. With improvements in hardware and software imaging technologies, alongside careful consideration to ionizing radiation exposure, orthodontists may soon be able to routinely monitor ERR and, as a consequence, be better equipped to respond to ERR progression and hence minimize morbidities associated with root destruction.

3.5 CONCLUSIONS

- There exists no statistically significant difference of absolute values or percentage change scores in the amount of ERR experienced in maxillary first molar teeth between the BAME, TAME, and no treatment groups.

Table 3.1 Age and sex distribution for the three groups.

		Age (years)	
Treatment	*n*	*Mean*	SD
BAME			
Male	8	14.13	1.58
Female	13	14.31	1.07
Total	21	14.24	1.32
TAME			
Male	5	14.54	1.19
Female	15	13.89	1.32
Total	20	14.05	1.35
Control			
Male	6	13.13	1.42
Female	15	12.75	1.03
Total	21	12.86	1.19

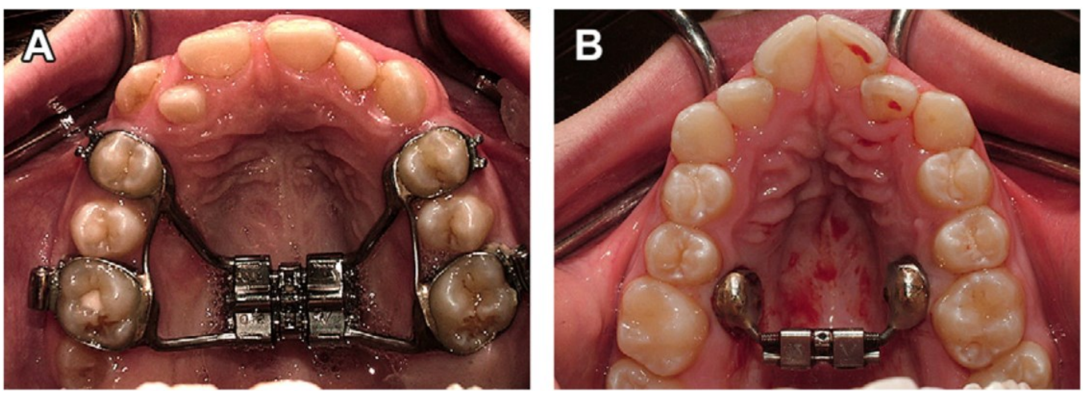
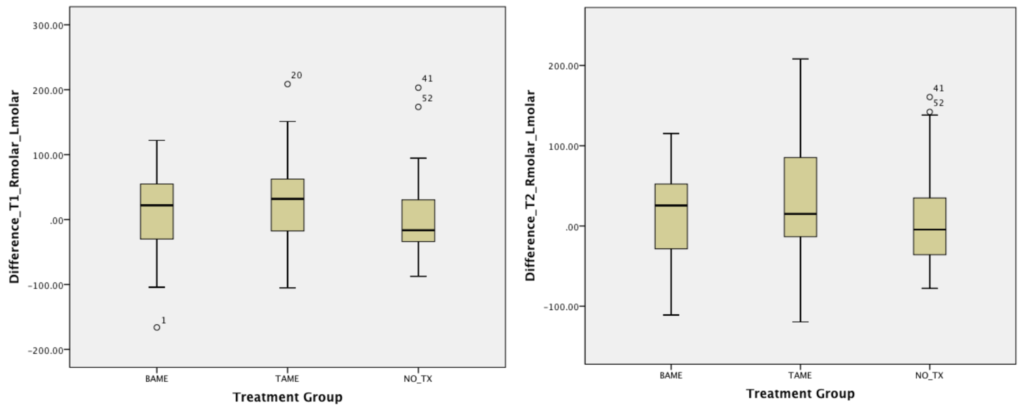


Figure 3.1 Type of maxillary expansion appliances used. A. Tooth-anchored maxillary expander. B. Bone-anchored maxillary expander.

(11)



*Difference units in mm^3 *Difference units in mm^3

Figure 3.2 Boxplots to assess outliers

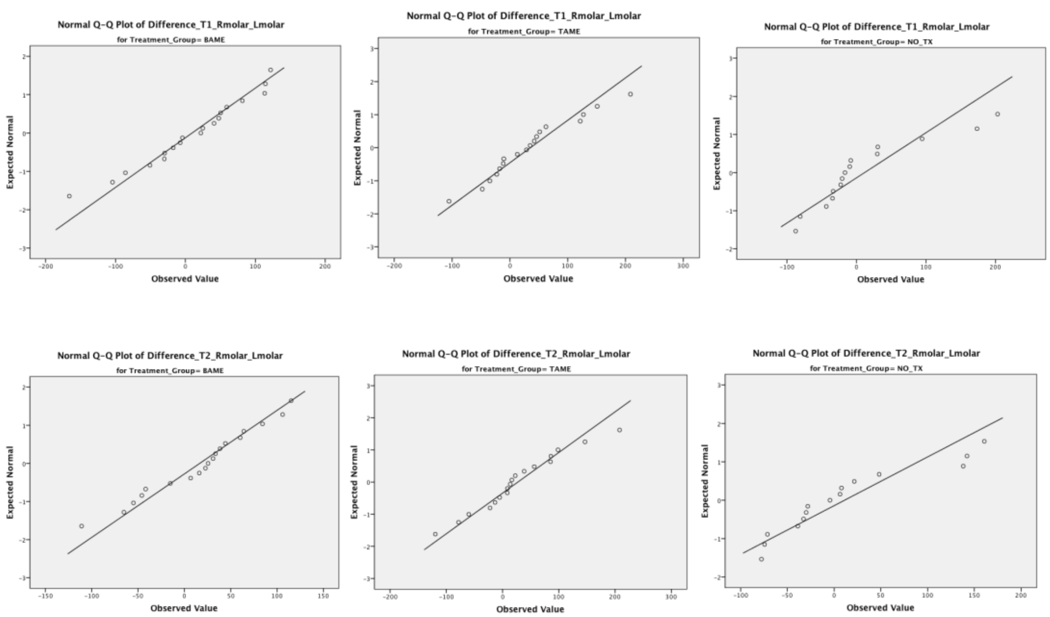


Figure 3.3 Q-Q plots to assess for normality of difference scores

Table 3.2 Paired samples tests *p* values

Test	*p* value
Paired samples test between left and right maxillary first molars at T1	0.088
Paired samples test between left and right maxillary first molars group BAME at T1	0.600
Paired samples test between left and right maxillary first molars group TAME at T1	0.071
Paired samples test between left and right maxillary first molars group NO_TX at T1	0.603
Paired samples test between left and right maxillary first molars at T2	0.065
Paired samples test between left and right maxillary first molars group BAME at T2	0.245
Paired samples test between left and right maxillary first molars group TAME at T2	0.162
Paired samples test between left and right maxillary first molars group NO_TX at T2	0.593

Table 3.3 ANOVA of random maxillary first molars at T1

ANOVA

Random_T1

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	90806.244	2	45403.122	1.629	.207
Within Groups	1365915.77	49	27875.832		
Total	1456722.01	51			

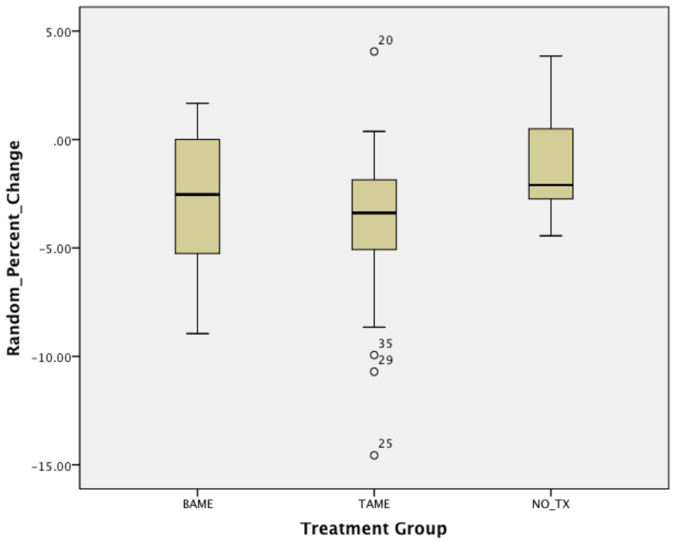


Figure 3.4 Boxplots of individual group percentage change scores

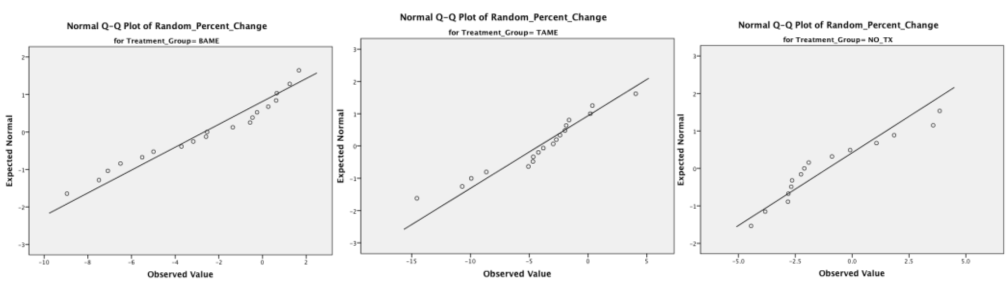


Figure 3.5 Q-Q plots to assess for normality of percentage change scores

Table 3.4 Descriptive statistics for individual group percent change

Descriptives

Random_Percent_Change

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
BAME	19	-2.6702	3.27739	.75188	-4.2498	-1.0905	-8.96	1.67
TAME	18	-4.1770	4.45015	1.04891	-6.3900	-1.9640	-14.56	4.06
NO_TX	15	-1.0729	2.57770	.66556	-2.5004	.3546	-4.44	3.85
Total	52	-2.7310	3.71002	.51449	-3.7639	-1.6981	-14.56	4.06

Table 3.5 ANOVA of percent change scores

ANOVA

Random_Percent_Change

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	78.945	2	39.472	3.104	.054
Within Groups	623.031	49	12.715		
Total	701.976	51			

Table 3.6 Descriptive statistics for individual group volume changes

Descriptives

Random_Difference

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
BAME	19	-31.5040	37.30504	8.55836	-49.4844	-13.5235	-87.93	18.08
TAME	18	-49.3177	53.01899	12.49669	-75.6834	-22.9520	-154.26	47.66
NO_TX	15	-13.1487	28.08256	7.25089	-28.7003	2.4029	-45.93	41.50
Total	52	-32.3755	43.06952	5.97267	-44.3661	-20.3849	-154.26	47.66

*Random_Difference units in mm^3

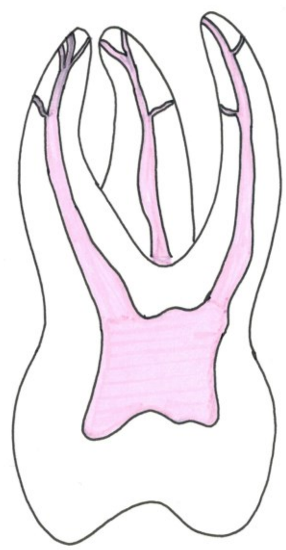


Figure 3.6 Example of pulpal canal architecture

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Chapter 4 – General Discussion

4.1 GENERAL DISCUSSION

Cone beam Computed Tomography (CBCT), since its introduction in the late 1990's, appears likely to be the most significant imaging advancement related to the field of dentistry. The technological advancements have progressed so rapidly resulting in decreased size, cost, and patient radiation exposure that in-office dental CBCT machines are now commonplace. The technological advancements have indeed outpaced the knowledge of what phenomenon relating to the field of dentistry we may accurately and reliably measure from the images themselves.

The advent of CBCT imaging has equipped clinicians and researchers with the ability to visualize in detail a patient's hard and soft tissues *in vivo* with reduced radiation dose compared to traditional medical CT imaging(1). In relation to the field of orthodontics, CBCT has enhanced the detection and visualization in areas such as external root resorption (ERR) (2-16), craniofacial growth patterns and development(17), impacted teeth and eruption pathways(18) bony defects including dehiscence and fenestration(19) and treatment related changes in addition to numerous other areas of interest. The use of CBCT imaging has not only improved diagnostic potential for certain dentistry-related phenomena, but numerous studies have employed CBCT to measure volumes of a variety of structures and materials *in vivo*. The highly accurate and reproducible volumetric data that may be acquired from CBCT images ranging from information on sinus graft materials(20) to condylar head morphological changes(21) to upper airway changes associated with treatment of obstructive sleep apnea(22-25) yields potential for investigations into a variety of subjects.

The exponential increase in the amount of radiographic information available from CBCT images is not without certain drawbacks. Additional patient radiation dose compared to traditional 2D imaging, increased expense, and the clinician's diagnostic needs must be carefully evaluated(1). Simply the clinician's desire for additional information does not necessarily match their diagnostic need for information as reviews have shown a lack of evidence supporting improvements in orthodontic diagnosis and treatment planning decisions(26,27). There exist certain areas where CBCT imaging proves useful such as impacted teeth, supernumerary teeth, ERR detection, surgical treatment planning, airway evaluation and additional areas where traditional 2D radiographs are unable to provide sufficient information(26,27). The clinician should therefore be responsible in assessing the patient's diagnostic imaging needs to effectively treat the presenting conditions with as low a radiation dose as possible.

The improvement in certain CBCT diagnostic abilities, including the detection of ERR(26), is difficult to quantify given the unfamiliar accuracy with which volumes in a CBCT image may be computed due to the challenges associated with image segmentation techniques. In order to perform the ultimate goal of *in vivo* detection of ERR in a retrospective study, a reliable CBCT image segmentation protocol had to be established, and was hence the initial study of this thesis(28). The initial study demonstrated that CBCT segmentation procedures employed for volume measurement of maxillary first molars is a repeatable and reliable process both intra- and inter-examiner when utilizing certain segmentation techniques. A maxillary first molar dental volume measurement protocol for CBCT images employing automated grayscale thresholding with manual human refinement on a 2D slice-by-slice basis in all 3 planes of space possessed excellent intra- and inter-rater reliability and precision(28). The method resulting in the worst intra- and inter-examiner reliability was the protocol that employed automated thresholding without human refinement due to issues with determination of boundaries with the cortical plates, adjacent dense lamina dura, proximity of erupting maxillary second molars, dense furcation areas, interproximal contacts, and dense bone islands.

Maxillary first molar 3D volume measurements of the entire tooth structure were more precise than 3D volume measurements of only the dental roots apical to the CEJ. The entire maxillary first molar volume, both crown, root, and pulpal tissues, was determined as the most accurate segmentation procedure. The reasons for this were numerous and included difficulties in the identification of the thin enamel of the CEJ as the anatomical crown transitions into the root, the large axial dental volume at the CEJ, and difficulties in delineating intricate pulpal canal architecture within the roots.

Given the usefulness of CBCT imaging in reliably measuring dental volumes, the second study of this thesis utilized the image segmentation protocol developed in the first study to retrospectively measure ERR *in vivo* associated with various designs of transverse maxillary expansion appliances. It was hypothesized that due to the relatively heavy transverse forces applied to the maxillary dentition in traditional tooth-anchored maxillary expansion (TAME) therapy, that movement of the point of force application away from the dentition itself and onto the bony skeletal base would serve to mitigate the adverse ERR effects proposed to be associated more strongly with TAME.

The investigation of a traditional TAME contrasted with a bone-anchored maxillary expansion (BAME) appliance was investigated against a control group (NO_TX) receiving no treatment. Based on the results, a statistically significant difference in the amount of ERR experienced in maxillary first molar teeth between the BAME, TAME, and NO_TX groups was not observed. A great deal of individual patient variability was present as seen in the spread of the data captured. The variability in the timing of the active root resorption phase and the reparative phase is unknown and therefore the greatest degree of resorption present is patient and appliance dependent and hence difficult to accurately determine.

A general summation of the conclusions reached from the aforementioned chapters, including the systematic review, is as follows:

- 2D periapical radiographs do not reveal external root resorption associated with maxillary expansion therapy, except for frank apical root resorption.
- 3D CBCT radiography displays statistically significant root volume loss associated with maxillary expansion therapy. However, when considering volume loss percentages, no statistical significance was found.

- The proposed maxillary first molar dental volume measurement protocol for CBCT images employing automated segmentation with manual human refinement on a repeated 2D slice-by-slice basis in all 3 planes of space possesses excellent intra- and inter-rater reliability and precision.
- Maxillary first molar 3D volume measurements of the entire tooth structure are more precise than 3D volume measurements of only the dental roots apical to the CEJ.
- There exists no statistically significant difference of absolute values or percentage change scores in the amount of ERR experienced in maxillary first molar teeth between the BAME, TAME, and no treatment groups.

4.2 STUDY LIMITATIONS

1) Due to the retrospective nature of the current study and lack of access to the CBCT machine used to collect the data, limitations were imposed upon our ability to verify the accuracy of the 3D dental tooth volume measurements. Focus was turned to precision and reproducibility of the dental tooth volume and measurements from both an intra- and inter-examiner perspective to address the inherent limitation. The published literature confirmed our image segmentation techniques were appropriate as utilized in studies that verified the volume measurements(29). However, even if the CBCT machine had been available to use, the maxillary first molars are teeth not commonly extracted for orthodontic purposes, so validation of a molar tooth volume imaged *in vivo* would be extremely challenging and be a significant limitation to determining measurement accuracy. In addition, studies that validate volumes of extracted premolars have

the issue of measuring a tooth with only a single root and no complex furcation area as is present in maxillary first molars.

2) The CBCT resolution of 0.25 mm, when balanced with patient radiation dose appears adequate to measure ERR predictably(16). However, improved CBCT resolution could have improved the visualization of smaller resorptive defects not detected with a 0.25 mm resolution(15).

3) The partial volume effect, a phenomenon associated with CBCT imaging as a whole, limits the differentiation of different tissue types at the border between materials. Increased resolution could limit the errors associated with the partial volume effect; however, patient radiation dose would be sacrificed.

4) Patient movement during CBCT image acquisition presented a larger effect than initially anticipated. Movement in either of the T1 or T2 images resulted in omission of all patient data for both maxillary first molars. A stricter clinical image acquisition protocol with patient education as well as an apparatus in place to stabilize the patient's head for the scan duration seem indicated to further enhance the diagnostic strength of future studies.

5) There exists the potential for incomplete root formation of the measured maxillary first molars resulting from delays in eruption. This was not apparent in the results, but could not be confirmed.

6) The collection of additional patient data at intermittent time points would be advantageous from a research perspective. This would allow identification of

additional periods of root resorption. When active resorption ceases and reparative process begin are patient dependent, but additional imaging could supply more information. However, this additional information would be unjustified at the expense of increased patient radiation dose.

4.3 FUTURE RESEARCH

Additional topics of study that could complement the research completed in this thesis are numerous. To remove the inherent variability that may be present with continued dental root development during the expansion process, studies employing adult patients requiring surgically assisted rapid palatal expansion could be attempted. Given the findings by Baysal *et al*(2) that all roots investigated (maxillary first premolars, second premolars, and first molars) displayed a decrease in mean root volume with maxillary expansion; there may be the consideration that the applied force may disrupt root development.

It would be beneficial for future 3D studies to address whether RME results in shorter/decreased volumes of roots on average as compared to a control group being subjected to no active treatment. Studies employing the collection of additional patient radiographic data at intermittent time points would be advantageous from a research perspective. This would allow identification of additional periods of root resorption. When active resorption ceases and reparative process begin are patient dependent, but additional imaging could supply more information. However, patient radiation exposure and diagnostic imaging needs require a careful balance to be established. The uses of CBCT imaging are to maximize the diagnostic information available to the clinician while limiting patient radiation exposure to make individualized treatment decisions while considering as many patient specific factors as possible.

In addition to investigating the effects of different maxillary expansion appliances on ERR, the investigation of different expansion activation protocols could be assessed. This would serve to establish if the expander activation protocol, either slow or rapid palatal expansion, has any appreciable effects on the amount or extent of ERR.

Similarly, investigating whether the amount of lateral expansion has an influence on ERR could be assessed. This would allow investigation into whether a longer period and distance of active expansion (at a controlled rate) has more detrimental effects than a shorter period and distance of lateral expansion.

On a related note, given the effects of tooth apex displacement with associated ERR, an assessment of ERR in relation to dental tipping of the tooth within the alveolus could be investigated to determine its effect.

Another potential avenue for further research involves a combined CBCT plus histological assessment of ERR associated with maxillary expansion. The reason being is that the reparative processes for ERR with the subsequent deposition of hard tissue within the resorption lacunae has been shown to have effects on periodontal fiber attachment in the area of reparative cementum deposition. (30,31) A study(32) investigating anchor teeth during retention periods of 14 to 53 weeks revealed sparse and inconsistent Sharpey's fibers depression into the cellular cementum that was different from that of normal cellular cementum. This perhaps can lead to an underestimation of the detrimental effects associated with ERR as repair of a root defect by cellular cementum is not necessarily synonymous with principal periodontal fiber reattachment in those areas. Simply visualizing the surface area or volume of hard tissue in the root may not provide a corresponding accurate estimation of viable surface area with periodontal fiber attachment. Hence, although the root volume may not decrease significantly, the resorptive and subsequent reparative processes may have a more substantial and detrimental effect on the surface area for periodontal ligament support. Perhaps the most accurate indication of the long-term support and viability of teeth having undergone resorption is the determination of the resorptive process at its most progressive with the assumption of a loss of periodontal attachment fibers in these areas. Further investigation is warranted both on a histological and an *in vivo* 3D radiographic approach.

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APPENDIX A: Ethics Approval

Health Research Ethics Board

308 Campus Tower
University of Alberta, Edmonton, AB T6G 1K8
p. 780.492.9724 (Biomedical Panel)
p. 780.492.0302 (Health Panel)
p. 780.492.0459
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Health Approval - HIA No Consent

Date:	October 18, 2013
Study ID:	Pro00042519
Principal Investigator:	Manuel Lagravere Vich
Study Title:	External root resorption associated with bone-anchored maxillary expansion and traditional rapid maxillary expansion as measured through cone beam computed tomography: a retrospective study
Approval Expiry Date:	October 17, 2014
Sponsor/Funding Agency:	McIntyre Fund - Division of Orthodontics - Department of Dentistry

Thank you for submitting the above study to the Health Research Ethics Board - Health Panel . Your application, including revisions received October 16 and 18, 2013, has been reviewed and approved on behalf of the committee.

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. It has been determined that the research described in the ethics application is a secondary analysis of medical data originally collected under the context of another research study for which subject consent for access to personally identifiable health information would not be reasonable, feasible or practical. Subject consent therefore is not required for access to personally identifiable health information described in the ethics application.

In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (October 17, 2014), you will have to re-submit an ethics application.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health approvals should be directed to (780) 407-604. Enquiries regarding Covenant Health approvals should be directed to (780) 735-2274.

Sincerely,

Glen J. Pearson, BSc, BScPhm, PharmD, FCSHP
Associate Chair, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).

UNIVERSITY OF ALBERTA   Alberta Health Services   Covenant Health