Anterior and Middle Cranial Base Growth and Development Changes as Assessed Through CBCT Imaging in Adolescents

by

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Abstract

Introduction: In this study three dimensional Cone beam computed tomography is used to evaluate intra-rater, inter-rater and accuracy of selected 3D landmarks of anterior and middle cranial bases. Growth related dimensional changes of anterior and middle cranial base structures are then assessed in adolescents with the use of landmarks.

Methods: CBCTs of 10 dry skulls were used to assess reliability and accuracy of landmarks. Secondly, CBCTs of adolescents at two time points (19 months apart) were assessed for dimensional changes due to growth using the landmarks selected in the first step.

Results: The majority of proposed 3D landmarks with the exception of lesser wing and foramen *Spinosum* showed acceptable intra-rater and inter-rater reliability and accuracy. Minor changes were observed in the anterior and middle cranial base structures due to growth.

Conclusion: The mid-sagittal area of the anterior cranial base from foramen *Caecum* to the *presphenoid* area in the antero-posterior dimension was found to be stable. Minor growth related dimensional changes were observed in the anterior and middle cranial bases in adolescents. The magnitude of the changes were very small and could be reflective of measurement error.

Preface

This thesis is an original work by Mona Afrand. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “Anterior cranial base changes assessed through CBCT”, No. 43800, February 6, 2014.

The systematic review in Chapter 1 of this thesis has been published as Afrand, M., Ling, C. P., Khosrotehrani, S., Flores-Mir, C., & Lagravère-Vich, M. O. Anterior cranial-base time-related changes: A systematic review. American Journal of Orthodontics and Dentofacial Orthopedics, 2014, 146(1), 21-32. I was responsible for the data collection and analysis as well as the manuscript composition. Ling, C.P. and Khosrotehrani, S. assisted with the data collection and contributed to manuscript edits. Flores-Mir, C., & Lagravère-Vich, M. O. were the supervisory authors and were involved with concept formation and manuscript composition.

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I would also like to acknowledge with gratitute the love and support of my husband Siamak and my parents. This work is dediacted to my deareset son who is the reason for me to keep going.

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Chapter 1: Introduction and systematic review of literature

1.1 Statement of problem

A stable reference structure is required for standardized records of dento-facial structures relationships assessed at different time points. Anterior cranial base structures' two-dimensional anterior-posterior stability have been showcased repeatedly (1). The most widely accepted method uses the anterior cranial base sagittal dimension (SN line) to superimpose two or more serial cephalometric tracings when evaluating the relationship of craniofacial structures at different time points (2). To our knowledge three-dimensional changes in size and displacement of the cranial base structures has not been reported yet. In order to evaluate the three-dimensional stability of the cranial base, first, the intra-rater and inter-rater reliability and accuracy of selected landmarks in the cranial base must be examined. Secondly, the changes in the linear measurements derived from previously proposed and validated landmarks should be evaluated at least at two different time points.

1.1.1 Research questions

Two research questions were identified:

Question #1:

a) Within the anterior and middle cranial bases, which landmarks are the most repeatable (intra-rater reliability) and reproducible (inter-rater reliability) on three-dimensional craniofacial images?

b) Are the best landmarks identified while answering the first question accurate and represent the anterior and middle cranial base structures?

Question #2: Are the anterior and middle cranial base structures dimensionally stable during adolescent years?

1.2 Systematic review of literature: Anterior cranial base time-related changes

Afrand, M., Ling, C. P., Khosrotehrani, S., Flores-Mir, C., & Lagravère-Vich, M. O. (2014). Anterior cranial-base time-related changes: A systematic review.American Journal of Orthodontics and Dentofacial Orthopedics, 146(1), 21-32.

1.2.1 Introduction

An understanding of craniofacial growth is crucial for an improved diagnosis, treatment planning, outcome evaluation and long term stability.(3)Historically orthodontists have used the cranial base structures as a reference structure to evaluate craniofacial growth. The anterior cranial base is considered to have completed its most significant growth prior to other facial skeletal structures.(4)Because of this, the anterior cranial base has long been considered as a stable craniofacial structure to be used for cephalometric superimpositions during the usual orthodontic treatment age range.(3,5)

The cranial base is initially formed in cartilage but then ossification centers appear early in embryonic life and with time they progressively replace the cartilage with bone. However, some cartilaginous growth centers called synchondrosis remain active in between ossified areas and mature at different time points of life. Bastir *et al* (4)described that the earliest structure to mature in shape and size in the skull was the midline cranial base (7.7 years).However, this has been lately questioned. Malta *et al (6)* found that the anterior cranial base is not stable in size and grows during all the pubertal phases (CS1 to CS6 cervical maturation stages). They reported that the anterior cranial base length (*Sella* to *Nasion*) increases until early adulthood.

Various methods have been described to evaluate craniofacial growth. Craniometry was the first measurement approach for evaluating growth since the

fifteenth century.(7)The advantage of this technique is that precise measurements can be made on dry skulls, but the limitation is that all the growth data collected is cross sectional.(3) Anthropometry was then used, as it is possible to follow up growth directly on each subject. Despite its accuracy and being regarded as the gold standard, obtaining growth measurements through direct measurements is difficult because they are time consuming, and require patient compliance to remain still for long period of time.(8) Early in the 1900's serial photographs started to be used to assess facial growth. However, they only show trends of growth rate and direction, and they lack accuracy for some measurements. Later during the last century metallic implant radiography method was instituted and provided new information about the growth pattern but the disadvantage was that it required placing implants on the subjects, which is not considered ethical anymore.(9) Vital staining methods were also used in experimental animals to evaluate growth, but because of its invasive nature they have only been used in humans to diagnose areas of rapid bone remodeling.(10)

Soon after the invention of the technique of lateral cephalometric x-ray in the 1930's, this technique became the most common way to evaluate facial growth among orthodontists. The disadvantage of this imaging technique is that three-dimensional structures are represented in two-dimensions. Several morphometric tools such as thin-plate spline analysis, elliptic Fourier analysis, finite element analysis and tensor shape co-ordinate analysis have been applied to two-dimensional cephalometric comparison. These methods have allowed for visualization of morphological changes without need for typical reference structures.(11)

In the late 1990's, three-dimensional (3D) digital imaging technique was introduced. This technique provides comprehensive information regarding anatomical relationships and eliminates some of the limitations encountered studying two-dimensional images.(12) Laser surface scanning and three-dimensional stereophotogrammetry methods are also result of recent technological advancements in three-dimensional imaging, however they are usually only applicable in three-dimensional facial surface scanning.(8)

As it can be perceived from this introduction, multiple methods have been used through the years to analyze craniofacial changes. Even though the anterior cranial base has been considered stable and used as the reference structure for superimposing radiographs, this has lately been questioned. As the use of the anterior cranial base as a reference structure is of paramount importance in orthodontics it would be extremely useful to do a comprehensive analysis of the evidence that is available to question its stability. Therefore the purpose of this systematic review is to give an overview of the studies evaluating growth and development of anterior cranial base, assess their methodological quality and evaluate their validity and accuracy.

1.2.2 Material and Methods

This systematic review was reported by using the PRISMA checklist as a template.(13)

In phase 1, only the titles and abstracts collected from the electronic database searches were considered. Articles that assessed craniofacial growth or analyzed treatment outcome but had a control group without treatment were considered. No

language limitations were applied. Studies assessing fetal growth with photographs only or assessing *frontal* x-rays only were excluded. Animal studies were also excluded.

In phase 2, in which copies of full articles were reviewed from those selected in phase 1, some articles were excluded if they did not specifically evaluate cranial-base growth, or if they were reviews or case reports. Ultimately, all included studies must have assessed the growth and development of the anterior cranial-base structures.

With the assistance of a senior health-sciences librarian, we conducted a computerized systematic search in 2 electronic databases. Medline (via OvidSP) and Embase (via OvidSP) were searched from their earliest records until June 15, 2013. The bibliographies of the selected articles were also hand searched for additional relevant studies that might have been missed in the electronic searches. In addition, a limited gray literature search was conducted with Google Scholar.

Specific medical subject headings and keywords were used in the search strategy of Medline (Table 1.1). The search strategy for the Embase database was derived from the former and was modified appropriately (Appendix 1.1). In both steps of the review process, 2 reviewers (M.A. and C.P.L.) independently reviewed titles and abstracts according to the inclusion and exclusion criteria noted above. Disagreements between the 2 reviewers were resolved through discussion until consensus was achieved.

Table 1.1 Search strategy for MEDLINE via OVIDSP (1950 to the present)

Search group	Medical subject heading (MeSH) or key word
1	Maxillofacial development/OR growth/
2	*skull/or *ethmoid* bone/or exp facial bones/or exp skull base/or exp*sphenoid* bone/OR exp *mandible/or *maxilla/OR cranial base.mp
3	Cephalometry/is, mt, st, td, ut [Instrumentation, Methods, Standards, Trends, Utilization] OR exp Cone-Beam Computed Tomography/is, mt, st, td, ut [Instrumentation, Methods, Standards, Trends, Utilization] OR exp Imaging, Three-Dimensional/is, mt, st, td, ut [Instrumentation, Methods, Standards, Trends, Utilization] OR superimpos*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] OR exp Methods/is, mt, st, ut [Instrumentation, Methods, Standards, Utilization]
4	1 AND 2 AND 3

Limitation: human subjects.

In both steps of the review process, 2 reviewers (M.A. and C.P.L.) independently reviewed titles and abstracts according to the inclusion and exclusion criteria noted above. Disagreements between the 2 reviewers were resolved through discussion until consensus was achieved.

From the articles that met the inclusion criteria, the same 2 reviewers extracted the data independently in duplicate. They compared the extracted data and resolved discrepancies by reevaluating the literature until consensus was achieved.

The data from the studies that met the inclusion criteria were study design, population characteristics (sample size, sex, age), method used to analyze cranial-base growth, results (e.g. change in percentage), and reliability and validity of the reported method (Table 1.2).

Table 1.2 .Summary of characteristics of included articles

	Article	Study design	Sample size and sex	Age	Method	Growth percentage	Results	Validity/ Reliability
1	Malta *et al* 2009 (6)	Longitudinal	36 f=21 m=15	Mean age at T1=10.4 (SD 0.98) ▪T1 Pre-peak (CS1 & CS2) ▪T2 Peak (CS3 & CS4) ▪T3 Post-peak (CS5 & CS6)	▪Lateral cephalometry ▪Linear measurements at T1,T2,T3 S-Ba , S-N, Ba-N, CC-Ba, CC-N, FC-Po	S-N: T1-T2: 3.5% increase (P<0.001) T2-T3: 4.0% increase (P<0.001) T1-T3: 7.1% increase (P<0.001)	▪The cranial base grows during all the pubertal phases. ▪The largest growth is during the interval between the pre-peak and the peak phases ,decreasing in the post-peak period. ▪This data shows that cranial base growth occurs until adulthood.	▪Inter-reliability determined for CVM, tracings and landmarks. ▪Intra-reliability of measurements determined, no measurement error reported ▪ICC reported more than 0.95 (0.946-0.998)
2	Jiang *et al* 2007 (14)	Longitudinal	28 f=15 m=13	Annual records from 13 to 18 years of age	▪Lateral cephalometry ▪Modified mesh diagram analysis ▪Scaled average 18 years diagram superimposed on the 13 year's average diagram	N/A	▪ The anterior crania base continues to grow and the length increases during the study period. ▪In females most structures increased in size uniformly across the 6 years of growth. There is disproportionately enhanced growth of the anterior cranial base upward in males only	▪ Reliability determined (does not mention intra or inter) ▪Measurement error: No more than 0.04 (Dahlberg's formula)
3	Franchi *et al* 2007 (15)	Longitudinal	34 f=10 m=24	▪T1 Prepubertal CS1 Mean age: 10 yrs ▪T2:Post pubertal SC6	▪Lateral cephalometry ▪Thin plate spline analysis registered at Ba,S, Na	S-N: T1-T2 : 7.1% increase (P<0.05)	▪The longitudinal changes in the shape of the cranial base from T1 through T2 were not significant ▪On the other hand, differences in (centroid) size changes were significant.	▪Intra-reliability determined for landmarks and CVM. ▪landmarks measured twice and the average was taken. No values reported.

4	Lewis *et al* 1988 (16)	longitudinal	20 f=12 m=8	▪ T1 : 17 or 18 years ▪ 3 to 8 succeeding x-rays for every one ▪One x-ray between 40 and 50 yr	▪Lateral cephalometry ▪S-N, Ba-N, Ba-S measured	N/A	▪ The mean age at which the maximum lengths were identified ranged from 29 to 39 years among the various dimensions. ▪There was small but real increments of growth after 17, 18 years.	None
5	Melsen 1974 (17)	Cross-sectional	126 f=50 m=76	Ages 0 to 20	▪Autopsy tissue blocks ▪Conventional histological and macroradiography ▪Categorized bone surfaces based on growth activity 1. apposition 2. resorption 3. inactivity	N/A	▪The *Cribriform* plate was stable after the age of 4. ▪ *Jugum Sphenoidale* (t-plane) showed appositional growth up to 4-5 ys and again in the pre-pubertal period. ▪Growth of both spheno-*ethmoidale* and *fronto-ethmoid* synchondroses completed by age 7 ▪ *Tuberculum sella* showed variable growth pattern until age 18. ▪ Anterior wall of *sella* was stable after age 5-6 ▪ posterior wall of *sella* showed resorption until 14-17(m&f) ▪ The *Sella* point moves downward and backward. ▪ The anterior part of the *sella* was the most stable in almost all individuals over 5 years old ▪Changes in *SellaTurcica* were due to resorption activity in the lower half of the posterior wall and the floor to some degree.	▪Reliability: two sets of double registration, a repeated blind registration of the first set of sections. Magnitude of error due to inconsistancy in the registration procedures was of order of 10%. No other values reported.

6	Steuer 1972 (18)	Longitudinal	54 f=31 m=23	▪Age range: 5-11 ys ▪40% of cases 8-10 ys ▪Annual x-rays ▪5 patients had 5 yrs interval records, one 7 years and one 8 years ▪Total 274 comparisons	▪Lateral cephalometry ▪Tracing from *dorsum sella* to planum sphaniodale was divided in to seven segments ▪At least three segments should be congruent for valid superimposition.	N/A	▪95 % of comparisons up to 5 years apart had 3 or more segments congruent, which indicates that superimposition on the middle outline of *sphenoidal* portion of cranial base is acceptable during the usual orthodontic age range, but generally the trend is toward less congruence with time because of slight craniofacial growth changes. ▪Deepening of the *hypophysial* fossa was noted in the recall group of seven cases that the cephalograms were taken a number of years after the last one.	▪None
7	Knott 1971 (19)	Longitudinal	66 f= 19 m=23	▪Measurement at ages T1:6, T2:9, T3:12 and T4:early adulthood ▪Mean age: males 25.1 ys females 25.8 ys ▪ 2/3 of subjects at age 15	▪Lateral cephalometry(Norma Lateralis Roentgenograms) ▪Linear measurements: N-F, F-W, W-P, P-O •Angular measurements: NPO, FPO, WPO	NF+FW+WP (N-S): T1-T3(6-12): 6.1% increase(no P-value) T3-T4 (12-adult): 5.1% increase(No P-Value) *Frontal* segment NF: T1-T4: 3.3% increase ($P<0.01$)	▪From age 6ys to age 12 ys for each sex, the *frontal* segment increases in average size by 2.8 mm, the *ethmoid* segment by 1.0 mm, no change in average size for the *presphenoid* dimension. ▪Downward movement of *Nasion* is found in measurements from the line extended through the *frontal* point and the *sphenoid* wing point and also relative to the line through the F and P points. The increase in NPW angle indicates upward movement of *Nasion* relative to *Presphenoid* segment.	▪Intra-reliability of measurements determined in instances greater than 0.2mm (average obtained).

8	Melsen 1969 (20)	Cross sectional	132 Dried skulls sex: Not specified	▪ 48: All Primary dentition erupted ▪64:Mixed dentition ▪20: 8s fully erupted	Lateral cephalometry of the skull ▪22 linear measurements & 2 angular	N-S: Primary-8s erupted: 10% increase Mixed-8s erupted: 2.3% increase S-S':(depth of *Sella Turcica*): Primary-8s erupted: 2.3% increase (No P-values)	▪ The reference point Sella, on an average was moved 2 mm downward and backwards in relation to the *Tuberculum Sella* from the full primary dentition stage to the stage when canines and premolars erupting, which indicates eccentric growth of the *sella turcica*.	▪Intra-reliability: measurements repeated on 10 skulls from different ages. No systematic error revealed. No values reported.
9	Stramrud 1959 (21)	Cross sectional	464 All males	▪ Individuals from 3 to15 years (average 30 individuals in each age group) and adults from 19 to 25 (34 cases)	▪ Lateral roentgenograms ▪7 linear measurements and 9 angular measurements	N/A	▪The anterior cranial fossa (N-S minus the thickness of the *frontal* bone) increases in length markedly until age 7 and then there is a slight increase until age of puberty. ▪ The *frontal* bone thickness increases from age 3 to adulthood. ▪ *Nasion* tends to move downward during growth when the internal cranial base flattens out and upward when a deflection of the internal cranial base takes place.	▪None(systematic error mentioned in some tables)

10	Ford 1958 (22)	Cross sectional	71 Sex:Not specified	Age : 0 to over 20	▪Dried skulls (measured by divider and ruler) ▪7 linear measurements	N/A	▪Pituitary point- *Nasion* dimension continues to grow after eruption of first permanents molars (6-8 ys) ▪The *cribriform* plate completes its growth by the age of 2 years ▪ The *Spheno-mesethmoid* synchondrosis ceases growth completely by age 7 ▪ Increase in the thickness of the *frontal* bone accounts for increase in the Pituitary point-*Nasion* diameter after eruption of the permanent first molars. This is associated with the increase in the size of the *frontal* sinus.	▪None
11	Bjork 1955 (23)	Longitudinal	243 All males	T1: 12 yrs T2:20 yrs	▪Lateral cephalometry ▪Anterior cranial base structural superimposition technique	N-S: T1-T2: 6.6% increase (No P value)	▪ The cranial base is elongated due to apposition at the glabella region ▪Eccentric remodeling of the *Sella Turcica* during growth results in displacement of the midpoint (S) backward and downward or upward ▪ In 90% of cases only a very small change could be detected relative position of the contour of the *ethmoid* plate relative to N-S line.	▪None

All selected studies were evaluated for bias methodologically according to a non-validated modified quality assessment instrument for clinical trials used by Gordon et al (24) (Table 1.3). Since all selected articles were observational, the criterion of the instrument was adjusted to evaluate this study type. The criteria assessing "randomization," "blinding," and "timing" were eliminated from the quality assessment tool, and a criterion to assess "validity" of the method was added. Articles with a score of 50% or less were categorized as poor or low quality. Good quality articles had scores over 50% and up to 75%. Any article receiving a score greater than 75% was considered to have high or excellent quality. If the collected data were considered to be adequate, a meta-analysis would have been planned.

Table 1.3 Methodologic scoring for the included studies

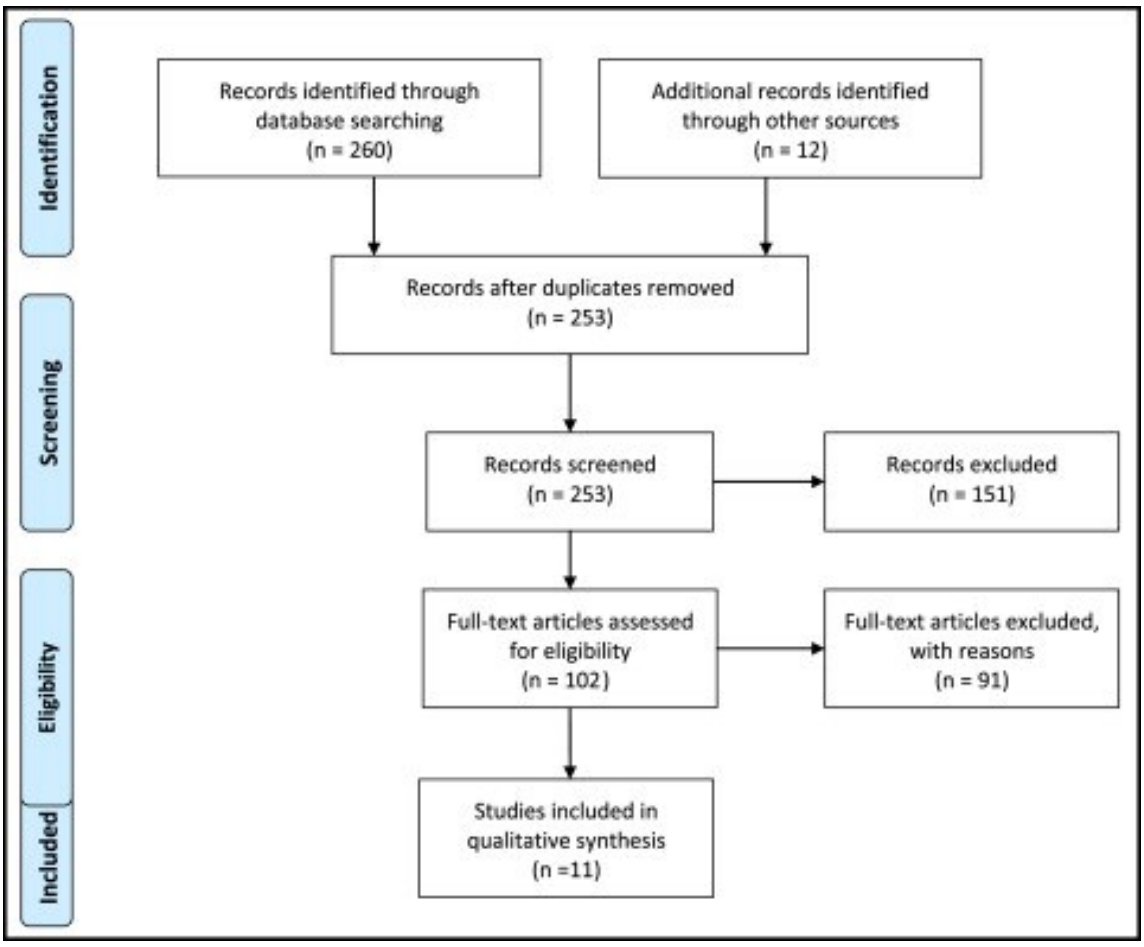
Study design (6 ✓)
A. Objective—clearly defined (✓)
B. Population—adequately described (✓)
C. Sample size—considered adequate (✓)
D. Selection criteria—clearly described (✓), adequate (✓)
E. Follow-up length—clearly described (✓)
Study measurements (4✓)
F. Measurement method—mentioned (✓), appropriate (✓)
G. Reliability—described (✓)
H. Validity—described (✓)
Statistical analysis (3✓)
I. Statistical analysis—appropriate (✓)
J. Presentation of data—exact *P* value stated (✓), variability measures (SD or CI) stated (✓)

Maximum number of ✓ = 13.

1.2.3 Results

A flow chart representing the selection of articles in each stage of the systematic review is presented in Figure 1.1. Searches of electronic databases, partial grey literature and Google Scholar resulted in 253 original articles. We were able to retrieve all the selected articles for full text assessment except for one article (25). Based on title and available abstract, only a total of 94 articles met the initial inclusion criteria and were selected for full article review. After a phase 2 review process, only11 articles satisfied the selection criteria. Eighty-three articles failed to satisfy the second set of selection criteria thus were excluded (Appendix 1.2).

Figure 1.1 Flow diagram



A summary of key data and results of the selected articles is presented in Table 1.2. The articles are mostly longitudinal studies, except for 4 cross-sectional studies(17,20-22). They are all in English and they were published between 1955 and 2009. Their sample sizes ranged from 28 to 464 individuals. Five studies did not report any reliability assessment.(21-23)(16,18) The accuracy of the measurements was not determined in any study.

The methodologic appraisal of risk of bias is outlined in Table 1.4. The methodologic quality of the studies ranged from moderate to low. Common weaknesses were failure to justify or calculate the sample size (all studies), insufficient statistical reporting (16,18,20,22,23) and failure to validate the accuracy of the findings(16-18,20-22).

Table 1.4. Methodologic scores of selected articles

Table 4. Methodological Score of Selected Articles												
Article	**Study design**					**Study measurements**			**Statistics**		**Total**	**% of Total**
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**		
Bjork A.1955	✓	≠	x	x✓	✓	✓✓	✓	x	#	xx	7	53.8%
Ford EHR.1958	✓	✓	x	✓✓	x	✓≠	x	x	x	xx	5.5	42.3%
Stramrud L. 1959	✓	✓	#	xx	x	xx	x	x	✓	✓✓	5.5	42.3%
Melsen B.1969	✓	#	#	##	x	✓#	#	x	#	#✓	7	53.9%
Knott GB.1971	#	✓	x	✓✓	✓	x#	#	x	#	x✓	7	53.9%
Steuer I. 1972	✓	✓	#	✓✓	✓	x#	x	x	#	xx	6.5	50.0%
Melsen B. 1974	✓	✓	✓	##	x	##	x	x	#	xx	5.5	42.3%
Lewis BL. 1988	✓	#	#	✓#	✓	##	x	x	#	#x	6.5	50.0%
Franchi *et al* 2006	✓	✓	x	✓✓	#	✓#	#	x	✓	✓✓	9.5	73.0%
Jiang *et al* 2007	✓	✓	x	✓#	✓	✓✓	#	x	#	✓✓	9.5	73.0%
Malta *et al* 2009	#	#	x	✓✓	✓	##	#	x	✓	✓✓	8.5	65.3%

A to J: methodological criteria in Table 3.
(✓) Fulfilled satisfactorily the methodological criteria (1 check point).
(≠) Fulfilled partially the methodological criteria (0.5 check point).
(x) Did not fulfill the methodological criteria (0 check point).

The studies that quantified the growth of the anterior cranial base, which is usually delineated in cephalometric studies by *Sella* and *Nasion,* demonstrated that the length of the anterior cranial base continues to increase during the adolescent years (average of 7.1% increase from CS1 to CS6).(6,15) Some studies reported forward movement of *nasion* until adulthood.(22,23) Finally, one study that followed the subjects until 40 to 50 years of age demonstrated small increments of growth in adulthood, and the maximum length was reached around 29 to 39 years of age.(16)

Histological and dry skull cross sectional studies reported that the *cribriform* plate completes its growth the latest by the age of 4 years. (17,19,22) Bases on this, it has been proposed that the *cribriform* plate is the first component of the anterior cranial base to reach its final development state.

Three studies with different methodologies (histology, dry skull measurements and longitudinal cephalometry) confirmed that the Spheno*ethmoid* synchondrosis ceases growth by age 7 (17,19,22) , therefore, the *presphenoid* region (the plane surface on the *sphenoid* bone, in front of *sella turcica*) is considered stable after age 7.

Downward or upward movement of *nasion* was reported by 1 study (19), and downward and backward displacement of *sella* was observed in 4 studies.(17,18,20,23)

A meta-analysis was not possible because the methodologies of the selected studies were too heterogeneous to justify combination of the study results.

1.2.4 Discussion

In this review, we aimed to analyze studies that had evaluated the growth of different areas of the anterior cranial base and evaluate their methodologic quality. Our results indicate a consistent agreement that the anterior cranial base as a whole is not a stable structure, and different areas of this structure complete growth at different stages of life. Considering that the anterior cranial base is composed of *frontal* (which includes *nasion*), *ethmoid, presphenoid* and *Sella tursica (*which includes *sella*) regions, based on the studies in this review, the *presphenoid* and the *ethmoid* regions should be considered as fully developed before the usual orthodontic age (by age 7 for the *presphenoid* and by age 4 for the *ethmoid* regions); however the *frontal* and *Sella Turcica* regions continue remodeling until early adulthood.

A longitudinal study of serial cephalometric radiographs reported only a 1-mm average increase in the length of the *ethmoid* region from ages 6 to 12 years.(19) The magnitude of this measurement most likely has no significance and could well be due to measurement errors. Moreover, measurements in millimeters should be taken with caution because they can be misleading and a source of error. Reporting changes in percentages would be more appropriate because these would take individual variations into consideration. One could argue that locating the *cribriform* plate structure on the lateral cephalometric radiographs can be difficult because of overlapping of bilateral structures in this area. Therefore, identifying and using the *cribriform* plate as a reference structure for 2-dimensional growth studies require high-quality lateral x-rays and experienced eyes. However, overlapping of structures is of no concern in three-

dimensional imaging techniques; thus, considering the *cribriform* plate in a three-dimensional superimposition could be valuable.

The *presphenoid* region's antero-posterior length was reported to be stable after the age of 7 years as assessed by different methods.(17,19,22) Some appositional activity was observed in the histologic assessments of the *presphenoid* region in the prepubertal stages.(17) Even though the appositional activity in this region would not change the length of *presphenoid* region, it would modify its height. Therefore, caution should be exercised when using this structure as a reference because it could lead to inaccurate vertical evaluation of growth.

It has been stated in the literature that about 86% of the growth of the anterior cranial base is considered complete by the age of 4.5 years; however, the remaining growth contributes to increases in the length of the anterior cranial base (*sella-nasion*) even after puberty.(26)

Increases in the thickness of the *frontal* bone, apposition in the glabella region, and increases in the size of the *frontal* sinus contribute to increases in the length of the anterior cranial base and forward movement of *nasion* until adulthood (3.3% increase in the *frontal* bone segment from age 6 until early adulthood, $P < 0.01$, as reported by Knott (19)).(21-23) A cross-sectional study assessing the growth of children from 3 years of age to early adulthood found that the distance from *nasion* to the nearest point on the internal contour of the *frontal* bone increases linearly during those years.(21) Even though the cross-sectional data of this study did not give information about individual variations of growth, the results agree with longitudinal evaluations of growth.

One longitudinal study reported that *nasion* moves downward or upward, depending on the angle measured or relative to the structures in the cranial base where the measurement was made.(19) The counteracting results reported in this study could be due to weak or no statistical analysis, depending on the measurement. The amount of upward movement of *nasion* was statistically insignificant (less than 1) over a 2year period. Measurement error was not reported. Whether *nasion* moves downward also remains questionable for the same reasons. No other studies evaluated the direction of movement of *nasion* during growth. Because *nasion* is outside the anterior cranial fossa, it is possible that it migrates during growth, since it is influenced by several structures: eg, the *frontonasal* suture, the *frontal* sinus, and the growth of the cranial base.

A unique histologic study of the cranial base showed that as a result of remodeling of the *sella* region, *sella* will be displaced downward and backward relative to the anterior wall of *sella turcica*.(17) Therefore, the size of *sella turcica* increases. The anterior part of *sella* was the most stable, and resting (inactive) bone was observed in almost all subjects over 5 years old. Changes in *sella turcica* were most likely to some degree due to resorptive activity in the lower half of the posterior wall and the floor. A 5-year longitudinal study evaluating exclusively the growth of the area, from *planum sphenoidale* to *dorsum* sella, indicated that this area has reasonable stability to be used for superimposition, but the same study mentioned that the *hypophysial* fossa deepened in a small sample of subjects who were observed for longer than 5 years. (18) Bjork (23) who presented the *sella-nasion* line as a stable reference for superimposing, also observed eccentric remodeling of *sella turcica* during growth,

resulting in displacement of *sella* downward and backward. He also recorded an elevation of the *tuberculum sella* in relation to other structures of the anterior cranial fossa. He might have taken into account the counteracting resorptive and appositional remodeling processes in the *sella* region and assumed that *sella* remains stable. With these observations, it seems that downward and backward displacements of *sella* occur during growth.(17,18,20,23) A cross-sectional study detected only a 2.3% displacement of *sella* from the deciduous dentition stage until adulthood.(20) The significance of the movement of *sella* remains to be investigated. Because resorption takes place on both the floor and the rear wall of *sella turcica*, both height and length of these structures would be affected, as well as the angular measurements of *sella* used in cephalometric analyses.

The *sella-nasion* line is a frequently used reference line to assess growth of both jaws; however, both *sella* and *nasion* could be displaced during growth and give rise to erroneous results when that line is used as the reference.(5) Technologic advances in imaging could be used to assess the changes of the anterior cranial-base structures during growth to obtain accurate results of the true changes in this area. For accurate results, interpretation of facial changes should be done only by superimposing on truly stable structures.

Limitations

Two-dimensional cephalometry is the most common technique used to evaluate growth of the cranial base.(6,9,11,14-16,18-21,27,27,28) All the studies that were considered to have good methodologic quality also used lateral cephalometric technique to

evaluate growth.(14,15,17,19,20) The studies with other techniques did not meet the requirements and were categorized in the poor-methodologic-quality category. The reason could be that more recent studies, which followed more rigorous statistical and methodologic protocols, used lateral cephalometric analysis to evaluate growth. Intra-examiner and inter-examiner reliabilities of landmark identification and measurement accuracy usually should be reported to validate the findings of the cephalometric analysis. Among the studies selected for this review, only 5 reported some kind of reliability measurements,(6,14,15,17,19,28) and only 1 study reported the Intraclass coefficient (6). No authors validated their findings and measurements.

No three-dimensional studies have yet quantified the growth of the anterior cranial base. A possible explanation might be that researchers pioneering these relatively new methods are still examining applications of three-dimensional imaging techniques. Most of the studies selected for this review were identified through hand searching.

Only 3 studies were selected through the systematic search.(6,15,18,28) The possible explanation could be that some of these studies were not indexed for MeSH terms in the databases, or the studies were published before the databases started. Possibly, eligible studies could have been missed in this stage, and this could have resulted in failure to identify all relevant reports and in selection bias.(29) Commonly accepted techniques to conduct a systematic review were used.

The quality of the studies was rated by 1 examiner (M.A.). Absence of 1 standard tool to assess the quality of observational studies could be an unavoidable risk of bias because the use of a nonvalidated tool has its own drawbacks.(30)

Of the selected studies, 4 evaluated the anterior cranial base from a cross-sectional database. Cross-sectional studies of growth have limited applications because they give no information about individual variations during growth.(12)

Most of the selected studies were published during the last century (1955-1988). (16-23) Many were incomplete, had poor descriptions of their methods, and were weak in statistical analysis and reporting of their findings. Some authors−eg, Ford (22), Steuer (18), and Melsen (17,20) are considered pioneers in this field, and their studies are referenced in many articles published today. These studies were unique and valuable when they were conducted, but they lack the major methodologic qualities of current research standards.

1.2.5 Conclusions

1. A consistent agreement was identified that the anterior cranial base as a whole is not a stable structure. Different areas of this structure complete growth at different stages of life.

2. The *cribriform* plate was found to be the first structure in the anterior cranial base to complete growth (by age 4), followed by the *presphenoid* region (by age 7), making them the best cranial-base superimposition areas.

3. *Sella turcica* remodels and moves backward and downward during growth. Bone apposition in the *frontal* region and the increase in the size of the *frontal* sinus (both affecting *nasion*) contribute to the increase in the length of the anterior cranial base (delineated by the *sella-nasion* distance) until adulthood.

1.2.7 Appendices

APPENDIX 1.1 SEARCH STRATEGY FOR EMBASE VIA OVIDSP (1974 TO PRESENT)

Search group	Medical subject heading (MeSH) or key word
1	exp maxillofacial development/ OR Growth/
2	exp *skull/ or anterior cranial fossa/ or *ethmoid* bone/ or facial bone/ or jaw/ or mandible/ or maxilla/ or middle cranial fossa/ or *sella turcica*/ or skull base/ or *sphenoid*/OR cranial base.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3	exp three-dimensional imaging/ OR exp cone beam computed tomography/ OR exp cephalometry/ OR superimpos*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] OR procedures/ or "imaging and display"/ or "mathematical and statistical procedures"/ or medical procedures/ or "photography and film"/ or "prediction and forecasting"/ or radiological procedures/
4	1 AND 2 AND 3

Limitations: Human subjects.

APPENDIX 1.2 ARTICLES EXCLUDED IN PHASE 2

Author	Reason
Muretic *et al* (1)	•Cranial base growth was not assessed
Cudia *et al* (2)	•Cranial base growth was not assessed
Bondi (3)	•Cranial base growth was not assessed
Colangelo *et al* (4)	•Cranial base growth was not assessed
Springate (5)	•Not assessing cranial base growth •No superimposition
Bartzela *et al* (6)	•Not assessing cranial base growth. •No superimposition.
Jahanbin *et al* (7)	•Anthropometric technique using only photographs • Not following growth.
Nielsen (8)	•Explains about structural analysis •Review article
Liu *et al* (9)	•Comparing a group of treated cases craniofacial characteristics with healthy individuals. •Cranial base not covered.
Kau *et al*(10)	•Longitudinal study of one case •Digital stereo photogrammetric surface acquisition •Assessed soft tissue changes
De Clerck *et al* (11)	•Not assessing cranial base growth •No superimposition.
Tai *et al* (12)	•Not assessing cranial base growth
Cevidanes *et al* (13)	•Not assessing cranial base growth
Cevidanes *et al* (14)	•Not assessing cranial base growth
Murata *et al* (15)	•Not assessing cranial base growth •No superimposition.
Cevidanes *et al* (16)	•Procruste analysis • Not assessing cranial base growth
Alexander *et al* (17)	•Just stated which technique used, no other details •Cranial base growth not covered
Standerwick *et al* (18)	•Not assessing cranial base growth
Baccetti *et al* (19)	•No superimposition on cranial base •Cranial base growth not assessed
Standerwick *et al* (20)	•Not assessing cranial base growth

Stahl *et al* (21)	•No superimposition on cranial base •Cranial base growth not assessed
Gu (22)	•No superimposition on cranial base •Cranial base growth not assessed
Turchetta *et al* (23)	•Procruste analysis •Cranial base growth not assessed
Penin (24)	•Just explaining Procruste superimposition technique
Thordarson *et al* (25)	•No superimposition, studying different individuals of different age •Cranial base growth was not assessed
Wahl (26)	•Review
Simon (27)	•Procuste analysis •Cranial base growth was not assessed
Veleminska *et al*(28)	•Creates a system to predict facial growth
Chang *et al* (29)	•Just mentioned were superimposed •Cranial base growth was not assessed.
Sakima *et al* (30)	•The stability of the cranial base sutures was not assessed
Greiner e*t al* (31)	•Not assessing growth
Goel *et al* (32)	•Not assessing cranial base growth.
Veleminska *et al* (33)	•2 groups of patients compared •Cranial base growth was not assessed.
Langford *et al* (34)	•Measuring maxillary volume on MRI on different age groups of children
Danguy *et al* (35)	•Explains architectural analysis
Guyot *et al* (36)	•Soft tissue analyzed
Alkhamrah *et a*l (37)	•Referenced to another article for the technique •Cranial base growth was not assessed.
Driscoll-Gilliland *et al* (38)	•Just mentions natural structures used for superimpositioning •Cranial base growth was not assessed.
Rothstein *et al* (39)	•Cross sectional data •Cranial base growth was not assessed.
Haffner *et al* (40)	•Explains how to orient three-dimensional xray
Efstratiadis *et al* (41)	•looked at mandibular movement •Cranial base growth was not assessed.
Breitsprecher *et al* (42)	• Cranial base growth was not assessed
Rousset *et al* (43)	• Cranial base growth was not assessed
Kusnoto *et al* (44)	•Not well explained exact landmarks and orientation of superimpositioning. •Cranial base growth was not assessed.

Buschang *et al* (45)	• Cranial base growth was not assessed.
Kapust *et al* (46)	•Cranial base growth was not assessed.
Pae (47)	•No superimposition •Cranial base growth was not assessed.
Hall *et al* (48)	•Only evaluating treated individuals.
Battagel (49)	•Not evaluated cranial base, just maxilla and mandible and soft tissue
Ferrario *et al* (50)	•Cranial base growth was not assessed
Isaacson (51)	•Review/editorial
Jensen *et al* (52)	• Cranial base growth was not assessed
Iseri *et al* (53)	•Cranial base growth was not assessed
Battagel (54)	•No superimpositioning, compared shape changes •Cranial base growth was not assessed
Huggare *et al* (55)	•Cranial base growth was not assessed
Buschang *et al* (56)	• Cranial base growth was not assessed
Cope *et al* (57)	•Cranial base growth was not assessed
Doppel *et al* (58)	•Cranial base growth was not assessed •Maxillary superimpostion method
Solow *et al* (59)	•Cranial base growth was not assessed
Vallee-Cussac (60)	Cranial base growth was not assessed
Coben (61)	•Review
Korn *et al* (62)	•Only assessed maxilla and mandible • Cranial base growth was not assessed
Jakobsson *et al* (63)	•Cranial base growth was not assessed
Motoyoshi *et al* (64)	•Cranial base growth was not assessed
Nielsen (65)	•Only maxillary superimposition discussed
Peltomaki (66)	•Cranial base growth was not assessed
Odegaard (67)	•Was not able to retrieve
Arai *et al* (68)	• Only orthodontically treated cases studied
McDonald (69)	•Case report
Lavelle (70)	•Cranial base growth was not assessed
Zeng (71)	•Cranial base growth was not assessed

Solow *et al* (72)	•Cranial base growth was not assessed
McNamara *et al* (73)	•Does not assess cranial base, only jaws
Burke *et al* (74)	•Soft tissue facial changes assessed
Son *et al* (75)	•Cranial base growth was not assessed
Baumrind *et al* (76)	•Cranial base growth was not assessed
Moss *et al* (77)	•Describing a new method to analyze growth •Cranial base growth was not assessed
Todd *et al* (78)	•Review
Coutand *et al* (79)	•Maxillary superimposition used
Lundstrom *et al* (80)	•Cranial base growth was not assessed
Fischer (81)	•Comparing different superimposition methods • Cranial base growth was not assessed
Oberholzer *et al*(82)	•Review
Cleall e*t al* (83)	• Cranial base growth was not assessed
Mills *et al* (84)	•Cranial base growth was not assessed
Shuff (85)	•Cranial base growth was not assessed
Moorrees *et al* (86)	•Describing mesh diagram method
Cronqvist (87)	•Cranial base growth was not assessed
Baume (88)	•Review
Hoyte (89)	•Review
Ranly (90)	•Review
Scott (91)	•Review

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Chapter 2: Anterior and middle cranial base landmark accuracy and reliability in three-dimensional imaging

2.1 Introduction

The cranial base represents the floor of the cranial cavity and separates the brain from other facial structures. It grows primarily by endochondral ossification of the synchondroses. Even though the synchondroses grow independently, growth of the brain tissue potentially influences the growth of cranial base as well.(31) The anterior cranial base is considered to have completed its most significant growth prior to other facial skeletal structures (4); therefore, cranial base structures and its landmarks have been used extensively as a stable reference structure in orthodontic diagnosis and treatment planning.

Thus far, two-dimensional cephalometry has been the tool most orthodontists use to complement their diagnosis and treatment planning, as well as to monitor the treatment progress. However, malocclusion is a three-dimensional problem that simultaneously affects anterior-posterior, vertical and transverse planes. Consequently, orthodontists are welcoming three-dimensional imaging techniques such as CBCT in their practices hoping to optimize diagnosis and treatment planning when it's use is indicated and justifiable.

CBCT images represent true anatomic linear measurements (1:1 ratio) of three-dimensional structures.(32) In addition, it has been shown that the linear measurements on three-dimensional surface models with a voxel size of 0.25 and 0.40 were accurate when compared with direct caliper measurements (absolute error of (0.05 ± 0.04 mm) for the 0.4-voxel group and (0.07 ± 0.05 mm) for the 0.25-voxel group. ICC>0.99).(33)

Linear and angular measurements have been used since the advent of lateral cephalometric radiographs by Broadbent (34) in early twentieth century to study

orientation of craniofacial structures and the amount of their displacement in time.(35) Linear and angular measurements are anchored in landmarks. Therefore, reliability and accuracy in identifying landmarks are important factors to minimize measurement errors. Even the smallest errors in landmark identification could potentially be a source of substantial error in overall treatment process.(36)

Reliability of a measurement establishes the degree the measurement procedure can be replicable. Landmark reliability assessment is twofold. Intra-rater reliability exhibits repeatability or the degree of stability when a measurement is repeatedly produced by the same rater under the same conditions. Intra-rater reliability determines reproducibility or the degree of the stability of a measurement when different raters repeat the measurements under the same conditions.(37)

There are many factors influencing landmark identification reliability. Quality of radiographic image, geometry of the structure to be identified, clarity of the definition of the landmark, operator experience level and contrast of the structure with the adjacent structures could all affect the reproducibility in landmark identification.(38-40,40)). Landmark identification error should not be ignored due to its potential magnitude. (41,42) Also, the degree of landmark identification error differs from landmark to landmark because of difficulty in accurately locating them.(43)

Three-dimensional landmarks have some advantage over two-dimensional location of landmarks.(38,44) Head positioning, rotational and geometric errors in two-dimensional imaging may easily affect the location of the landmark or lead to poor visualization. Inferior precision and accuracy of two-dimensional landmark location reproducibility is well documented in the literature.(41,45-47) In three-dimensional

landmark identification the problems with anatomic superimposition and magnification are avoided and allows a less distorted and unobstructed view of craniofacial structures(46), therefore a more precise location of the landmarks is expected.

Some studies have investigated clinical significance of intra-rater and inter-rater reliability of two-dimensional landmark identification. Errors of 0.59mm in the x-axis and 0.56 mm in the y axis were reported as with acceptable accuracy in a meta-analysis.(48) A systematic review also concluded that landmark error can be reduced by repeated practice and gaining experience to within 0.5 mm for two-dimensional CT.(38) Oliveira *et al* (49,50) reported the inter-rater mean value differences of three-dimensional landmarks on CBCT ≤ 1 mm in 76.6 % of the landmark coordinates and only in 2.2% the mean exceeded 2 mm. Variations less than 1 mm in three dimensional cranial base landmark on CBCT has been considered not clinically significant by Lagravère et al (40).

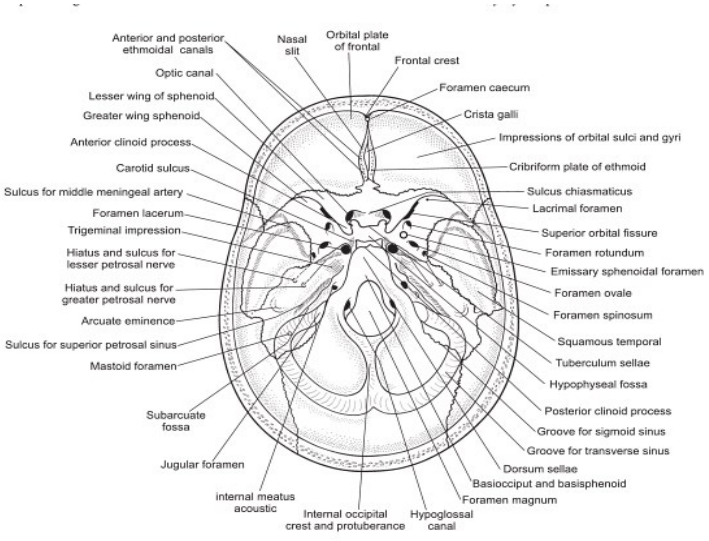
Landmarks with highest reproducibility should be identified and considered in angular and linear measurements to minimize measurement errors and reinforce reliability of diagnostic interpretations from cephalometric analyses whether in two-dimensional or three-dimensional.

The purpose of this study was to identify three-dimensional anatomical landmarks in the anterior and middle cranial bases (Figure 2.1 and Table 2.1.) that are accurate and reproducible on CBCTs, with the purpose of using them to assess the cranial base growth through linear measurements.

Table 2.1 Anatomic structures constructing the anterior and middle cranial bases (51)

	Anterior border	Floor	Posterior border
Anterior cranial base	-*Frontal* bone	-*Orbital* plate of the *frontal* bone -*Cribriform* plate of the *ethmoid* bone -Anterior part of the *sphenoid* body and its lesser wings	-Lesser wings -Anterior *clinoid* processes – -*Tuberculum sellae*
Middle cranial base	-Posterior border of the lesser wings -Anterior *clinoid* processes -Anterior border of the sulcus chiasmaticus of the *sphenoid* bone.	-Body and greater wings of the *sphenoid* bone -*Squamous temporal* - Anterior surface of the *petrous temporal* -Anterior inferior angle of *parietal* bone	-Superior border of the *petrous temporal* -Posterior *clinoid* processes -*Dorsum* sellae

Figure 2.1 Anatomy of the cranial fossae



2.2 Methods and materials:

Ten well-preserved, dry skull specimens were used in this study. The skulls were mounted in a double-layered Plexiglas box (26 X 24.6 X 22 cm). The outer compartment of the box was 5.1 mm at the base and 2.5 cm wide on each side. The outer compartment was filled with water in order to simulate soft tissue attenuation without changing the CBCT machine settings (Figures 2.2 and 2.3).(40)The specimens were mounted onto a pedestal inside a CBCT scanner (ICAT, Imaging Science International, Hatfield, PA, USA). A standardized protocol of the ICAT was used (large field of view 9inx12in, voxel size 0.30mm, 120kVp, 23.87mAS, 8.9 seconds).

Figure 2.2 Plexiglas containing a skull mounted in I-CAT machine

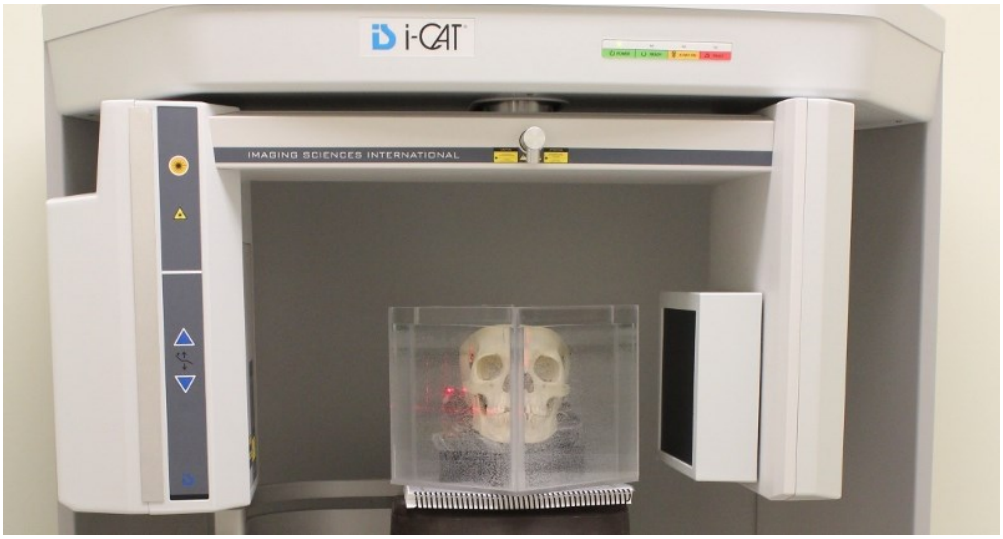


Figure 2.3 Plexiglas filled with water

Each skull was imaged two times, once without any radiopaque material (Gutta Percha, Dentsply-Maillefer, Tulsa, OK) and the second time with radiopaque material placed to locate selected anatomical landmarks (Figure 2.4 and 2.5). These references (radio-opaque material) identify the true anatomical location of landmarks. The landmarks selection was based on visual inspection of the dry skulls for canals, foramina, intersection of sutures, and tip of a projected structures that were identifiable in the anterior and midline cranial bases.

Figure 2.4 Dry skull marked with Gutta Percha (CBCT image on the right)

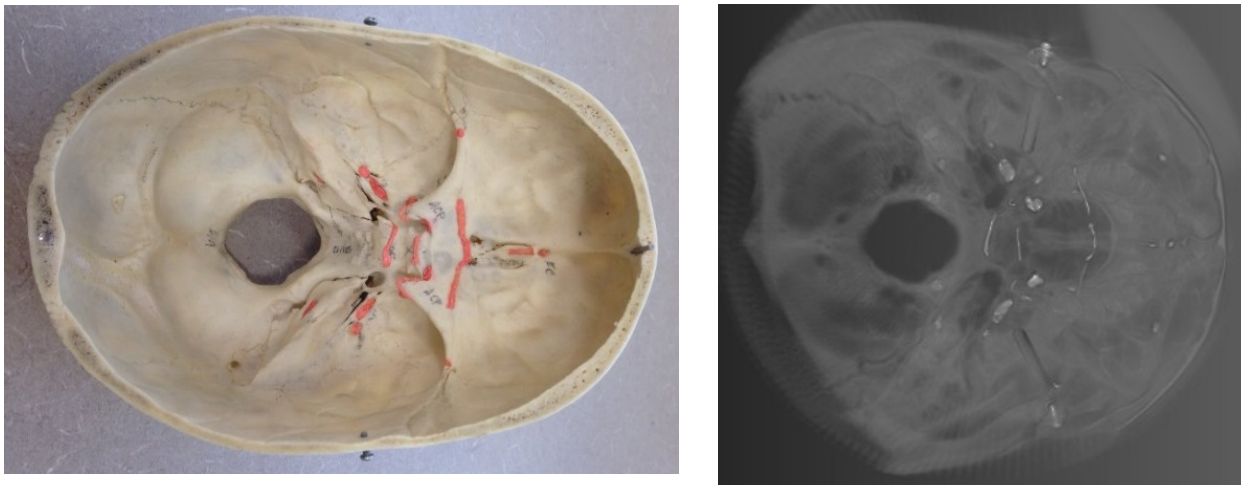
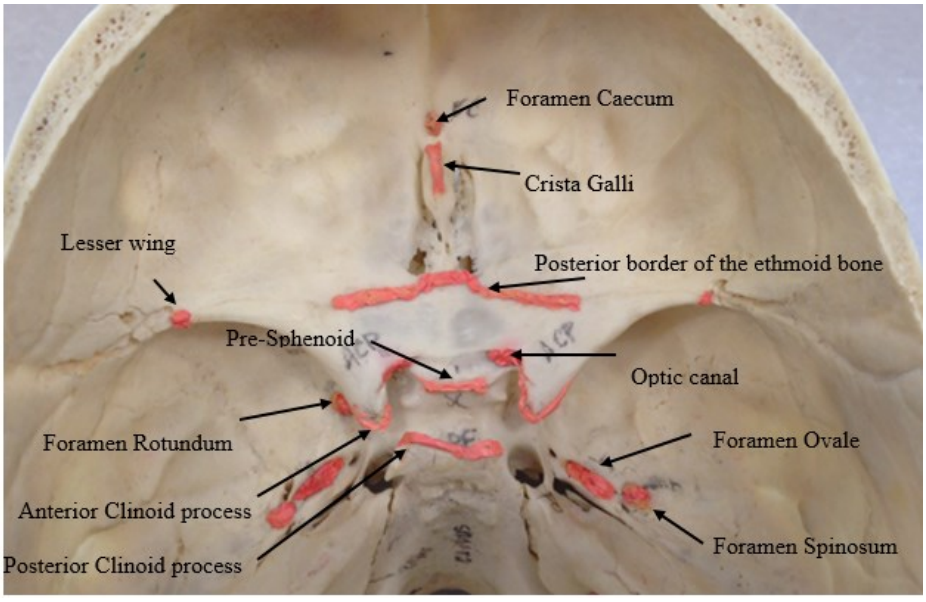
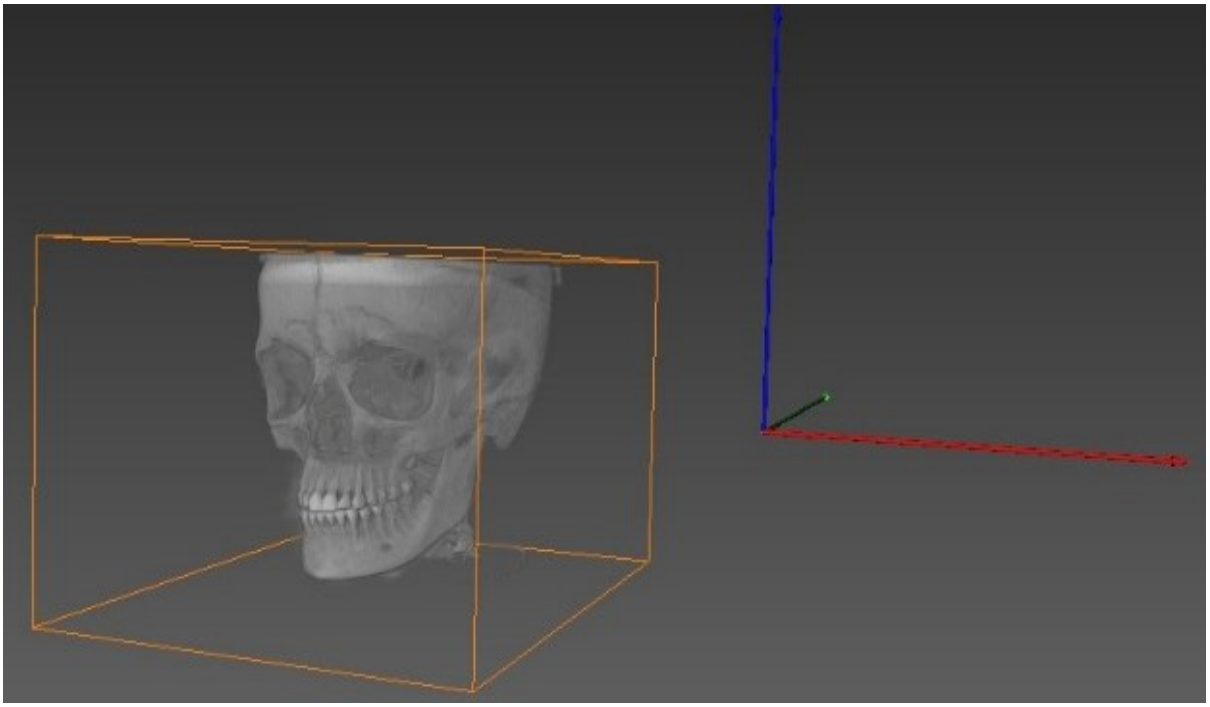


Figure 2.5 Dry skull marked with Gutta Percha (Magnified)



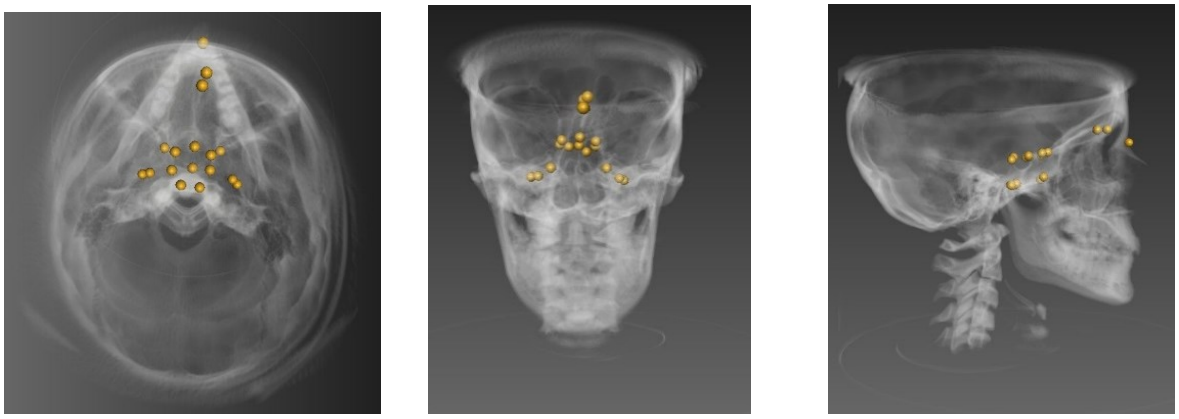
Raw images were exported into a DICOM file, which were subsequently loaded into Avizo version 7.0 software (Visualization Sciences Group, Burlington, MA, USA) for analysis. A Cartesian coordinate system was used throughout where the x-y, x-z, and y-z planes represent the axial (right-left), coronal (superior-inferior), and sagittal (anterior-posterior) planes respectively (Figure 2.6).

Figure 2.6 Orientation of the 3 X (red),Y(green) and Z(blue axes)



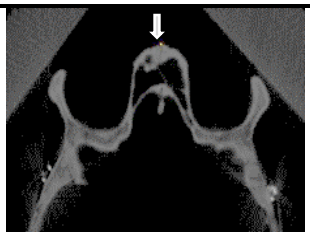
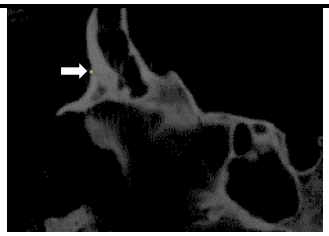
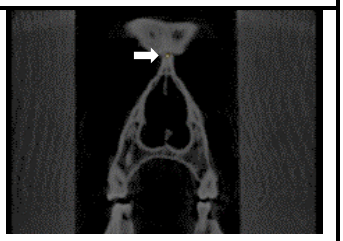
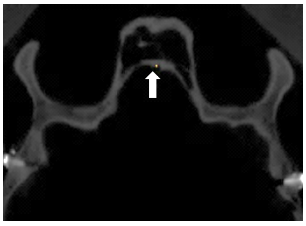
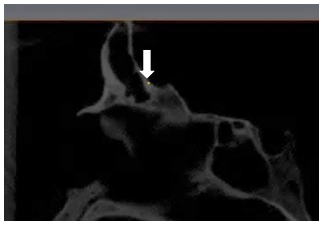
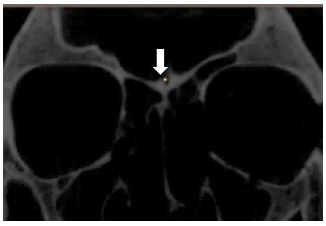
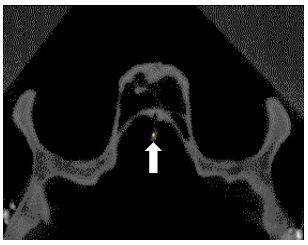
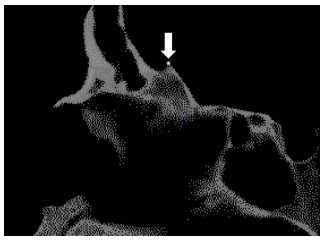
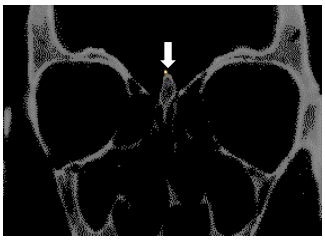
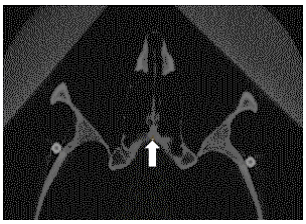
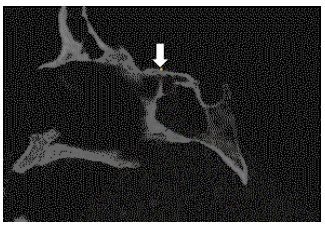
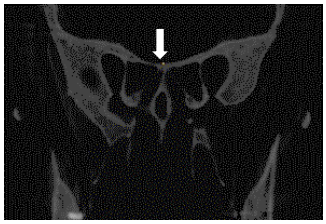
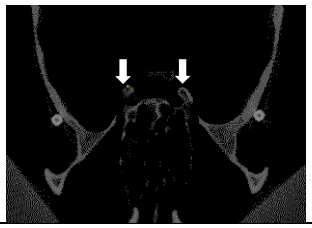
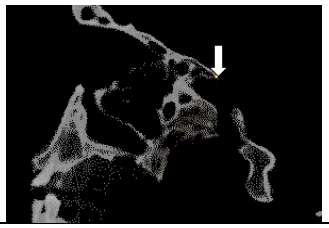
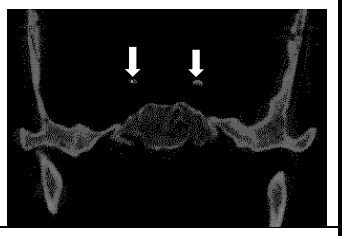
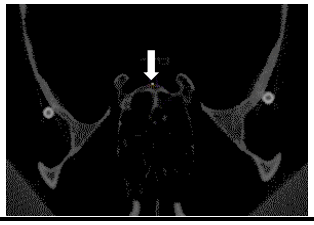
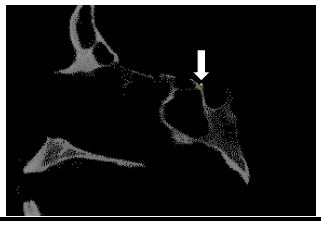
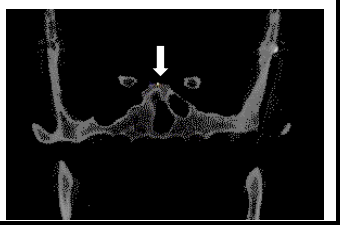
In total nineteen anatomical landmarks, located in the anterior and middle cranial fossae, were selected for further analysis (Figure 2.7). The left posterior *Clinoid* process structure was missing in two of the skulls. Therefore this landmark (PCL.L) was only assessed in 8 skulls.

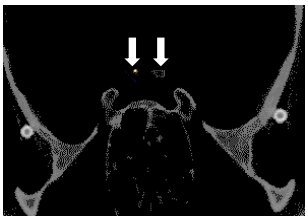
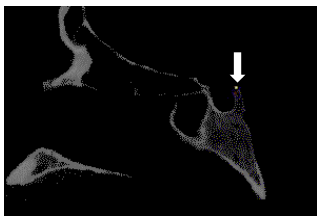
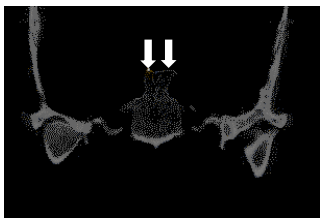
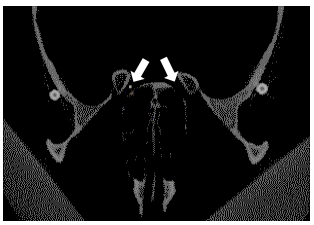
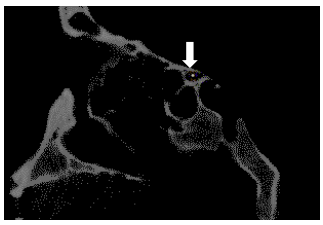
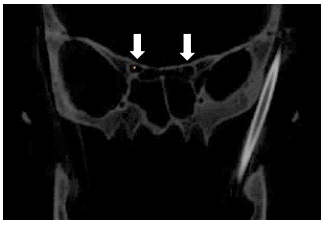
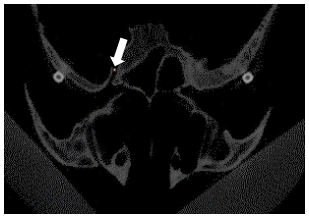
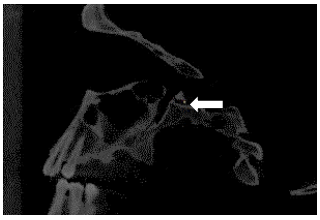
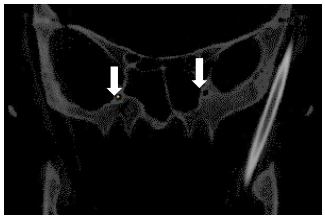
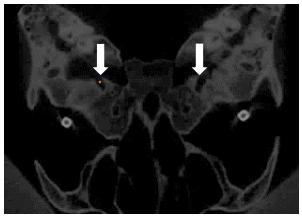
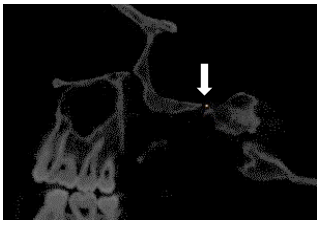
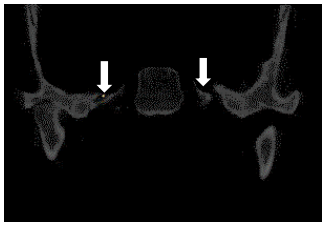
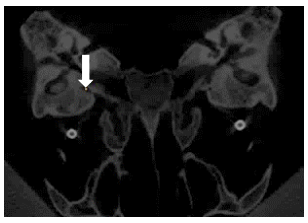
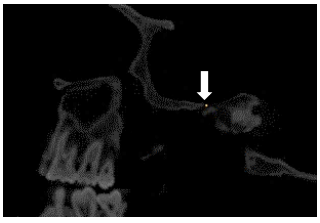
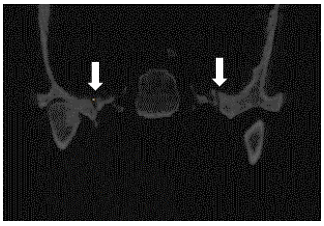
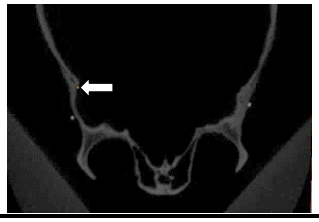
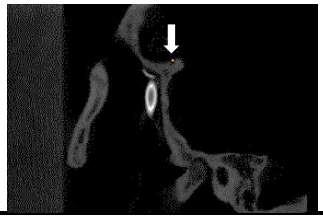
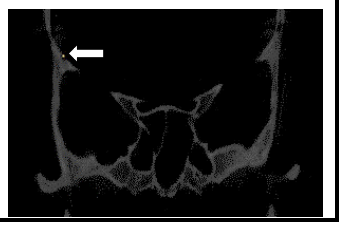
Figure 2.7 Landmarks in axial, coronal and sagittal view (left to right) as visualized in Avizo software version 8.0



The x-y, y-z, and z-x locations of each landmark have been defined, in order to standardize the anatomic identification in the three planes of space and to guide the selection of the most precise location in the sagittal, axial, and coronal views (Table 2.2).

Table 2.2 Three-dimensional Landmarks

Landmarks	Axial view (XY)	Sagittal view (YZ)	Coronal view (XZ)
Nasion **(Na)** The most anterior part of the fronto-nasal suture			
Foramen *Cecum* **(Ce)** The most middle superior point			
Crista galli **(Cg)** The tip			
Posterior *Ethmoid* **(Eth)** The most middle superior posterior point of the *ethmoid* bone			
Anterior *clinoid* **processes (ACL-R& ACL-L)** Most middle superior point			
Pre-Sphenoid **(PreSph)** Most middle posterior superior point of *Tuberculum* sella			

Posterior *clinoid* processes (PCL-R & PCL-L) Most middle superior point			
***Optic* canals (Op-R & OP-L)** Most middle point of well-defined circumference of the *Optic* canal			
Foramina *Rotundum* (Rt-R & Rt-L) Most middle point with defined borders as it enters the cranial fossa			
Foramina *Ovale* (Ov-R & Ov-L) Most middle superior point as it enters the cranial fossa			
Foramina *Spinosum* (Sp-R & Sp-L) Most middle superior point as it enters the cranial fossa			
Lesser wing (Lw-R & Lw-L) Most superior lateral point of the lesser wing of *Sphenoid* bone			

The principal investigator marked the landmarks in the software using the virtual spherical marker of 0.25 mm diameter in the X, Y and Z axes. The center of the spherical marker is considered as the position of the landmark by the software, therefore the size of the spherical marker does not affect the position of the landmark. The principal investigator marked the landmarks three times on the images without Gutta percha, with each measurement trial being at least 1 week apart. Two other examiner (one orthodontist and one dental student) also located the landmarks once for each image without Gutta percha for reliability purposes. Each examiner was familiarized and trained with the visualization software. For investigator blinding, the images were identified by code and analyzed in random order.

In addition, to assess accuracy of the anatomic landmarks selected in the first step, the dry skull three-dimensional images with Gutta percha were read by the principal investigator once. The readings from one randomly selected reading of the images without Gutta percha were compared to the readings of the images with Gutta percha. Since skulls could not be oriented exactly the same in the CBCT machine (while imaged without Gutta percha and with Gutta), the landmark coordinates generated at each time could not been compared for this purpose. Therefore, thirty one linear measurements were generated using the landmarks (Table 2.8). As stated before the PCL.L landmark was assessed in only 8 skulls, in consequence any measurement containing this landmark was assessed in 8 skulls (Eth-PCL.L, Op.L-PCL.L, PCL.L- Rt.L linear measurements).The following equation was used to measure the distance between each two anatomic landmarks with three-dimensional coordinates.

$$d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2}$$

Where d is the distance (mm) between the two anatomic landmarks and x_1, y_1, z_1 and x_2, y_2, z_2 are the coordinates of the two landmarks at the two end of the linear measurement. Each landmark was included in at least 3 linear measurements in different orientations to be able to assess it in all dimensions.

2.3 Statistical analysis

A standard statistical software package (SPSS version 20 for PC, IBM) was used for data analysis.

Reproducibility and repeatability (reliability) of the selected anatomical landmarks were assessed by measuring intra-rater and inter-rater reliability.

Intra-rater reliability was assessed using Intraclass Correlation Coefficient (ICC) to measure agreement between the three measurements done by the principal investigator on the skulls without Gutta percha, for each landmark in each three axes of X, Y and Z. A single measure with consistency under two-way mixed model was chosen as we want to ensure consistency in one rater's individual measurements while the subjects were chosen randomly.

To assess inter-rater reliability Intraclass Correlation Coefficient (ICC) was used to measure agreement between one randomly selected reading out of three readings of the principal investigator, and two other raters' single measurement of the skulls without Gutta percha. A single measure with absolute agreement under two-way mixed model was

chosen as we want to ensure both raters are in absolute agreement while the subjects were chosen randomly.

In addition, the absolute mean difference of intra-rater and inter-rater measurements (absolute mean difference between measurement trials) were reported in millimeters in all axes (x, y and z), which describe the dispersion of landmark identification in a way understandable by orthodontist.

Accuracy of the anatomic landmarks was also assessed using Intraclass correlation coefficient (ICC). ICC was conducted to measure agreement between the linear measurements on the images without Gutta percha and images with Gutta percha. A single measures with consistency under two-way mixed model was chosen as we want to ensure consistency in one rater's individual measurements while the subjects were chosen randomly.

ICC values were interpreted by the general guidelines presented by Portney and Watkins (52). (Table 2.3)

Table 2.3 ICC guide

ICC > 0.90	Excellent agreement
ICC > 0.75	Good agreement
0.51< ICC <0.74	Moderate agreement
ICC <0.50	Poor agreement

2.4 Results:

2.4.1 Intra-rater reliability

Intra-rater reliability for the x, y and z coordinates of most landmarks was good to excellent, equal or greater than 0.80 (Table 2.4). Profile plots are presented in appendix 2.1 and example of scatter plots in appendix 2.2. Only two landmarks lesser wing right and left (LW-R and LW-L) showed poor to moderate intra-rater reliability in the x axis (0.55 for both) (Table 2.3). Scatter plots of intra-rater reliability of LW-R and LW-L are presented in appendix 2.3.

Table 2.4 ICC of intra-rater reliability for landmarks in X, Y and Z axes

	Intra-rater reliability								
	x			y			Z		
Landmarks	ICC	ICC (Lower Bound)	ICC (Upper Bound)	ICC	ICC (Lower Bound)	ICC (Upper Bound)	ICC	ICC (Lower Bound)	ICC (Upper Bound)
ACL-L	0.89	0.72	0.97	0.99	0.98	1.00	0.99	0.98	1.00
ACL-R	0.82	0.57	0.95	0.99	0.98	1.00	0.99	0.97	1.00
Ce	0.98	0.95	1.00	1.00	0.99	1.00	0.99	0.98	1.00
Cg	0.95	0.85	0.99	0.99	0.96	1.00	0.99	0.98	1.00
Eth	0.80	0.54	0.94	0.99	0.97	1.00	0.99	0.97	1.00
Na	0.90	0.73	0.97	0.99	0.98	1.00	0.99	0.96	1.00
Op-L	0.93	0.81	0.98	0.99	0.97	1.00	1.00	0.99	1.00
Op-R	0.92	0.78	0.98	0.98	0.95	1.00	1.00	0.99	1.00
Ov-L	0.82	0.57	0.95	0.93	0.82	0.98	0.99	0.98	1.00
Ov-R	0.96	0.88	0.99	0.94	0.83	0.98	1.00	0.99	1.00
PCL-L	0.91	0.73	0.98	0.98	0.95	1.00	1.00	0.99	1.00
PCL-R	0.89	0.71	0.97	0.98	0.95	1.00	1.00	0.99	1.00
PreSph	0.93	0.82	0.98	0.97	0.91	0.99	0.99	0.98	1.00
Rt-L	0.97	0.91	0.99	0.99	0.96	1.00	1.00	0.99	1.00
Rt-R	0.98	0.94	0.99	0.99	0.96	1.00	1.00	0.99	1.00
Sp-L	0.95	0.86	0.99	0.99	0.97	1.00	0.99	0.98	1.00
Sp-R	0.98	0.94	0.99	0.96	0.90	0.99	1.00	0.98	1.00
LW-L	0.55	0.16	0.84	0.90	0.73	0.97	0.93	0.82	0.98
LW-R	0.55	0.16	0.84	0.96	0.88	0.99	0.92	0.78	0.98

Mean error (differences) from repeated landmark identification by the same examiner in all three axes were equal or less than 1 mm with the exception of left Lesser wing LW.L (3.1 mm in X, 2.3 mm in Y and 1.6 mm in Z axes) and right Lesser wing LW.R (3.5 mm in X, 2.0 mm in Y and 2.1 mm in Z axes). In addition, the mean error for both *Optic* canal left (OP-L) and Forman *Ovale* left (OV-L) in Y axis was 1.3 mm (Table 2.5).

Table 2.5 Intra-rate absolute mean differences (mm) in coordinates of the landmarks in X, Y and Z axes based on three readings.

Intra rater absolute mean differences													
		X				Y				Z			
Landmark	N	Mean	Minimum	Maximum	Std. Deviation	Mean	Minimum	Maximum	Std. Deviation	Mean	Minimum	Maximum	Std. Deviation
ACL-L	10	0.54	0.00	1.33	0.42	0.47	0.00	0.67	0.32	0.67	0.00	1.33	0.54
ACL-R	10	0.34	0.00	0.67	0.35	0.34	0.00	0.67	0.35	0.87	0.00	2.00	0.63
Ce	10	0.07	0.00	0.67	0.21	0.27	0.00	1.33	0.47	0.33	0.00	1.33	0.47
Cg	10	0.13	0.00	0.67	0.28	0.74	0.00	2.67	0.80	0.33	0.00	2.00	0.65
Eth	10	0.47	0.00	1.33	0.45	1.00	0.67	2.00	0.56	0.67	0.00	2.00	0.54
LW-L	10	3.13	0.67	7.33	2.11	2.27	0.00	6.67	2.44	1.60	0.67	4.67	1.27
LW-R	10	3.47	0.00	9.33	3.06	2.00	0.00	6.00	2.04	2.14	0.67	4.67	1.40
Na	10	0.27	0.00	0.67	0.35	0.33	0.00	2.00	0.65	0.40	0.00	0.67	0.35
Op-L	10	0.27	0.00	0.67	0.35	1.27	0.67	2.00	0.66	0.47	0.00	1.33	0.45
Op-R	10	0.67	0.00	2.00	0.70	1.00	0.00	2.67	0.96	0.27	0.00	0.67	0.35
Ov-L	10	0.53	0.00	1.33	0.53	1.27	0.67	3.33	0.96	0.60	0.00	2.00	0.80
Ov-R	10	0.47	0.00	0.67	0.32	0.80	0.00	3.33	0.98	0.47	0.00	1.33	0.55
PCL-L	8	0.50	0.00	1.33	0.47	0.58	0.00	2.00	0.75	0.50	0.00	1.33	0.59
PCL-R	10	0.87	0.00	2.00	0.55	0.67	0.00	1.33	0.54	0.40	0.00	1.33	0.47
PreSph	10	0.27	0.00	0.67	0.35	0.87	0.00	2.00	0.83	0.80	0.00	2.00	0.61
Rt-L	10	0.27	0.00	0.67	0.35	0.54	0.00	1.33	0.42	0.27	0.00	0.67	0.35
Rt-R	10	0.33	0.00	1.33	0.47	0.47	0.00	0.67	0.32	0.34	0.00	0.67	0.35
Sp-L	10	0.47	0.00	1.33	0.45	0.33	0.00	1.33	0.47	0.67	0.00	2.00	0.63
Sp-R	10	0.27	0.00	0.67	0.35	0.60	0.00	2.00	0.58	0.60	0.00	1.33	0.49

Based on these findings the two landmarks LW-R and LW-L were eliminated from the analysis at this point and were not assessed for inter-rater reliability. The poor to moderate intra-rater reliability in the x axis was in concordance with the principal examiners difficulty in perceiving the right and left lesser wing anatomical structures radiographically. These landmarks were initially observed and selected by observing a dry skull and failed to be reliable radiographic landmarks.

2.4.2 Inter-rater reliability

In the x axis most landmarks (17 landmarks after elimination of LW.R and LW.L) had good inter-rater reliability of greater than 0.78 with the exception of right anterior *clinoid* process (ACL-R), left anterior *clinoid* process (ACL-L), *Ethmoid* (Eth) and right posterior *clinoid* process (PCL-R) , *Presphenoid* (PreSPh) and left foramen *Rotundum* (RT-L) that had moderate inter-rater reliability (ICC of 0.61, 0.72, 0.70, 0.73, 0.57and 0.55 respectively) and PCL-L that had poor inter- rater reliability in x axis (ICC of 0.46) (Table 2.6).

Additionally Inter-rater reliability for the y coordinates of the majority of the landmarks was excellent and greater than 0.96 with the exception of four landmarks Ov.R, Ov.L, Sp.R and Sp.L that had good inter-rater liability (ICC of 0.80, 0.87, 0.76 and 0.79 respectively). Only *Ethmoid* (Eth) had moderate inter-rater reliability of 0.72 in y axis (Table 2.6). Inter-rater reliability for the z coordinates of all landmarks was excellent and greater than 0.95.

Table 2.6 ICC values of inter-rater reliability

	Inter-rater reliability								
	x			y			Z		
Landmarks	ICC	ICC (Lower Bound)	ICC (Upper Bound)	ICC	ICC (Lower Bound)	ICC (Upper Bound)	ICC	ICC (Lower Bound)	ICC (Upper Bound)
ACL-L	0.72	0.20	0.92	0.99	0.98	1.00	1.00	0.99	1.00
ACL-R	0.61	0.08	0.88	0.99	0.96	1.00	0.99	0.98	1.00
Ce	0.95	0.86	0.99	0.99	0.97	1.00	0.96	0.87	0.99
Cg	0.90	0.69	0.97	0.98	0.94	0.99	0.98	0.94	1.00
Eth	0.70	0.33	0.91	0.72	0.32	0.92	0.96	0.87	0.99
Na	0.79	0.52	0.94	1.00	0.98	1.00	0.98	0.93	0.99
Op-L	0.80	0.48	0.94	0.98	0.94	1.00	1.00	0.99	1.00
Op-R	0.88	0.71	0.97	0.98	0.93	0.99	1.00	1.00	1.00
Ov-L	0.79	0.44	0.94	0.87	0.60	0.96	0.99	0.95	1.00
Ov-R	0.93	0.82	0.98	0.80	0.53	0.94	0.99	0.97	1.00
PCL-L	0.46	0.03	0.83	0.97	0.92	0.99	1.00	0.99	1.00
PCL-R	0.73	0.28	0.92	0.98	0.93	0.99	1.00	1.00	1.00
PreSph	0.57	0.18	0.85	0.99	0.96	1.00	0.99	0.97	1.00
Rt-L	0.55	0.15	0.85	0.96	0.90	0.99	0.96	0.90	0.99
Rt-R	0.94	0.83	0.98	0.96	0.90	0.99	0.98	0.94	0.99
Sp-L	0.78	0.50	0.93	0.79	0.53	0.94	0.99	0.97	1.00
Sp-R	0.91	0.76	0.97	0.76	0.48	0.93	0.99	0.97	1.00

Profile plots in Appendix 2.4 represent the inter-rater reliability in all three axes and scatter plots of landmarks with moderate or poor inter-rater reliability are presented in appendix 2.5. Mean differences from landmark identification by the three raters in all three axes were equal or less than 1.3 mm with the exception of *Ethmoid* (Eth) in y axis (4.5 mm in Y axis and 1.4 mm in the Z axis) and both right and left foramina *Ovale* (Ov-R and Ov-L) in Y axis (1.7 mm and 1.9 mm respectively) (Table 2.7).

Table 2.7 Inter-rate absolute mean differences (mm) in coordinates of the landmarks in X, Y and Z axes based on three readings

Inter rater absolute mean differences													
		x				Y				Z			
Landmarks	N	Mean	Minimum	Maximum	Std. Deviation	Mean	Minimum	Maximum	Std. Deviation	Mean	Minimum	Maximum	Std. Deviation
ACL-L	10	1.13	0.67	2.00	0.45	0.40	0.00	0.67	0.35	0.60	0.00	1.33	0.49
ACL-R	10	1.20	0.67	2.00	0.42	0.67	0.00	1.33	0.31	0.80	0.00	2.00	0.52
Ce	10	0.20	0.00	0.67	0.32	0.60	0.00	2.00	0.73	1.00	0.00	3.33	1.05
Cg	10	0.34	0.00	0.67	0.35	0.94	0.00	3.33	0.90	0.60	0.00	2.67	0.80
Eth	10	0.74	0.00	2.00	0.58	4.47	0.00	2.00	4.02	1.40	0.00	2.67	1.06
Na	10	0.60	0.00	1.33	0.38	0.40	0.00	1.33	0.47	0.60	0.00	1.33	0.49
Op-L	10	0.60	0.00	1.33	0.38	0.80	0.00	2.00	0.52	0.34	0.00	0.67	0.35
Op-R	10	0.80	0.00	1.33	0.42	0.87	0.00	2.00	0.63	0.07	0.00	0.67	0.21
Ov-L	10	0.87	0.00	1.33	0.45	1.93	0.00	6.67	1.85	1.13	0.00	2.00	0.55
Ov-R	10	0.54	0.00	1.33	0.42	1.67	0.00	8.00	2.29	0.93	0.00	2.00	0.72
PCL-L	8	1.17	0.00	2.67	0.93	1.08	0.00	2.00	0.61	0.50	0.00	1.33	0.47
PCL-R	10	1.33	0.00	3.33	1.04	0.87	0.00	2.00	0.63	0.20	0.00	0.67	0.32
PreSph	10	0.93	0.00	2.67	0.84	0.47	0.00	2.00	0.63	0.80	0.00	1.33	0.42
Rt-L	10	1.13	0.00	4.67	1.41	1.07	0.00	2.00	0.64	1.20	0.00	4.67	1.29
Rt-R	10	0.60	0.00	1.33	0.66	0.93	0.00	2.00	0.56	0.87	0.00	4.00	1.18
Sp-L	10	0.87	0.00	2.67	0.83	1.20	0.00	9.33	2.89	1.07	0.00	2.00	0.64
Sp-R	10	0.60	0.00	2.00	0.58	1.07	0.00	8.67	2.69	1.07	0.00	2.00	0.72

2.4.3 Accuracy

The ICC shows good to excellent agreement for the majority of the linear measurements analyzed for accuracy (ICC of higher than 0.75 with the exception of moderate agreement of Op.R-Op.L, PCL.R-PCL.L and Rt.L-Ov.L being 0.73, 0.67 and 0.71 respectfully (Table 2.8).

Table 2.8 ICC for accuracy of linear measurements

Distances	Intraclass Correlation	95% Confidence Interval	
		Lower bound	Upper bound
ACL.L-Sp.L	0.87	0.56	0.97
ACL.R-ACL.L	0.92	0.71	0.98
ACL.R-Cg	0.91	0.69	0.98
ACL.R-Sp.R	0.80	0.37	0.95
Ce-PreSph	0.89	0.63	0.97
Ce-Sp.R	0.97	0.89	0.99
Cg-PCL.R	0.81	0.41	0.95
Cg-Ce	0.76	0.28	0.93
Cg-OV.R	0.96	0.86	0.99
Eth-PCL.L	0.78	0.24	0.95
Eth-Sp.L	0.81	0.41	0.95
NA-CE	0.86	0.55	0.96
NA-PreSph	0.91	0.67	0.98
NA-Rt.R	0.96	0.85	0.99
Op.L-Ov.L	0.81	0.40	0.95
Op.L-PCL.L	0.96	0.82	0.99
Op.R-Ov.R	0.82	0.44	0.95
Op.R-Op.L	0.73	0.22	0.93
Op.R-PCL.R	0.92	0.70	0.98
Ov.R-Ov.L	0.93	0.75	0.98
PCL.L-Rt.L	0.85	0.42	0.97
PCL.R-PCL.L	0.68	0.02	0.93
PCL.R-Rt.R	0.86	0.53	0.96
PreSph-Ov.L	0.77	0.30	0.94
PreSph-Rt.R	0.88	0.58	0.97
Rt.L-Ov.L	0.71	0.18	0.92
Rt.R-Ov.R	0.90	0.66	0.98
Rt.R-Rt.L	0.97	0.88	0.99
Sp.L-Rt.L	0.81	0.39	0.95
Sp.R-Rt.R	0.96	0.86	0.99
Sp.R-Sp.L	0.99	0.97	1.00

The mean difference of all linear measurements without Gutta percha and with Gutta percha was equal or less than 2.1 mm with the exception of the distance between *Crista galli* (Cg) to Posterior *clinoid* process right (PCL-R) which is 3.7 mm (appendix 2.6).

2.5 Discussion

The repeatability and reproducibility of the placement of cranial base (anterior and middle parts) anatomical landmarks on three-dimensional CBCT were investigated in this study. We identified some unique landmarks in the cranial base that could not be identified in two-dimensional images. Intra-rater, inter-rater agreement and accuracy was assessed by using the Intra Class Correlation Coefficient (ICC) and mean linear differences.

The majority of the selected landmarks had excellent intra-rater reliability in the three axes of x, y and z. Poor to moderate intra-rater reliability of the two landmarks LW-R and LW-L, in addition to principal investigator's difficulty in perceiving these landmarks radiographically, were the reasons to eliminate them from the list of landmarks as they failed to be reliable three-dimensional anatomical landmarks. All other landmarks showed acceptable accuracy and were true representative of their anatomical location. The final decision was to maintain and use all the landmarks in growth assessment study since they have good intra-rater reliability and accuracy.

Although intra-rater reliability is important in both research and clinical practice, for the purpose of diagnosis and treatment planning, the inter-rater reliability becomes more important as there should be consistency in decision making (52,53). Yet the inter-rater reliability is in general lower than intra-rater reliability as it was observed in our study.(41)

In our study, landmarks in the anterior and middle cranial bases were considered. Most of the structures of the middle cranial base are only visible in coronal and axial views only and not in sagittal view due to overlapping of structures. Therefore

the middle cranial base has not been studied in lateral cephalograms which are taken in sagittal view.

Below, each suggested landmark will be discussed individually:

Nasion

Nasion, in this study showed mostly excellent intra and inter-reliability and absolute mean differences of intra-rater and inter-rater readings of less than or equal to 0.6 mm. It's been concluded repeatedly in the literature that this landmark is a very reliable landmark to be used in three-dimensional imaging. (40,43,54) Schlicher et al (43) reported overall 1.02 mm inter-rater consistency when 9 orthodontic residents identified *nasion* on 19 patients CBCTs (age range 18-35). Kim et al (55) found that *nasion* has the least intra-rater measurement error of less than 1 mm in all planes on 5 dry skulls and 20 adult patients' CT images. The good reliability is due to location of this landmark being at the connection of two clearly identifiable sutures along the midline.

Foramen *Caecum*

Foramen *Caecum* is located anterior to *cribriform* plate of *ethmoid* bone and posterior to the *frontal* bone, within the *frontoethmoidal* suture. Its lumen is usually filled with fibrous tissue continuous with periosteal dura mater. Autopsy of 201 individuals ranging from neonates to adults showed that this foramen varies in size. Macroscopically no veins have been observed passing through it.(56) However whether this foramen is patent in neonates and a passage of veins from nasal mucosa to the superior sagittal sinus still remains controversial in the literature.(57) Foramen *Caecum* similar to *nasion* found to have excellent intra and inter-rater reliability of ICC of more than 0.94 and absolute

mean differences of inter and intra-rater measurement trials of equal or less than 1 mm. The Z axis (vertical) was the one with highest mean inter-rater difference of 1.00 mm. The opening of the lumen is usually slanted and is not on a true horizontal plane therefore the raters objective decision on marking the landmark on the vertical plane could vary depending on where they consider the lumen entrance (leveled with the highest border or the lowest border or the middle). Kim et al (55) also found Foramen *Caecum* to have the least measurement error of less than 1mm in all planes.

Crista galli

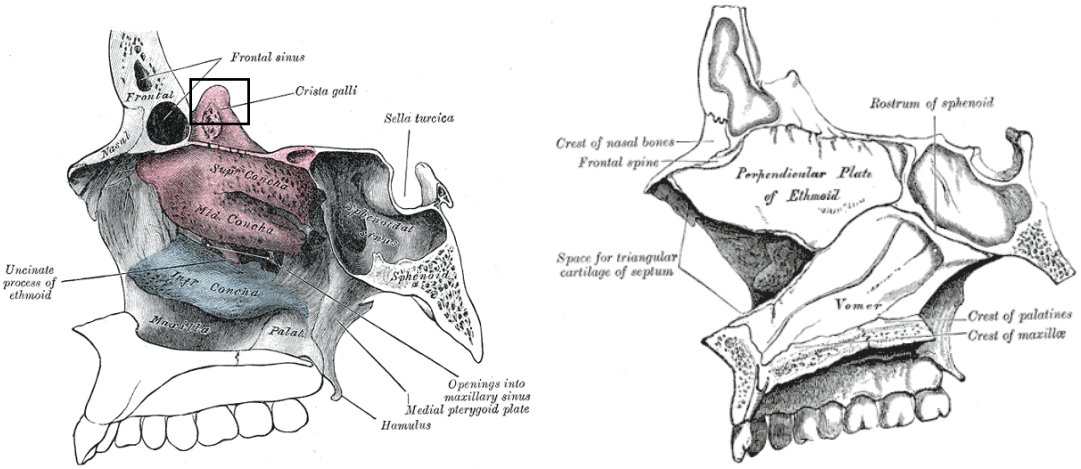
Crista galli is a median ridge of bone that projects from the *cribriform* plate of the *ethmoid* bone. Titiz et al (58) reported landmark identification severity of the most superior point of the *crista galli* simple in three-dimensions and the intra and inter observer standard deviations of this landmark was less than 1mm. Their results are in concordance with our results. As the *crista galli* landmark presents the tip of a spike, the simplicity of identifying it makes it a reproducible landmark.

Ethmoid

Ethmoid landmark chosen in the present study was to define the middle of the spheno-*ethmoid* suture. However the suture is not identifiable on a three-dimensional CBCT image. Therefore, the landmark was defined as the most middle posterior superior point of *Ethmoid* bone, immediately in front of the *Sphenoid* Sinus. The most appropriate view to identify this landmark is the sagittal view passing through the perpendicular plate of the *Ethmoid* bone. This landmark showed moderate inter-rater reliability in X and Y planes and higher mean difference in inter-rater readings. The highest error was in Y

axis (sagittal) of 4.5 mm. This large error is easily explained due to variations in anatomy of this area. In some individuals, small air cells could be present at the junction of the *ethmoid* and *sphenoid* bones (figure 2.8 left image). The air cell makes it impossible to precisely identify the junction of the two bones. *Ethmoid* landmark description in our study did not clarify the location of landmark in case of presence of such anatomical variation. Possible way to reduce variability and error would be to determine whether the anterior or posterior border of the air cell should be considered.

Figure 2.8 Anatomy of *Ethmoid* and *Sphenoid* bone in sagittal view. Not the presence of an air cell between *sphenoid* and *Ethmoid* on the left image and its absence on the right image.

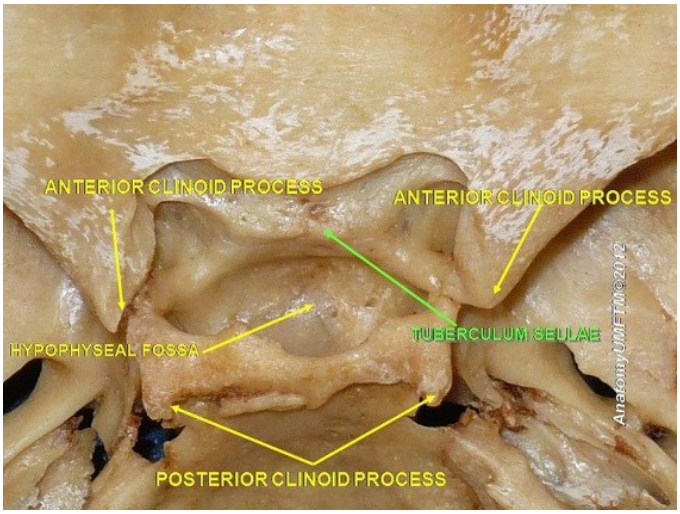


Presphenoid

The most middle posterior superior point of *Tuberculum* sellae defines this landmark. The *Tuberculum* sellae is an elevation forming the posterior boundary of the pre

chiasmatic sulcus and the anterior limit of the *hypophysial* fossa (Figure 2.9). The inter-rater reliability was moderate in X axis (ICC=0.57) due to inconsistency of individuals in marking the midpoint of a line. However, the inter-rater mean measurement difference in X axis was 0.93 ± 0.84 mm. This landmark can be used interchangeably with the constructed floating *sella* landmark in vertical and horizontal measurements as shows acceptable reproducibility and low measurement error. *Presphenoid* landmark should be used cautiously for transverse measurements.

Figure 2.9 Anatomy of the *Tuberculum* Sellae and the anterior and posterior *clinoid* processes



Anterior and Posterior *Clinoid* processes

The anterior *clinoid* processes are the posteromedial projections of the lesser wings while the posterior *clinoid* processes are anterolateral projection of the *dorsum* sellae of

the *sphenoid* bone. These two landmarks are located on the curvature of the anterior and posterior processes, which makes it difficult to unquestionably mark the middle point of the curvature. Therefore, lower inter-reliability ICC values were observed (poor to moderate). In addition the inter-rater absolute means measurement differences were more than 1 mm but still less than 1.5 mm. Naji et al (59) reported excellent reliability of the most middle superior point of the posterior *clinoid* processes and absolute mean measurement of less than 0.5 mm in all three axes on CBCTs.

Optic canals

The *optic* canal posterior opening is in the middle cranial fossa at the lateral margin of the chiasmatic sulcus. Its roof and the floor are formed by the superior and inferior processes of the lesser wing of the *sphenoid* bone and the mesial wall is formed by the body of the *sphenoid* bone. It has an oblique trajectory which makes a 36 to 40 degrees angle with the mid-sagittal plane. Kim et al (55) found the greatest discrepancy in the intra-rater measurement error for *optic* canal (1.30 mm in X axis) which was explained by difficulty in locating landmarks associated with hollow tubes or foramina. However they did not define clearly their landmarks therefore comparison of the results is not possible. Our results showed intra-rater absolute mean measurement difference of 1.0 mm and 1.3 mm in y axis (sagittal) for *optic* canal right and left respectively. The angle of the opening of the *optic* canal (similar to foramen *caecum*) to the middle cranial fossa relative to the mid-sagittal plane can explain slightly higher mean differences. In addition we observed good inter-rater reliability and inter-rater absolute mean measurement difference of less than 0.9 mm.

Foramen *Rotundum*

Foramen *Rotundum* is generally 3.4 mm long and connects the middle cranial fossa and the pterygo-palatine fossa. It is been observed to have a consistent shape and anatomy.(60) Our results were in concordance with Lagravère et al (40). Foramen *Rotundum* provided high intra-rater reliability. Surprisingly, we obtained moderate inter-rater ICC value of 0.55 for the foramen *Rotundum* left in the x axis. However, we found excellent inter-rater reliability for the right Foramen *Rotundum*. Even though, this is not easy to explain and could possibly be due to outliers present in the dataset affecting ICC, we concluded high reliability for Foramen *Rotundum*.

Foramen *Ovale*

Foramen *Ovale* is situated on the posteromedial surface of the greater wing of the *Sphenoid* bone and forms a communication between the middle cranial fossa with the infra-temporal fossa. Ginsberg *et al* (60)reported consistency in its shape and location except for occasional absence of its medial wall. Asymmetry in size or shape (oval or round) has been reported in 23-30% of cases, but complete absence of Foramen *Ovale* has not been reported.

Relatively larger lumen diameter in addition to minimal anatomical variation, makes this foramen highly reliable as concluded by our results (Inter-rater reliability > 0.75) and Lagravère et al (40).

Foramen *Spinosum*

Foramen *Spinosum* which is a small opening located postero-laterally to the foramen *Ovale* is generally 2 to 4 mm long with an average diameter of approximately 1.5 to 3.0

mm. It is usually round or oval in shape.(60) Its unilateral absence is reported in 0.4–1% of cases but is rarely absent on both sides. (61). Ginsberg et al (60) observed absence of the foramen *Spinosum* in 3.2% of their patients when assessed on CT scans. Incomplete formation is common. For example medial wall defects have been reported in up to 26.8%.(61)

The greatest discrepancy was observed in Foramen *Spinosum*. Relatively small size and high degree of variability in its anatomy makes it the least reliable landmark among all the landmarks chosen in our study. The mean differences in inter-rater measurements of both right and left *Spinosum* foramina were between 1-1.20 mm in Y(sagittal) and Z (vertical) axes which remains within clinically acceptable range, but this is the only landmark with more than one mm discrepancy in two out of three axes on both its right and left counterparts. In addition, the standard deviation of inter-rater mean difference of measurement is relatively high in the Y axis (2.69-2.89 mm). 3mm deviation could place the landmark out of the true anatomical foramen due to its small diameter. Most probably observers had difficulty recognizing the foramen *Spinosum* from other small openings that might be present in the proximity or it could be explained by the complete absence of the foramen. In addition, compared to other landmarks, identifying this landmark was very time consuming and required numerous verifications in different axes. In contrary to our conclusion, Lagravère et al (40) recommended Foramen *Spinosum* as an acceptable landmark for future three-dimensional superimpositions.

General remarks

Overall, all the landmarks introduced in our study have acceptable inter-rater and intra-rater reliabilities and could potentially be used in craniofacial analysis of growth or treatment outcome, or as reference points for future three-dimensional superimpositions. The exception would be the foramen *Spinosum* due to the reasons discussed previously.

Based on degree of anatomical variability of the structures, and definition of the landmarks, the landmarks *Nasion*, *Crista galli*, anterior *clinoid* process, posterior *clinoid* process, foramen *Rotundum* and foramen *Ovale* were highly reliable and readily identifiable. Identifying landmarks foramen *Caecum*, *Ethmoid*, *pre-sphenoid* and *optic* canal showed mild variability among the raters in one or several axes (in general moderate ICC > 0.5). Higher inter-rater agreements could be obtained by improving the definition of *Ethmoid*, foramen *Caecum* and *Presphenoid*.

The choice of the landmark selected for any analysis is highly dependent on the purpose of the analysis. It is important to have knowledge of landmark identification error in all three axes of X, Y and Z. For example, landmarks with large vertical error should be avoided in assessing vertical structural measurements.(62)

Major et al (62) reported the standard deviation of error in two-dimensional cephalometric and recommended avoiding landmarks with identification error over 1.5 mm. They also called any error more than 2.5 mm inappropriate. Lagravère et al (40) considered variation of 1 mm in CBCT landmark identification unlikely to have clinical significance. Mah et al (63) considered variations of 0.5 mm not clinically relevant while

variation between 0.5 to 1 mm of possible clinical significance. In our study, the majority of mean measurement differences is less than 1 mm and 1.3 mm for intra-rater and inter-rater measurements respectively. The inter-rater mean measurements are slightly higher than the arbitrary limit of clinical significance proposed by some authors. Yet, the clinical significance of landmark identification error depends on the accuracy required for each landmark depending on the type and level of difficulty of the treatment, and the purposes of the study.(50)

Furthermore, the individual craniofacial morphology (the anatomy of the bony structure) directly affects the precision of landmark identification. Landmarks located in a curvature or at an anatomical prominence (such as anterior *clinoid* process), when compared with the points defined by the boundary structures, such as *nasion* show higher measurement variability.(41)

There exists a large variability in methods authors use in calculating and reporting measurement error. Therefore, comparing results of studies does not lead us to reliable results. For example, we reported ICC and the absolute mean differences of the repeated measurements. Some studies report the standard deviation values as a measure of repeatability (58,62). Dahlberg's formula was used by Kim et al to report error of appointing landmarks.(55) Standardizing methods of calculating measurement error would greatly increase the accuracy of interpretation and pooling the data from different studies.

Limitation of the study

There are numerous factors that should be considered when applying the results of this investigation to clinical situations. First and foremost, this study was performed on dry skulls. The reliability of landmark identification on live individuals may be affected by decrease in image quality due to soft tissue attenuation and consequently decrease in ICC values. Incorporating use of Plexiglas box filled with water in our study design was to imitate soft tissue and reduce error.

We conducted this study on 10 dry skull specimens. As recommended by Springate (64) a higher number (25-30 cases) of specimen would be advantageous to increase the power of the study and the statistical analysis.

Some landmarks showed higher inter-rater measurement errors and less ICC values in specific axes. This could be due to difference in raters' technique. Each rater might have focused on a different plane when marking a landmark. Some landmarks are easier to identify in one or two planes and pose difficulty in the third plane (50). As choosing the suitable plane for landmark placement requires time and experience, landmark identification reliability could be improved by defining a specific plane in which the landmark is easily identifiable.

The Avizo software used in this study requires a significant learning curve. The raters in this study, even though trained, had different levels of experience with the software. In addition, the software does not allow viewing the landmarks in all three planes as the same time. The observer requires to change the plane to check the

position of the landmark in different planes. A more user friendly software could facilitate and expedite raters' learning and increase inter-rater agreement.

The measurement of accuracy of landmarks was assessed through comparison of linear measurements on the same skull images twice, once without gutta percha and once with gutta percha on the landmarks. It should be noted that this method does not provide information about the actual three-dimensional location of the landmarks. This technique indirectly assesses accuracy of the landmarks, but could be vulnerable to error. Developing a technique that would allow to evaluate accuracy of the three-dimensional landmark independently is recommended.

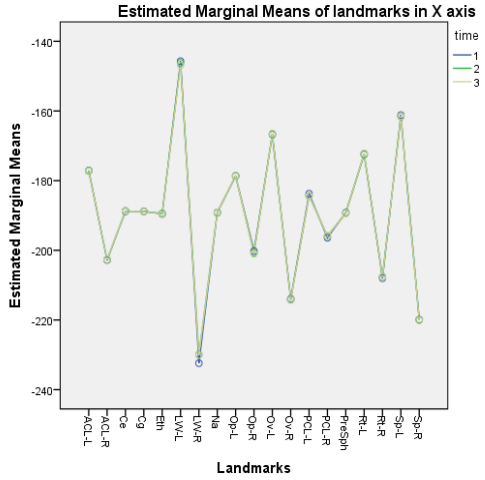
3.6 Conclusion

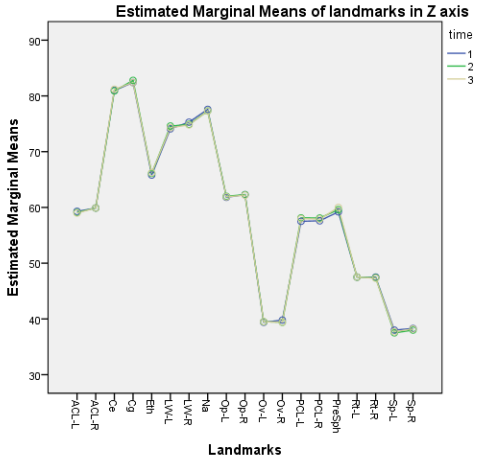
For the purpose of our research, all the landmarks assessed in this study (except right and left lesser wing landmarks) showed acceptable intra-rater reliability and accuracy to be used in our future growth assessment study (next chapter).

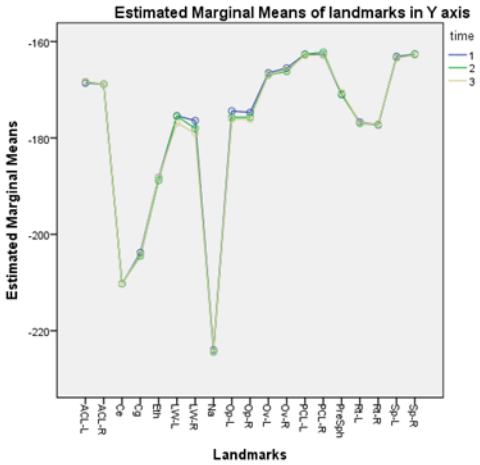
In general all the proposed 3D landmarks with the exception of lesser wing and foramen *Spinosum* showed acceptable intra-rater and inter-rater reliability and could be used for future growth assessment and 3-dimensional superimposition analysis if their individual limitations are fully understood.

2.7 Appendices

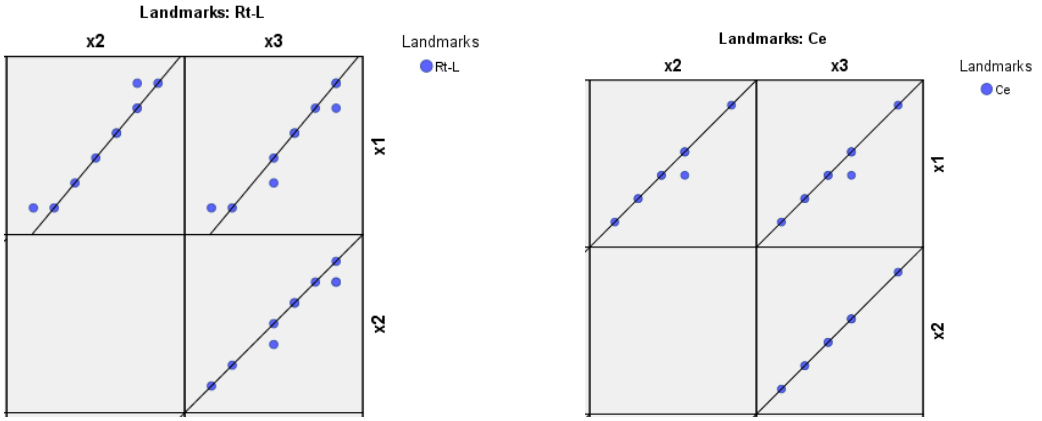
APPENDIX 2.1 PROFILE PLOTS OF INTRA-RATER RELIABILITY



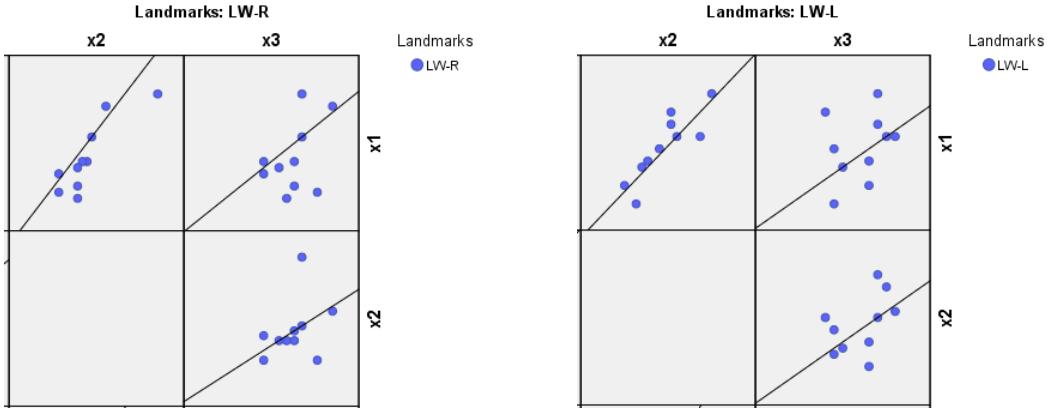




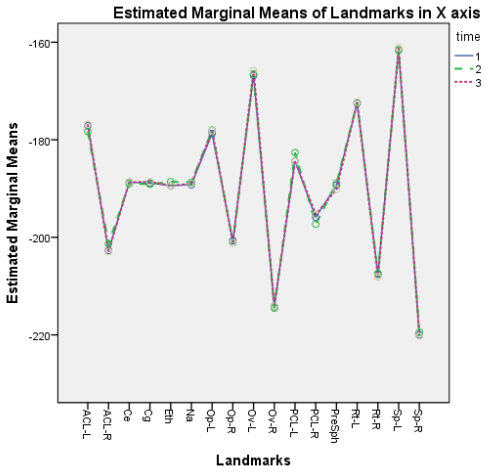
APPENDIX 2.2 EXAMPLE SCATTER PLOTS OF LANDMARKS WITH EXCELLENT INTRA-RATER RELIABILITY (FORAMEN *ROTUNDUM* LEFT (LEFT) AND FORAMEN *CAECUM* (RIGHT) IN X AXIS)

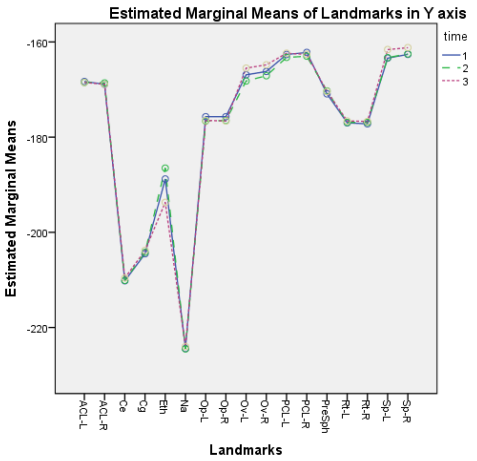


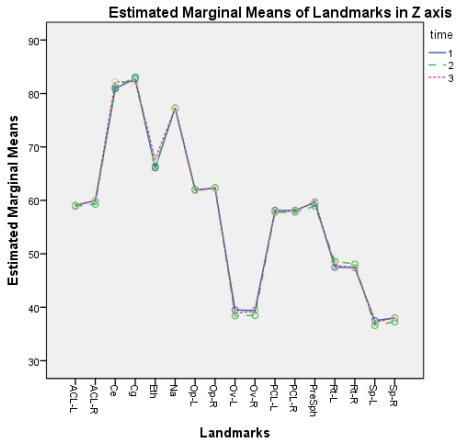
APPENDIX 2.3 SCATTER PLOTS OF LANDMARKS WITH POOR INTRA-RATER RELIABILITY IN X AXIS.



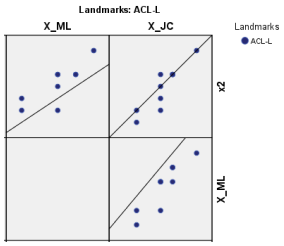
APPENDIX 2.4 PROFILE PLOTS OF INTER-RATER RELIABILITY

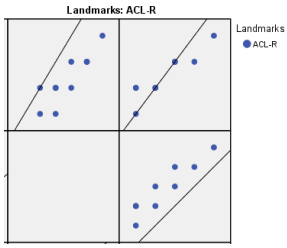


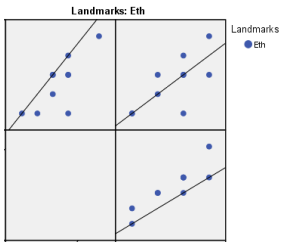


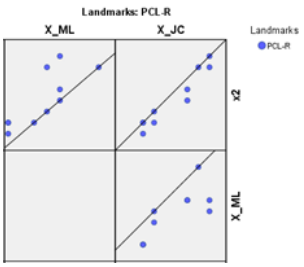


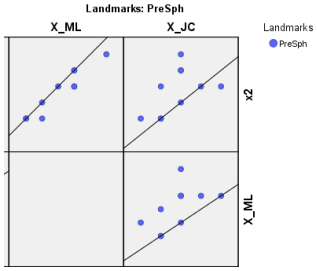
APPENDIX 2.5 SCATTER PLOTS OF LANDMARKS WITH MODERATE OR POOR INTER-RATER RELIABILITY IN X OR Y AXES.

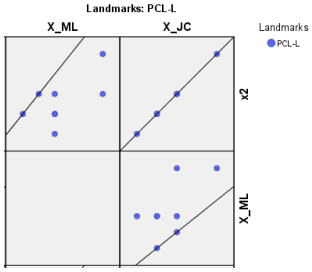


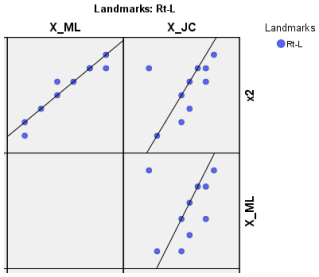


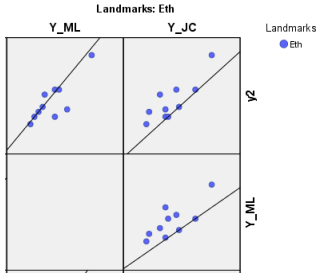












APPENDIX 2.6 MEAN, MINIMUM, MAXIMUM AND STANDARD DEVIATION OF LINEAR MEASUREMENTS WITHOUT GUTTA PERCHA, WITH GUTTA PERCHA AND THEIR DIFFERENCE.

		Without gutta percha				With gutta percha				Difference	
Distance	N	Mean	Minimum	Maximum	Std. Deviation	Mean	Minimum	Maximum	Std. Deviation	Mean difference	Std. Deviation
ACL.L-Sp.L	10	27.35	21.99	30.60	2.73	27.99	24.77	31.24	2.01	0.94	0.99
ACL.R-ACL.L	10	25.68	23.24	29.02	1.87	25.35	22.47	29.01	2.15	0.67	0.53
ACL.R-Cg	10	44.90	40.84	48.40	2.22	45.01	41.17	49.07	2.32	0.78	0.49
ACL.R-Sp.R	10	28.94	26.96	31.82	1.45	29.04	26.82	32.65	1.71	0.74	0.66
Ce-PreSph	10	44.97	42.02	48.90	2.40	45.38	42.88	48.59	1.98	0.65	0.86
Ce-Sp.R	10	71.84	67.70	75.68	2.96	72.34	68.47	76.20	3.09	0.69	0.52
Cg- PCL.R	10	42.89	35.42	52.60	5.04	45.40	36.99	55.62	5.93	3.74	1.72
Cg-Ce	10	6.32	3.17	9.47	2.06	6.45	5.55	8.52	1.11	0.84	0.76
Cg-OV.R	10	63.41	58.40	69.85	3.77	63.32	57.84	69.60	4.14	0.82	0.67
Eth-PCL.L	8	27.99	21.92	38.79	5.55	26.57	22.49	32.05	3.63	2.03	2.69
Eth-Sp.L	10	47.84	40.65	56.61	5.09	48.59	41.87	57.32	4.28	2.06	2.05
NA-CE	10	14.87	10.66	19.52	2.69	16.36	12.76	22.28	2.89	1.93	0.67
NA-PreSph	10	56.55	51.72	62.87	3.22	58.05	54.09	64.67	3.23	1.79	0.96
NA-Rt.R	10	59.23	56.19	65.76	2.77	60.83	57.32	68.11	3.11	1.60	0.83
Op.L-Ov.L	10	27.04	24.20	30.32	1.59	27.52	25.56	31.53	1.93	1.03	0.54
Op.L-PCL.L	8	14.97	11.03	21.81	3.32	14.80	11.39	21.61	3.07	0.66	0.58
Op.R- Ov-R	10	28.36	26.19	31.67	1.47	27.97	25.54	31.54	2.10	0.87	0.70
Op.R-Op-L	10	21.50	17.21	27.10	3.17	22.16	17.99	24.57	2.27	1.58	1.35
Op.R-PCL.R	10	15.17	11.11	22.99	3.67	14.60	10.25	25.03	4.47	1.30	1.14
Ov.R-OV.L	10	46.72	42.03	52.50	2.94	47.38	43.07	53.75	3.05	1.03	0.73
PCL.L-Rt.L	8	22.38	18.58	25.26	2.38	21.91	18.42	26.04	2.11	1.06	0.71
PCL.R-PCL.L	8	11.45	6.65	15.35	3.21	11.51	8.84	15.63	2.10	1.78	1.08
PCL.R-Rt.R	10	22.59	18.57	25.60	2.38	21.89	17.44	25.57	2.37	1.07	0.93
Presph-Ov.L	10	31.07	27.50	34.64	2.27	31.45	29.53	35.74	1.92	1.20	0.80
PreSph-Rt.R	10	23.06	20.50	26.91	2.14	23.14	20.60	25.81	1.80	0.80	0.51
Rt.L-Ov.L	10	13.65	10.85	16.53	2.11	14.08	11.54	19.20	2.17	1.36	0.91
Rt.R-Ov.R	10	14.98	12.47	18.19	2.11	14.60	11.73	17.68	2.48	0.84	0.64
Rt.R-Rt.L	10	37.19	31.62	41.78	3.54	36.57	31.64	41.02	3.08	0.69	0.78
Sp.L-Rt.L	10	19.68	16.30	22.63	2.34	20.56	16.68	24.24	1.98	1.10	1.16
Sp.R-Rt.R	10	21.37	17.54	24.70	2.33	21.32	16.90	23.88	2.52	0.50	0.41
Sp.R-Sp.L	10	58.63	53.40	64.84	3.74	59.03	53.91	65.37	3.82	0.51	0.30

Chapter 3: Growth changes in the anterior and middle cranial bases assessed through cone-beam computed tomography (CBCT) in adolescents

3.1 Introduction

Knowledge of growth and development of the craniofacial structures is the corner stone in the orthodontic profession. Without understanding the normal growth pattern of the head, diagnosis and treatment planning is likely doomed to fail.

Studies have stated that the growth of the anterior cranial base is completed early in life and before other craniofacial structures (18,22,65). For this reason the anterior cranial base has been used as a reference structure in diagnosis and treatment planning of the craniofacial complex.

It has been stated in the literature that about 86% of the growth of the anterior cranial base is considered complete by the age of 4.5 years and that the remaining growth contributes to increases in the length of the anterior cranial base (sella-*nasion*) even after puberty.(26) The growth in length of the anterior cranial base has been investigated based on measurement of the three osseous components: 1) *frontal*, 2) *ethmoid*,3) *sphenoid* regions.

Increases in the thickness of the *frontal* bone, apposition in the glabella region, and increases in the size of the *frontal* sinus contribute to increases in the length of the anterior cranial base measurements like N-S line and forward movement of *nasion* until adulthood (3.3% increase in the *frontal* bone segment from age 6 until early adulthood(19)).(21-23)

The antero-posterior length of the *presphenoid* region was reported to be stable after the age of 7 years as assessed by cross sectional and longitudinal

studies.(17,19,22) A 5-year longitudinal study evaluating exclusively the growth of *planum sphenoidale* to *dorsum* sella, reported its reasonable stability to be used for superimposition, but the same study mentioned that the *hypophysial* fossa deepened in a small sample of subjects who were observed for longer than 5 years.(18) Bjork (23) also observed remodeling of *sella turcica* during growth, resulting in displacement of *sella* downward and backward. He recorded an elevation of the *tuberculum sella* in relation to other structures of the anterior cranial fossa. The *cribriform* plate of the *ethmoid* is also considered stable after age of 4.(19,22)

As one can observe, data on changes in cranial fossa post natal growth is directed predominantly to sagittal growth changes. To determine stability of structures in all three planes of space (coronal, axial and sagittal) further analysis is required. As it is known the cephalocaudal growth gradient not only exists in the body but there is one in the face as well.(31) It would be interesting to see whether growth in the cranial base follow the same gradient.

Using measurements to study human proportions has been reported since the fifteenth century. Leonardo da Vinci (1452-1519) was probably one the first people who applied head measurements in to practice. He used variety of lines on his pen and ink drawings to break the human skull in to smaller parts to understand the human form. Today, for dental, maxillofacial surgery and orthodontic applications cone-beam computed tomography (CBCT) can potentially overcome some of the limitations that all other previous methods of imaging and measuring techniques have portrayed. Analysis of CBCTs allows assessment of three-dimensional dental, skeletal, and soft-tissue changes for both growing and non-growing patients.

A stable reference structure is required for standardized record of the relationship between dento-facial structures assessed at different time points. Anterior cranial base structures' two-dimensional stability in the sagittal plane has been determined repeatedly (1). Most widely accepted method uses the anterior cranial base sagittal dimension (SN line) to superimpose two serial cephalometric tracings to evaluate relationship of structures at different time points (2). To our knowledge three-dimensional change in size and displacement of the cranial base structures has not been analyzed yet. In our study, the anterior and middle cranial base structural changes due to growth in adolescents will be assessed in three-dimensions using cone beam computed tomography. The results of our study will determine which components of the anterior and midline cranial bases are stable in size in three-dimensions during this specific time period. These structures if proven to be stable can be used in three-dimensional superimposition techniques.

3.2 Material and Methods

This investigation is a retrospective observational longitudinal study, approved by the University of Alberta research ethics board.

The CBCT data used in this study was collected from a private practice (Mill Valley, CA) generated by a 2nd generation I-CAT machine (8.9sec exposure time, 16x13 FOV, 0.4 voxel size). 148 patients who had initial (pre-orthodontic treatment) and final (post orthodontic treatment) CBCT x-ray records generated between December 2008 and December 2011 were selected. The patients had class I and II malocclusion and received full fixed orthodontic treatment. Some of the patients had tooth anchored

expansion appliances. The assumption is that orthodontic treatment does not influence the growth of the cranial base.

Random numbers were assigned for the 148 patients. 12 cases of patients over 16 years of age at time point 1 were excluded. We had access to a final number of 99 patients with available initial and final CBCTs. Among them a final sample of 60 patients were selected.

Inclusion criteria:

1) In order to get a sample that includes all age ranges, 30 individuals with age range 11- 13 and 30 individuals with age range of 13-15.5 who had the largest interval between T1 and T2 CBCTs in their age range were selected. The interval between T1 and T2 ranged from 1.2 years to 2 years apart with most samples being 1.4 -1.8 years apart (Patients with CBCTs beyond that range were not included in order to get a more homogenous sample in terms of difference between initial and final CBCT)

2) Good quality CBCTs at both time points

The mean age of patients at the time of the first CBCT was 13 ± 1.1 years (minimum of 11 years and maximum of 15.4 years). The mean age at time point 2 and the mean of time difference between the two time points are presented in Table 3.1. The sample included 17 males and 42 females (sex of one of the patients was not recorded).

Table 3.1 Minimum, maximum and mean age at T1, T2 and the difference

	N	Minimum	Maximum	Mean	Std. Deviation
Age at T1	60.0	11.0	15.4	13.0	1.1
Age at T2	60.0	12.7	17.0	14.6	1.1
T2 -T1 (years)	60.0	1.2	2.0	1.6	0.2

The 19 landmarks which shown previously in chapter 2 to have acceptable intra-rater reliability and accuracy (Tables 2.4 and 2.8) were marked on three-dimensional images at time point 1 (pre-treatment) and time point 2 (post-treatment). Twenty linear measurements were generated (Table 3.2) using the following equation at each time point using the Cartesian coordinates of the landmarks.

$$d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2}$$

Where d is the distance (mm) between the two anatomic landmarks and x_1, y_1, z_1 and x_2, y_2, z_2 are the coordinates of the two landmarks at the two end of the linear measurement.

Each landmark was included in multiple linear measurements of different orientations to be able to assess all dimensions (superior-inferior, anterior-posterior, right-left).

Table 3.2 Linear measurements

Anterior-Posterior (A-P)	
1. Na – Ce	The distance between *Nasion* and foramen *Cecum*
2. Na – Eth	The distance between *Nasion* and posterior border of the *ethmoid* bone
3. Ce – eth	The distance between foramen *Cecum* and the posterior border of the *Ethmoid* bone
4. Eth- Presph	The distance between the posterior border of the *ethmoid* bone and posterior limit of *tuberculum sella*
Right-Left (R-L)	
1. ACL.R – ACL.L	The distance between the anterior *clinoid* processes right and left
2. PCL.R _ PCL.L	The distance between the posterior *clinoid* processes right and left
3. Op.R- Op.L	The distance between the *Optic* canals right and left
4. Rt.R - Rt.L	The distance between the foramina *Rotundum* right and left
5. Ov.R - Ov.L	The distance between the two foramina *Ovale* right and left
6. Sp.R - Sp.L	The distance between the two foramina *Spinosum* right and left
Superior-Inferior (S-I)	
1. Ce – Cg	The distance between foramen *Cecum* and tip of the *crista galli*
2. Na – Ov.R	The distance between *Nasion* and foramen *Ovale* right
3. Na – Ov.L	The distance between *Nasion* and foramen *Ovale* left
4. Op.R – Rt.R	The distance between *Optic* canal right and foramen *Rotundum* right
5. Op.L – Rt.L	The distance between *Optic* canal left and foramen *Rotundum* left
6. Presph – Ov.R	The distance form *tuberculum sella* to foramen *Ovale* right
7. Presph-Ov.L	The distance form *tuberculum sella* to foramen *Ovale* left
8. MidRts – Presph	The distance between the right and left foramina *Rotundum* to posterior limit of *Tuberculum* Sella
9. MidOvs – Presph	The distance between the right and left foramina *Ovale* to posterior limit of Tuberculum *Sella*
10. MidSps – Presph	The distance between the right and left foramina *Spinosum* to posterior limit of *Tuberculum Sella*

3.3 Statistical analysis

A standard statistical software package (SPSS version 20, Chicago, Ill) was used for data analysis. A sample size of 60 was selected without a power analysis due to lack of preliminary study at the time of data collection. In addition, 60 specimens are two times more than the number of specimen usually recommended to determine significance in our research settings. (64) Growth changes in the cranial base were assessed by repeated measures multivariate analysis of covariance MANCOVA (followed by post-hoc analysis) with one within-subject factor of Time with 2 levels (T1 and T2), while considering the patients' age at the initial imaging as covariate.

There were twenty (20) continuous dependent variables which are the distances measured in millimeters between two landmarks (table 3.2). Descriptive statistics were generated for each variable (Appendix 3.1).

Patients' age at the initial imaging was considered as a covariate to control for differences in age of individuals at time point 1. To avoid misleading results, the influence of individual's age at initial imaging was controlled by implementing it in the statistical analysis as a covariate. The purpose of including a covariate is to remove the variability of age across individuals at the time of the initial CBCT from the measure of growth.

Prior to completing testing statistical significance, model assumptions were evaluated. The repeated measures MANCOVA hypotheses tested could be found in Appendix 3.2. A *p* value less than 0.05 was considered as significant.

Prior to performing the repeated measures MANCOVA statistical analysis, the data was checked for model assumptions. All data was checked for multivariate normality, visually via Q-Q plot and box plot of the Mahalonobis distance of the difference between time 1 and time 2 of each distance (dependent variable) (Appendix 3.3). The assumption of normality was met as assessed visually. Assumption of linearity of repeated measures was met as assessed by bivariate scatter plots of variables (Appendix 3.4). Sphericity assumption was not applicable to Time factor since it only has two levels. Homogeneity of regression slopes was satisfied as a significant interaction did not exist between time and age (Appendix 3.5). Correlation was assessed by regression analysis on age (covariate) and difference between T2-T1 for all the dependent variables. Age as a covariate was not well correlated with either of the repeated response variables (Appendix 3.6). In addition, the overall repeated measures MANCOVA test results suggest that age did not have a significant effect as a covariate ($F(20,39)=1.526$, $P=0.127$, Wilks' $\Lambda = 0.561$, partial $\eta^2 =0.439$), consequently, the covariate was eliminated and the analysis was repeated without the covariate.

3.4 Results

The repeated measures MANOVA test (without a covariate) revealed evidence of a statistically significant difference between the mean of distances at T1 compared to T2 on the combined dependent variables, $F(20,40) = 6.555$, $p < .0001$; Wilks' $\Lambda=0.234$; partial $\eta^2 = 0.766$. The partial eta square of the time factor (partial $\eta 2 = 0.766$) determines that time change accounted for 77% of the total variability in the linear measurements. In other words 77% of the variability in measurement at T1 and T2 are

explained by time (growth). Naturally occurring individual variability, procedural variability like landmark positioning, measurement error and partial volume effect could be possible sources of the remaining variability in the data. Post hoc analysis with a Bonferroni adjustment results are presented in table 3.2.

Table 3.2 MANOVA pairwise comparisons

Distance	Mean Difference T2-T1	St Deviation	P value	95% Confidence Interval for Difference		Percentage change
				Lower Bound	Upper Bound	
Na_ Ce	0.68	1.07	<0.0001	0.41	0.95	4.9%
Na_Eth	-0.02	1.84	0.940	-0.51	0.48	N/A
Ce_Eth	-0.34	1.93	0.182	-0.84	0.16	N/A
Eth_Presph	0.55	2.14	0.048	0.01	1.09	2.9%
ACL.R_ ACL.L	0.18	0.98	0.173	-0.08	0.43	N/A
PCL.R _ PCL.L	0.12	1.61	0.576	-0.30	0.54	N/A
Op.R_Op.L	0.98	2.05	<0.0001	0.45	1.50	4.1%
Rt.R_Rt.L	0.81	0.74	<0.0001	0.62	1.01	2.2%
Ov.R_Ov.L	0.53	1.28	0.003	0.18	0.88	1.1%
Sp.R_Sp.L	1.05	1.04	<0.0001	0.77	1.32	1.7%
Ce_Cg	0.12	1.17	0.399	-0.17	0.42	N/A
Na_Ov.R	0.72	1.04	<0.0001	0.43	1.00	0.9%
Na_Ov.L	0.59	1.20	<0.0001	0.29	0.90	0.8%
Op.R_Rt.R	0.02	0.94	0.826	-0.20	0.25	N/A
Op.L_Rt.L	0.05	0.87	0.633	-0.17	0.28	N/A
Presph_Ov.R	0.53	1.19	<0.0001	0.25	0.81	1.6%
Presph_Ov.L	0.50	1.36	0.007	0.14	0.86	1.5%
MidRts_Presph	0.35	0.91	0.003	0.12	0.58	2.1%
MidOvs_Presph	0.46	1.21	0.003	0.16	0.75	2.0%
MidSps_Presph	0.48	1.32	0.006	0.14	0.81	1.9%

The pairwise comparisons revealed evidence that the mean of the following linear measurements increase from time 1 to time 2 (table 3.2).

- Na - Ce mean distance increases by 0.68 mm (95% CI:0.41 – 0.95, P<0.0001)
- Op.R - Op.L mean distance increases by 0.98 mm (95% CI:0.45 – 1.50, P<0.0001)
- Rt.R – Rt.L mean distance increases by 0.81 mm (95% CI: 0.61 – 1.00, P<0.0001)
- Sp.R – Sp.L mean distance increases by 1.04 mm (95% CI: 0.77 – 1.32, P<0.0001)
- Na – Ov.R mean distance increases by 0.72 mm (95% CI: 0.43 – 1.00, P<0.0001)
- Na – Ov.L mean distance increases by 0.59 mm (95% CI: 0.29 – 0.90, P<0.0001)
- Presph – Ov.R mean distance increases by 0.53 mm (95% CI: 0.25 – 0.81, P<0.0001)
- Ov.R – Ov.L R distance increases by 0.53 mm (95% CI: 0.18 – 0.88, P=0.003)
- PreSph – Ov.L distance increases by 0.50 mm (95% CI: 0.15 – 0.86, P=0.007)
- MidRts – PreSph distance increases by 0.35 mm (95% CI: 0.12 – 0.58, P=0.003)
- MidOvs – PreSph distance increases by 0.46 mm (95% CI: 0.16 – 0.75, P=0.003)
- MidSps – PreSph distance increases by 0.48 mm (95% CI: 0.14 – 0.81, P=0.006)

There was suggestive but weak evidence (Appendix 3.7) that the distance Eth-PreSph increases by 0.55 mm over time (95% CI: 0.01 – 1.10, P=0.048).

There was no evidence of difference in mean distance measurements from T1 to T2 for other levels of orientation (Na_Eth, Ce_Eth, ACL.R_ ACL.L, PCL.R _ PCL.L, Ce_Cg, Op.R_Rt.R, Op.L_Rt.L)

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3.5 Discussion

Orthodontists are usually interested to see whether their patients are still growing or not. In order to make that decision, some stable reference structures are needed. The serial images are superimposed on stable structures to see changes in growing facial structures. Historically, the anterior cranial base sagittal dimension has been used as a reference structure in lateral cephalometry superimpositions. In this study, the growth of the human skull base in adolescent years is studied with the use of CBCT. The stability of anterior and middle cranial base structures was assessed in sagittal, coronal and axial dimensions during approximately 19 months in adolescents. Although statistical differences were evident between some measurements from T1 to T2, there are factors affecting the interpretation of the results. The voxel size of 0.4 mm could affect the results. Since the majority of the mean differences in measurements from T1 to T2 are less than 1 mm (Standard deviations ranging from 0.87 to 2.14), 0.4 mm voxel size error at both ends of a linear measurement could easily cause a magnitude of zero to 0.8 mm difference in the difference. With the above mentioned, the statistically significant results should be interpreted cautiously.

Measurement error should be considered in interpreting the numerical data. There are a number of sources of error influencing the numerical data. Variation in landmark identification directly contributes to measurement error due to cumulative nature of error.(66) In addition, in three-dimensional images compared to two-dimensional, an extra dimension would be an extra source of error.

Another source of measurement error in linear measurements is that the closer the two landmark constituting the segment, the greater is the percentage of the error introduced.(42)

In the present study, the anterior and middle cranial bases were assessed in three planes of anterior-posterior, right-left and superior-inferior.

Negligible change was found in the anterior-posterior measurements. Even though, 4.9% increase in the distance between *nasion* and foreman *Caecum* was observed. This distance is relatively small (about 13 mm), therefore measurement error does amplify and become more evident in smaller distances (42,67). Increase in the thickness of the *frontal* bone, apposition in the glabella region, and increases in the size of the *frontal* sinus contribute to increases in the length of the anterior cranial base and forward movement of *nasion* until adulthood (3.3% increase in the *frontal* bone segment from age 6 until early adulthood, $P < 0.01$, as reported by Knott (19); (21-23). These findings are similar to the our results however, in our study we are looking at a relatively short period of time (average of 19 months) and it is self-evident that significant change would not be observed in 1.6 years (approximately 19 months) length of time.

Given that the middle part of the anterior cranial base (*ethmoid* bone and *presphenoid* region) reach adult dimensions by about the 7^{th} year (1,68) , one should not overlook the stabilization of this area. We were not able to detect any change in the position of *nasion* except for one measurement Na-Ce during our study period. The findings of our study on antero-posterior position of *nasion* were contradictory, as one of the measurements including this landmark (Na-Eth) did not show any change while the other (Na-Ce) showed some change (the effect of the length of this segment on the

findings was discussed earlier). However, *nasion* has been reported as an undesirable landmark to be included in measurements as its position changes with age and makes the cranial base measurements unreliable.(19,69) The anterior cranial base measurements excluding the *frontal* bone would possibly contribute to more accurate measurements. The foramen *Caecum* which is the true anterior point of the cranial base (70), or the tip the *crista galli* could be possible alternatives to *nasion* on CBCT.

From the results of this study, it could be observed that the mid-sagittal area of the anterior cranial base from foramen *Caecum* to the *presphenoid* area in the antero-posterior dimension is stable during the average 19 months of evaluation (mean age of 13 years). This finding is in concordance with other studies that assessed the growth of this part of the cranial base. (1)

The changes in right-left dimension were assessed by measuring the distance between the right and left anterior and posterior *clinoid* processes, *optic* canals and foramina *Rotundum*, *Spinosum* and *Ovale*. Interestingly, the distances measured between foramina and canals which were measured by placing a marker of 0.25 mm at the center of the identifiable circumference of the canal or foramina (position of the identifiable circumference was different for each landmark, landmark definition is presented at table 2.2) showed evidence of increase in size. No change was observed between the right and left anterior and posterior *clinoid* processes. However, the mean amount of increase in these transverse distances was equal or less than 1.05 mm (≤1.05 mm). The largest amount of increase was observed in between *optic* canals right and left (4.1% or 0.95 ± 2 mm). The examiner showed high intra-rater reliability in

marking all the landmarks included in the study (Table 2.4, x axis). Changes in the transverse dimension of the cranial base have not been studied previously.

The superior-inferior dimension was assessed by 10 linear measurements (table 3.1). Among those, five linear measurements were from *Pre-sphenoid* landmark to another true or constructed landmark in the middle cranial base. There was evidence of some change in all these five vertical linear measurements. But this change was within 1.5 to 2 % of the original distance (mean change was less than 0.53 mm). Nevertheless, Melsen (17) recognized some appositional activity in the histologic assessments of the *presphenoid* region in the prepubertal stages that would modify the height of the region. Bjork (9) also observed opposition on the *Tuberculum sellae* from late juvenile years to adulthood on serial lateral radiographs. The finding of our study supports the above studies' findings in a way. One could argue that statistically significant increase in the vertical length of the middle cranial base; even though small (≤ 0.53 mm or 1.5-2.1 %), measured from *Pre-sphenoid* region is merely due to measurements error. However, the intra-rater reliability of identifying the landmarks used in vertical measurements showed excellent results. It is not easy to firmly draw a conclusion whether there is true change in vertical dimension due to appositional activity in the *pre-sphenoid* region. Further investigation of CBCTs taken at longer intervals would definitely help in clearer conclusions.

All in all, minor changes were observed in the anterior and middle cranial base structures assessed in this study. The magnitude of the changes were very small and could be reflective of measurement error. The recommendation would be to repeat the study on a different sample in the future to confirm findings. Isolated segments of cranial

base where the landmarks are not shared in multiple distances are preferable. Fewer variables would increase the power of the statistical analysis and reduce cumulative effect of measurement error.

Limitations

Some important limitations exist in our study. First the stability of the cranial base structures were assessed during relatively short amount of time. The CBCTs included in our study were on average 19 months apart during adolescent years. This limitation is due to the data available to us. Ideally, a long term observation time with more frequent CBCTs at longer intervals would give a better picture of the possible changes and helps clarifying the areas of doubt with limited observation time.

Secondly, it should be noted that the twenty linear measurements were derived from the same CBCT image and were constructed from a total of seventeen landmarks. This means that each landmark was used in at least two or more linear measurements and its measurement error was employed in computation of each of these measurements. Although, this limitation problem is not limited to our study and is inherent to any cephalometric study using linear or angular measurements.

Another source of measurement error in three-dimensional radiographic imaging in this study is the possible effect of the segmentation process. The surface model construction in CBCT is based on the voxel based data. A threshold value specifies each structures whether it is bone or soft tissue. The threshold value and gray value entered by the operator in to the CBCT machine determines the image accuracy. Also, the CBCT imaging lacks beam homogeneity which means that the gray value of the

voxels of the CBCT of the same individual at different time points differ. (45,66) In our study, the main method of landmark identification was multi-planar by checking the landmarks on axial, coronal and sagittal slices. This technique would decrease the measurement error compared to relying only on surface model for location of the landmark.

There were more female patients included in our sample than males (42 females versus 17 males). We did not consider gender in our data analysis. As it is known that girls' growth timing is different from boys, the results could be affected if gender was taken in to account.

3.6 Conclusions

The superior-inferior, anterior-posterior, right-left dimensions of the anterior and middle cranial base structures showed minor changes during the average 19 months of our study. The mid-sagittal area of the anterior cranial base from foramen *Caecum* to the *presphenoid* area in the antero-posterior dimension was found to be stable. However, it should be noted that these results are only applied to the age range of our sample (Mean age at T1 was 13.1± 1.1 years ranging from 11 to 15.4).

The magnitude of the changes observed were very small and could be reflective of measurement error. The recommendation would be to repeat the study on another sample in the future to confirm these findings

3. 7 Appendices

APPENDIX 3.1 DESCRIPTIVES OF REPEATED MEASURES FOR ALL DISTANCES

		T1				T2				Difference T2-T1			
Distances	N	**Mean at T1**	Std. Deviation	Minimum	Maximum	**Mean at T2**	Std. Deviation	Minimum	Maximum	**Mean**	Std. Deviation	Minimum	Maximum
Na_ Ce	60	**13.20**	2.25	9.00	18.00	**13.88**	2.60	9.00	19.89	**0.65**	1.07	-2	4
Na_Eth	60	**43.50**	3.93	35.00	52.00	**43.48**	4.03	33.08	52.00	**0.02**	1.85	-4	6
Ce_eth	60	**32.49**	4.14	21.61	41.10	**32.16**	4.26	21.14	39.79	**-0.30**	1.92	-4	3
Eth_Presph	60	**17.80**	3.38	9.94	24.00	**18.35**	3.47	11.39	26.43	**0.52**	2.14	-6	6
ACL.R_ ACL.L	60	**23.93**	2.09	20.16	28.00	**24.11**	1.82	20.19	28.00	**0.23**	0.98	-1	3
PCL.R _ PCL.L	60	**11.79**	2.50	7.00	18.00	**11.91**	2.41	7.00	18.00	**0.08**	1.61	-3	4
Op.R_Op.L	60	**22.75**	2.59	17.14	32.00	**23.73**	2.72	19.00	31.00	**0.95**	2.05	-5	6
Rt.R_Rt.L	60	**35.86**	3.14	27.71	47.00	**36.67**	3.12	28.59	47.00	**0.72**	0.74	-1	2
Ov.R_Ov.L	60	**47.94**	2.71	40.90	54.00	**48.47**	2.93	42.40	54.00	**0.42**	1.28	-3	3
Sp.R_Sp.L	60	**60.50**	3.37	54.18	70.00	**61.54**	3.38	55.00	70.00	**1.03**	1.04	0	5
Ce_Cg	60	**7.15**	2.34	2.38	13.00	**7.27**	2.37	2.00	13.00	**0.13**	1.19	-2	4
Na_Ov.R	60	**77.53**	3.57	67.30	85.00	**78.24**	3.81	68.72	88.00	**0.78**	1.04	-2	4
Na_Ov.L	60	**77.36**	3.56	69.89	85.00	**77.95**	3.64	69.53	86.00	**0.67**	1.20	-3	3
Op.R_Rt.R	60	**17.52**	1.90	13.28	22.00	**17.55**	2.06	13.13	22.00	**0.03**	0.94	-3	2
Op.L_Rt.L	60	**16.97**	1.84	13.33	22.00	**17.02**	1.88	13.00	21.00	**0.02**	0.87	-2	2
Presph_Ov.R	60	**33.48**	1.88	28.71	37.00	**34.00**	2.31	29.02	38.00	**0.48**	1.19	-2	3
Presph_Ov.L	60	**32.84**	2.36	26.58	38.00	**33.34**	2.47	27.51	38.00	**0.55**	1.36	-2	3
MidRts_Presph	60	**16.61**	2.21	11.59	21.00	**16.96**	2.29	11.84	21.00	**0.23**	0.91	-2	3
MidOvs_Presph	60	**22.88**	1.92	18.63	28.00	**23.33**	2.12	18.00	27.25	**0.48**	1.21	-3	3
MidSps_Presph	60	**25.08**	1.97	21.00	31.00	**25.55**	2.25	21.00	32.39	**0.48**	1.32	-3	4

APPENDIX 3.2: HYPOTHESIS TESTS FOR REPEATED MEASURES MANCOVA STATISTICS

Hypotheses for the interaction between age (Covariate) and the factor Time (model assumption)

*H*0: There is no interaction between Age and Time

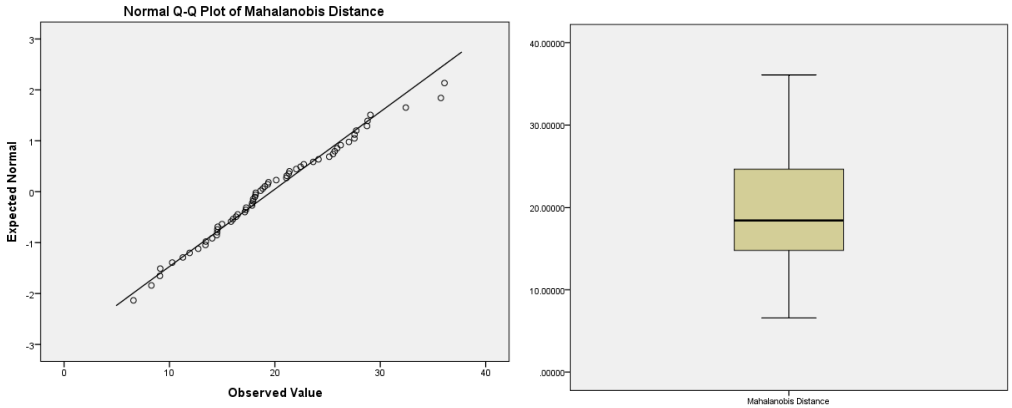
Ha : There is an interaction between Age and Time.

Main hypothesis

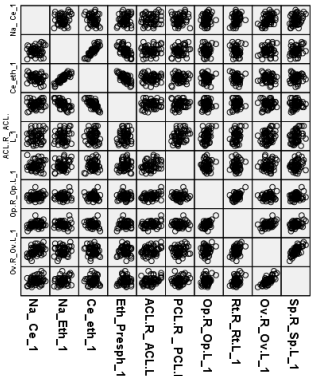
*H*0 : The mean of the twenty different linear measurements, when considered jointly, were the same at T1 and T2, when age was considered as a covariate.

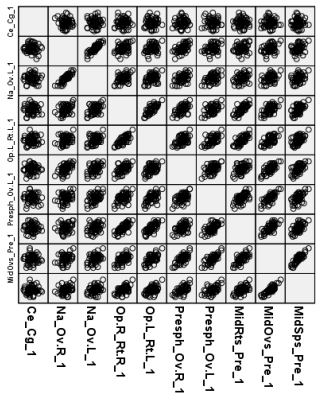
Ha: The mean of the twenty different linear measurements, when considered jointly, were not the same at T1 and T2, when age was considered as a covariate.

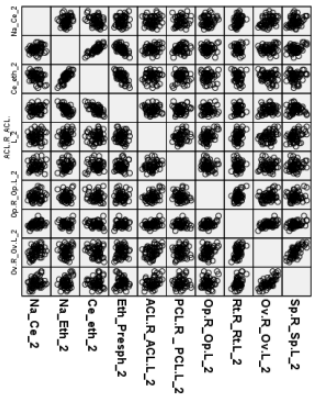
APPENDIX 3.3 Q-Q PLOT (LEFT) AND BOX PLOT (RIGHT)OF THE MAHALANOBIS DISTANCE.

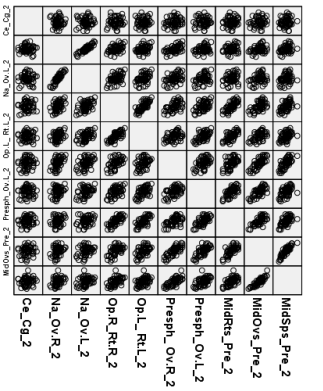


APPENDIX 3.4 BIVARIATE SCATTER PLOTS OF MEASUREMENT AT T1 (ABOVE) AND T2 (BELOW) . ALL THE VARIABLES WERE NOT INCLUDED AT ONE TIME DUE TO LIMITATION OF SPSS IN GENERATING A READABLE 20X20 TABLE. 8 VARIABLES WERE ADDED IN EACH TABLE.









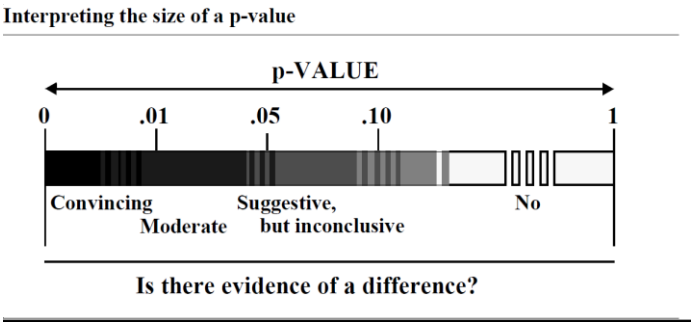
APPENDIX 3.5 REPEATED MEASURES MANCOVA RESULTS FOR INTERACTION BETWEEN AGE AND TIME

	F-STATISTIC	P-VALUE (WILK'S LAMBDA)	PARTIAL ETA SQUARE
TIME X AGE	1.106	0.382	0.362

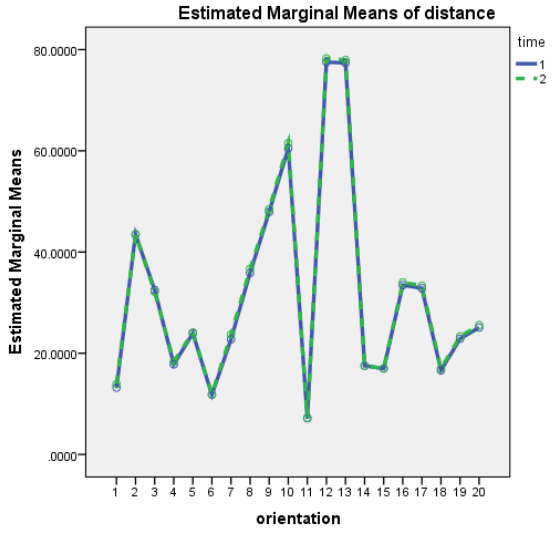
APPENDIX 3.6 PEARSON CORRELATION FOR AGE (COVARIATE) WITH T2-T1 DIFFERENCE OF DISTANCES

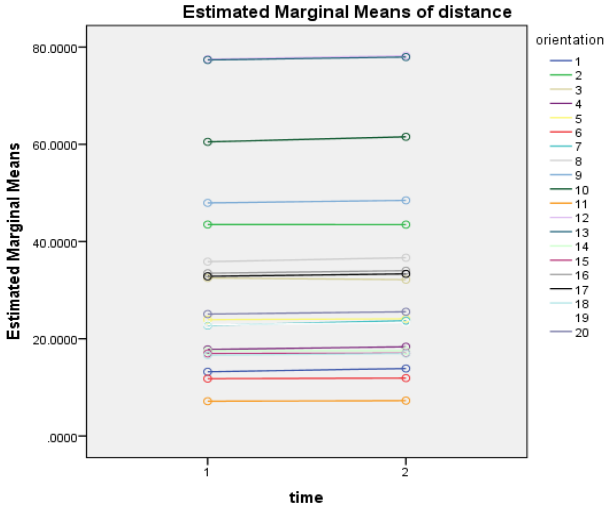
Distance difference T2-T1	Pearson correlation (r)
DiffNa-Ce	0.111
DiffNa-Eth	0.095
Diff Ce-eth	-0.006
Diff Eth-presph	-0.101
Diff ACL.R-ACL.L	0.030
Diff PCL.R - PCL.L	0.100
Diff Op.R- Op.L	-0.180
Diff Rt.R - Rt.L	-0.103
Diff Ov.R - Ov.L	-0.117
Diff Sp.R - Sp.L	-0.328
Diff Ce - Cg	-0.233
Diff Na - Ov.R	-0.228
Diff Na- Ov.L	-0.191
Diff Op.R-Rt.R	0.054
Diff Op.L - Rt.L	0.017
Diff Presph -Ov.R	-0.071
Diff Presph - Ov.L	-0.026
DiffMidRts - Presph	0.107
DiffMidOvs - Presph	-0.044
DiffMidSps - Presph	0.000

APPENDIX 3.7 INTERPRETATION OF THE SIZE OF P-VALUE



APPENDIX 3.8 PROFILE PLOTS OF ESTIMATED MARGINAL MEANS OF DISTANCES





Chapter 4: General discussion

4.1 Discussion

The main objective of this thesis was to assess the normal growth and development changes in the anterior and middle cranial bases in a specific period during adolescence. The changes of the structures relative to each other was assessed over an average period of 19 months using three-dimensional cone beam tomography (CBCT) images acquired from an I-CAT machine.

Two research questions were identified:

Question #1:

a) Within the anterior and middle cranial bases, which landmarks are the most repeatable (intra-rater reliability) and reproducible (inter-rater reliability) on three-dimensional craniofacial images?

b) Are the best landmarks identified while answering the first question accurate and represent the anterior and middle cranial base structures?

Question #2: Are the anterior and middle cranial base structures dimensionally stable during adolescent years?

The research started by determining the intra-rater and inter-rater reliability of nineteen anatomical landmarks in CBCT images. Most of the landmarks are not commonly used in cephalometric analysis since it is not possible to identify them on two-dimensional cephalometric analysis. The landmarks were initially selected on dry skull and then checked for reliability on CBCTs. They needed to be easily identifiable, as the tip of the spine, or projections and the center of foramina. Two landmarks

selected were on a flat surface (*ethmoid* and *pre-sphenoid*), which could make them harder to locate.

For the purpose of our research, all the landmarks assessed in this study (except right and left lesser wing landmarks) showed acceptable intra-rater reliability and accuracy to be used in the growth assessment study of this thesis.

In general all the proposed 3D landmarks with the exception of lesser wing and foramen *Spinosum* showed acceptable intra-rater and inter-rater reliability and could be used for future growth assessment and 3-dimensional superimposition analysis if their individual limitations are fully understood.

The following landmarks were proposed:

Nasion, foramen *Caecum*, tip of *crista galli*, *ethmoid*, *pre-sphenoid*, anterior *clinoid* process, posterior *clinoid* process, *optic* canal, foramina *Rotundum* and *Ovale* (Table 2.2).

Finally, the landmarks identified and assessed in the first part, were used to compare linear measurements between two time points. The mid-sagittal area of the anterior cranial base from foramen *Caecum* to the *presphenoid* area in the antero-posterior dimension was found to be stable. Minor changes were observed transversely and vertically in the anterior and middle cranial base structures assessed in this study. Transverse assessment of the growth of the cranial base has not been done previously. The magnitude of the changes were very small and could be reflective of measurement error. The recommendation would be to repeat the study in another sample and analyze these areas to confirm findings.

4.2 Limitations

Reliability chapter:

There are numerous factors which should be considered when applying the results of this investigation to clinical situations. First and foremost, this study was performed on dry skulls. The reliability of landmark identification on live individuals may be affected by decrease in image quality due to soft tissue attenuation. Incorporating use of Plexiglas box filled with water in our study design was to imitate soft tissue and reduce error.

We conducted this study on 10 dry skull specimens. As recommended by Springate (64) a higher number (25-30) of specimen would be advantageous in positively affecting the reliability of our results.

Some landmarks showed higher inter-rater measurement errors and less ICC values in specific axes. This could be due to difference in raters' technique. Each rater might have focused on a different plane when marking a landmark. Some landmarks are easier to identify in one or two planes and pose difficulty in the third plane (50). As choosing the suitable plane for landmark placement requires time, experience, landmark identification reliability could be improved by defining a specific plane in which the landmark is easily identifiable.

The Avizo software used in this study requires a significant learning curve. The raters in this study, even though trained, had different levels of experience with the software. In addition, the software does not allow viewing the landmarks in all three planes as the same time. The observer requires to change the plane to check the

position of the landmark in different planes. A more user friendly software could facilitate and expedite raters' learning and increase inter-rater agreement.

Growth assessment chapter

First the stability of the cranial base structures were assessed during relatively short amount of time. The CBCTs included in our study were 18 months apart. This limitation is due to the data available to us. Ideally, a long term observation time with more frequent CBCTs at longer intervals would give a better picture of the possible changes and helps clarifying the areas of doubt with limited observation time.

Secondly, another source of measurement error in three-dimensional radiographic imaging in this study is the possible effect of the segmentation process. The surface model construction in CBCT is based on the voxel based data. A threshold value specifies each structures whether it is bone or soft tissue. The threshold value and gray value entered by the operator in to the CBCT machine determines the image accuracy. Also, the CBCT imaging lacks beam homogeneity which means that the gray value of the voxels of the CBCT of the same individual at the same time points differ. (45,66) In our study we identified the landmarks on axial, coronal and sagittal slices. This technique would decrease the measurement error compared to relying only on surface model for location of the landmark.

There were more female patients included in our sample than males (42 females versus 17 males). We did not consider gender in our data analysis. As it is known that girls' growth timing is different from boys, the results could be affected if gender was taken in to account.

4.3 Future recommendations

1. Ideally landmark identification reliability assessment should be done on a sample of human CBCTs. This will eliminate the effects of absence soft tissue structures in dry skulls on the precision of landmark identification.

2. The patients included in our study had two CBSTs taken at 19 months apart. Growth assessment studies are usually done longitudinally and monitor patients for long-term. In order to get a clear image of true changes in anterior and middle cranial base, repeating the study on CBCTs taken farther apart or assessing growth on serial CBCTs is recommended.

3. In our study, we did not differentiate sex of the sample, and both female and male were pooled in to one sample. This was partly due to the need to maintain statistical analysis under control and avoid complicating the analysis by looking at too many variables at the same time. Comparing male and female in terms of timing of growth is recommended.

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