Accuracy and reliability of CBCT imaging for adenoid hypertrophy screening among a sample of oral maxillofacial radiologists and orthodontists and by an automated commercial imaging software

by

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ABSTRACT

Objectives. This thesis project aimed to investigate the diagnostic performance of different dental specialists and a popular dental imaging software to evaluate adenoidal hypertrophy compared with the current reference standard diagnosis by a Otorhinolaryngologist – Head and Neck Surgeon (OHNS) using Nasopharyngoscopy (NP). The specific questions to be answered were: (1) the reliability and accuracy of orthodontists when using Cone-Beam Computer Tomography (CBCT) imaging to evaluate adenoid hypertrophy as compared to the OHNS; (2) the accuracy and reliability of Oral Maxillofacial Radiologists (OMFRs) when evaluating CBCT imaging for adenoid hypertrophy screening as compared with OHNS, and (3) the correlation of volumetric and cross-sectional measurements generated from a CBCT automatic segmentation and 3D reconstruction for evaluating adenoid hypertrophy determined by OHNS.

Materials and Methods. A pool of already available CBCT patient heads scans and their respective NP-based adenoid hypertrophy diagnosis were explored for this thesis project. Randomly selected orthodontists from a Canadian city and a significant number of boarded-certified OMFRs from North America were invited to participate. Both specialist samples evaluated 10 CBCT reconstructions via InVivo software viewer and classified the adenoid hypertrophy as mild (0-25%), moderate (26-50%), advanced (51-75%) and severe (higher than 75%). Intraclass Correlation (ICC) and Kappa test were used to test consistency and agreement between participants. These results were later compared to the reference standard diagnosis in an attempt to determine the dental specialists accuracy and reliability. In the last part of this project, 38 scans were reconstructed using Dolphin © Imaging software, which provided automated area and volume measurements of a delimited airway area. This study followed a previously validated method to map the nasopharyngeal area/volume. Two previously trained and calibrated operators applied the standardized method. ICC confirmed their intra- and inter- operator reliability. The capability of the software measurements of volume (mm^3) and minimal cross-sectional area (mm^2) of the upper airway was correlated with the level of obstruction determined by the OHNS by using Spearman's Rank Correlation (ρ).

Results. Overall, the inter-rater reliability of the fourteen orthodontists was excellent (ICC=0.941; CI 95% = 0.882-0.984). On the contrary, their accuracy against NP was poor (ICC_{mean}= 0.39; ICC_{range} = 0.00 - 0.74). Their "statistical mode" accuracy, representing the value that appears the most, was moderate (ICC=0.753; CI 95% 0.119-0.937). Thereafter a Kappa (K) test analyzed the data grouped dichotomously, as healthy and unhealthy, and the orthodontists poor accuracy was still confirmed K_{mean}= 0.44 and K_{range}= 0.20-0.80. In contrast, the reliability between the thirteen OMFRs were good (ICC=0.79; CI 95% 0.63-0.93). The "statistical mode" was very good (ICC=0.81; ICC_{range} =0.43-0.94). The accuracy of OMFRs against NP was good, ICC_{mean}= 0.69; 0.43-0.94). In average, the K_{mean}= 0.77 and K_{range}= 0.62-0.92 demonstrated a good agreement between the OMFRs and OHNS. The individualized results from each evaluator, Orthodontists and OMFRs, were also presented and investigated according to their performance. The results of the CBCT automatic segmentation and 3D reconstruction software capability showed that intra- and inter-operator reliability was excellent (ICC > 0.95); however, the correlation of the software measurements for both, volume (ρ = -0.222) and minimal cross-sectional area (ρ= 0.192), were weak and not statistically significant.

Conclusion. The reliability of Orthodontists and OMFRs (inter-examiner reliability) to classify adenoid hypertrophy on a 4-level scale was excellent and very good, respectively. Both groups of specialists improved when the adenoid hypertrophy was classified dichotomously as healthy/unhealthy and analyzed via Kappa test. Participating orthodontists showed large variability with poor agreement of the adenoid obstruction degree compared to the OHNS

diagnosis (reference standard). This suggested that orthodontists had overall poor diagnostic accuracy for this specific scenario. These findings also suggested that orthodontists were making consistent and systematic errors in their evaluation process. The OMFRs' reliability was greater than 80% assuring their consistency and accuracy on screening adenoid hypertrophy using CBCT scans. Finally, health professionals should not rely solely on CBCT volumetric and cross-sectional measurements produced by the evaluated automatic reconstruction software to assess an upper airway constriction related to adenoid hypertrophy. The software was reliable, but the generated output for volume and cross-sectional area did not reflect very well the actual constriction determined by the OHNS via NP.

PREFACE

This thesis is an original work by Camila Pachêco Pereira. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "CBCT reliability for diagnosis of Upper Airway Dysfunction" under number Pro00043684 and "Imaging software validity to determine nasopharynx lumen" under number Pro00044649. No part of this thesis has been previously published.

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LIST OF ABBREVIATIONS

2D = Two-Dimensional

3D = Three-Dimensional

AHI = Apnea Hypopnea Index

ALARA = As Low As Reasonable Achievable

CBCT = Cone-Beam Computer Tomography

CT = Computed Tomography

DICOM = Digital Imaging and Communications in Medicine

FOV = Field of View

ICC = IntraClass Correlation

IgA = Immunoglobulin A

INS = Intranasal Spray

K = Kappa test

MCA = Minimal Cross-sectional Area

MRI = Magnetic Resonance Imaging

NP = Nasopharyngoscopy

OHNS = Otolaryngologist - Head and Neck Surgery

OMFR(s) = Oral Maxillofacial Radiologist (s)

OR = Odds Ratio

OSA or OSAS = Obstructive Sleep Apnea Syndrome

PNV = Predictive Negative Value

PPV = Predictive Positive Value

PSG = Polysomnography

RCDC = Royal College of Dentists of Canada

SBD = Sleep-disordered breathing

ROC = Receive Operator Characteristics

VNP = Videonasopharyngoscopy

Chapter 1: Introduction

1.1 Anatomy of Upper Airway Space

1.1.1 Anatomic delimitations

The upper airway space is defined as the anatomical region including all upper airway structures from above the vocal cord to its two exterior openings, the mouth and the nose.[1] The anatomic structures of the upper airway space are responsible for air conduction, for regulating the inhaled air with heat and humidity, and for the local immunologic defense by preventing external bodies to go through to the lower airway space. Other oral functions where they participate directly or indirectly are swallowing, speech and mastication.

This region includes several sub regions: the nose, the oral cavity and the tongue.

The nose consists of:

- External nose: the base lies on facial bone; anterior border named dorsum; the apex at the tip of the nose; the bony parts resulting from the fusion of the nasal bones and the midline and frontal and maxillary nasal process; the lower cartilaginous part;
- Nasal cavity: a stratified squamous epithelium on the anterior part of the nasal cavity posterior to the nostrils. It's responsible for thermic regulation. The nasal vestibule consists of resistors that slow down the air to allow it to be warmed and humidified on inspiration.
- Nasal Septum: constituted of two air passages and the choanae, which is separated by the nasal septum (ethmoid bone, septal cartilage and crest of maxilla and vomer);
- Turbinates: bone projections from the lateral wall of the nose into the nasal cavity.

The oral cavity consists of:

- The oral cavity boundaries include the teeth and periodontal tissues (anteriorly), hard and soft palates (superiorly) as well as inferiorly by the tongue and floor of the mouth and posteriorly by the pharynx.
- The tongue is composed of tissue and mucosa; it represents the muscular organ of the mouth.

The pharynx is located posteriorly to the nose and oral cavity. It is composed of three regions:

- The first sub region, nasopharynx, is lined by the pseudostratified columnar epithelium and communicates with the nasal cavities through the nasal choanae and with the middle ear through the Eustachian tube. The pharyngeal tonsils or adenoids are located in the posterior wall.[1]
- The second sub region, the oropharynx, lies behind the oral cavity, around the level of the hyoid bone and histologically is lined by nonkeratinized-stratified squamous epithelium. The tongue base represents its anterior wall; the palatine tonsils and tonsillar pillars compose the lateral walls.[1]
- The third sub region, laryngopharynx, fills up the space between the base of the tongue and the esophagus, posteriorly to the epiglottis and histologically lined by stratified squamous epithelium.[1]

In conclusion, the posterior upper airway consists of one region posteriorly to the nasal structures (nasopharynx) and the other posterior to the oral cavity (oropharynx). They both lie above the esophagus and larynx. The epiglottis separates the oropharynx into the laryngopharynx. Figure 1.1 illustrates the regions of the upper airway space.

The tonsils are lymphoid tissues on each side of the oropharynx between the palatopharyngeal and palatoglossal arch.[1] The Waldeyer's Ring is a medical term that consists of the arrangement of the lymphoid tissues located on the pharynx, it comprises of two palatine tonsils, the pharyngeal tonsil (adenoid tissue), the lingual tonsil and the intervened tissue. The hypertrophy of these structures could be the main causal factor of airway obstruction.

1.2 Adenoids

1.2.1 Embryology

During the 3rd month of embryogenesis, the adenoids start their development. The glandular primordial associates it with infiltrating lymphocytes at the posterior nasopharynx. The sagittal folds begin their formation at the same time as the pharyngeal crypts, around the 5th month. The adenoids are completely formed by the 7th month when its surface is covered with pseudostratified ciliated epithelium.[2]

1.2.2 Anatomy

The adenoids or pharyngeal tonsils are anatomically located above the palatine tonsils and behind the soft palate and nose, and they are attached to the posterior wall of the nasopharynx. Its apex pointed to the nasal septum and the blood supply comes from the following arteries: facial, the pterygoid canal and the pharyngeal branch of the internal maxillary artery. The epithelium is pseudostratified ciliated epithelium and is infiltrated by the lymphoid follicles. The adenoids' innervation is derived from nerves such as the glossopharyngeal and the vagus.[2]

The close anatomic relationship with the Eustachian tubes and the choanae implicates the adenoids in the etiology of infections of the ears, nose and sinuses.[3] Recurrent infections could result in chronic alterations such as SDB and OSAS.

Each tissue system follows its own growth pattern. The Scammon's growth curve is a visual representation of the relative proportion of completed growth of different body systems.

This depiction shows the variation/amount of growth divided into tissue systems; the lymphoid tissues are one of them. It shows that the lymphoid tissue attains its maximum percentage of relative size between 8 and 16 years but start to regress in size after 15yo. (Figure 1.2). The variation on the growth spurts depends on many factors (genotype, environmental and functional factors). The factors (influenced by the space occupied by organs and cavities) are one of these elements that affect the dentofacial complex development, commonly cited as adenoid facies.[4]

1.2.3 Physiology & Microbiology

The adenoids are also known as pharyngeal tonsils. This complex network of lymphatic tissue is attached to the back wall of the nasal pharynx. It is covered by a delicate film of mucus and its surface consists of ciliated epithelial cells.[5] The adenoids contain mucus-secreting glands to lubricate this film. Its function is to secure mucosal protection of the nasopharynx, as the mucus retain infectious agents and particles inhaled by the nose to the pharynx.[5] Tonsils and adenoids play an important role in the secondary immune system response as they are constantly exposed to antigens.[2] The latter coming both from the inhaled air and the food. The immunologic structure of the adenoids (as well the tonsils) is divided as follows: the reticular crypt epithelium, the extra follicular area, the mantle zone of the lymphoid follicle, and the germinal centre of the lymphoid follicle.[5] Membrane cells and antigens presenting cells transport the antigen through the epithelial layer and present them to T-helper cells. When sufficient antigens are present this stimulates the B-cells in the germinal zone of the lymphoid follicle to differentiate and produce antibodies.[2] Overall, the adenoids are more involved in the production of mostly secretory Immunoglobulin A (IgA), the polymeric receptor, than the tonsils. IgA is secreted as an early form of defense and transported to the surface providing local immune protection[2,5]

The pharyngeal tonsils can increase in size significantly as part of an immune response reaction from pathogens potentially causing polymicrobial infections.[5] The most common infection is caused by an aerobic Group A Beta-haemolytic streptococcus bacteria.[2,6] The increase of an adenoid's size could be partial or total and causes upper airway obstruction at the nasopharyngeal level.[6]

1.2.4 Hypertrophy

1.2.4.1 Definition

Adenoids are a conglomerate of lymphoid tissues, which could be enlarged as a result of intense immunologic activity.[7] They became populated with bacteria during the first week of life and therefore enlarged in response to the antigenic stimulation until puberty, when they regress in size.[8] Their hypertrophy is mostly seen in children between 5 months and 6 years of age. In a child, the adenoid hypertrophy may be the result of recurrent infections or inflammation of the nasopharyngeal space.[9] One of the most common causes of upper airway dysfunction, especially in children, is tonsilar hypertrophy.[7] It is linked to the increase of respiratory disturbance index.[1]

1.2.4.2 Diagnosis

The diagnosis of the upper airway dysfunction is primarily made on the basis of a medical history as well as evaluation of clinical findings.[6] Its major symptom is the nasal obstruction and it could be accompanied by snoring, breathing interruption during sleep, growth rate, tendency to fall asleep during the day, behavioural difficulties and/or chronic runny nose.[10] To supplement the initial assessment, Ear, Nose and Throat specialists (ENTs) may execute direct or indirect clinical visualization of the area through a nasopharyngoscopy, which details are described on a section below.

1.2.4.2 Prevalence

The prevalence of adenoid hypertrophy in children was stated by previous studies as 14.3-30% on a 1995 study[11], 49,8% on school-aged children[12], 19,5% on a 4-14 years old children and

57,7% on a recent study by Bitar and team in 2009[13]. Sleep-disordered breathing is common, it's reported in 2 to 4% of middle-aged persons.[14] For children, in the same age range of this study's patients, the prevalence of pediatric OSA patients seen by OHNS complaining of nose obstruction were estimated to the 140,000 in United States in 1994.[2]

1.3 Diagnostic Accuracy

Mouth breathing is highly prevalent and it is frequently caused by obstructive adenoids hypertrophy. The Nasopharyngoscopy, the reference standard, is performed by an OHNS; as a family doctor rarely performs this examination as a screening tool.

Diagnostic tests demonstrate their ability in detecting disease or the absence of disease. Sensitivity and specificity are common terms when testing diagnostic accuracy. The major inconvenience of both specificity and sensitivity is that they are of no practical use on helping on the estimation of the probability of disease in individual patients.[15] The importance of predictive values, represented by a positive or negative predictive value, is mandatory to the practical/clinical translation and use of diagnostic tools.

1.3.1 Sensitivity

The portion of unhealthy people who will present a positive result represents sensitivity. This measure will demonstrate the ability of the test to recognise the truly diseased patient. In health care, the clinical practice of the test is mandatory; the sensitivity will tell us how accurate the test is in identifying patients with the disease.[15]

Nasopharyngoscopy (NP) is the reference standard test to detect adenoid hypertrophy. Several studies that compared NP with other screening tools.[16] demonstrated that NP is a highly accurate diagnostic method, sensitivity 92% and specificity 71%, in addition to being easy to perform in children who are cooperative. The NP is the preferred test of choice in diagnosing difficult cases because it is safe, objective and dynamic. On the other hand, different tools are adopted to screen adenoid hypertrophy because a NP is out of the scope of the dental field. These alternatives are known to present low sensitivity. A study presented 66% of sensitivity on radiographic evaluation of adenoids due to the subjectivity of the evaluator.[17,18]

1.3.2 Specificity

The specificity of a test is the proportion of people without the disease who will have a negative result on the diagnostic test.[15] This concept will only identify people who are healthy. Specificity of a test tells us the ability of this test to correctly identify the true negative and, if so, in what proportion.[15]

1.3.3 Predictive Positive Value and Predictive Negative Value

The Positive Predictive Value (PPV) means the change of a test being positive if the patient has actually the disease. It is likely that a disease-carrying patient will test positive. In the other hand, the Negative Predictive Value (NPV) is the likelihood of a no disease-carrying patient testing negative.[19]

The diagnostic accuracy/ability of a test will be ideal if the Sensitivity, Specificity, PPV and NPV have a value of 1. These values varies from 0-1 on which the results will be less useful if near "zero".[19]

1.3.4 Receiver Operating Characteristic (ROC) curve

The ROC curve is a fundamental tool for diagnostic tests and it is based on disease and non-diseased subjects. It shows sensitivity (true positive rate) and the specificity (100-Specificity) for different cut-off points of tests. It shows the sensitivity and specificity as pairs. The interpretation of this curve allows the analysis of test's performance of the test. The best cut-off point will be the one in which the true positive value is near 100 and the false negative value reaches 0.[19]

1.4 Effects of airway dysfunction

1.4.1 Effects in general health

From breast-feeding until the young adult age, upper airway dysfunctions can influence craniofacial development. SBD is a group of sleep disorders characterized by disturbances in the normal pattern of respiration during sleep. Frequently, the signs of SDB are: complaints of excessive daytime sleepiness, loud snoring, witnessed apnea and gasping for air.[20]

In adults, studies indicate that bed partners of SDB patients frequently complain that snoring, breathing pauses, gasping for air and excessive movement disrupt their own sleep. [21,22] Thus, there is evidence that bed partners of SDB patients experience both poor quality sleep and reduced quality of life.

Especially in children, the quality of life could be affected by SDB side effects such as alterations in the sleep pattern, delay in the systemic growth, attention deficit accompanied by low grades at school, signs of hyperactivity, irritability and impaired concentration and even aggression stereotype.[10,21,22] Sleep and nose-problems negatively affect the quality of life of mouth breathers. The effects of the SDB have been described as a public health concern.[22]

1.4.2 Effects in the craniofacial growth

Mouth breathing is specifically relevant to the dentist scope. A combination of traits produces the phenotype named "adenoidal facies".[23] Mouth breathing has been proposed as a significant factor for altered craniofacial growth[24-26] with a concomitant dental malocclusion. The description of this pattern includes narrow maxillary arch, posterior crossbite, and long face height with clockwise mandibular growth rotation, anterior open bite and mandibular retrognathia.[27,28] As well, chronic mouth breathers clinically present dry mouth, gingival recession, dry lips, gingival recession and high incidence of teeth decay.

1.4.3 Obstructive Sleep Apnea Syndrome (OSAS)

OSAS is the most common mortality factor of SDB. This airway obstruction may be associated with snoring and apnea episodes. OSAS in children has the characteristic of recurrent episodes of elevated upper airway resistance accompanied with partial or complete obstruction of the airway space. It could be clinically associated with snoring occurring three or more nights during a week.[29] The clinical diagnosis of OSAS needs to be confirmed by overnight PSG, the actual reference standard. The severity of OSAS is classified according to an apnoea hypopnoea index (AHI) above two per hour, 2/h. Since 2011, levels of AHI to OSAS diagnosis was established as mild 2-5 episodes; moderate 5-10 and severe >10.[30]

1.4.3.1 Polysomnography as a reference standard

Polysomnography (PSG) is the reference standard to diagnosis and classifies the level of OSAS.[31] The technique is complex, encompasses high cost for public health and patients and requires the spending of a full night in a sleep laboratory.[32] Complications associated with polysomnography have stimulated research to explore alternatives methods of OSAS diagnosis that present reliable results.[33] Biomarkers have been seen as an alternative method to screen OSAS patients, and its potential to diagnose OSAS has been evaluated. Biological markers such as blood, saliva, urine and exhaled breath condensate were synthesized in a scoping review.[34] In this scoping review, all studies published in the literature were collected and blood was the most frequent biological marker tested. The ideal scenario is to identify markers with high specificity and sensitivity, to be applied in a large scale optimizing the screening of the potential OSAS patient. The viability of markers in children was explored in the same age range as our study.[35] This systematic review concluded that kallikrein-1, Uromodulin, Urocortin-3, and Orosomucoid-

1, all biological markers obtained from urine, if combined, have enough accuracy to be adopted as a diagnostic/screening test in children with or without OSA.[35]

Other sequalae of adenoids hypertrophy besides dentofacial abnormalities and OSA include sinusitis and recurrent otitis media could be clinically detected as inflamed gums, increase of teeth decalcification and dry lips.

1.5 Imaging in the diagnosis of upper airway dysfunction as related to physical obstruction

There are several non-invasive tools to investigate the physiological dysfunction of the upper airway. The airflow deficit is produced directly by a reduction in length and diameter in the airway space. The video or static imaging provides functional and anatomical information to the clinician.

Two of the most useful techniques include Videonasopharyngoscopy, an optical system allowing evaluation of the upper airway tract using a flexible endoscope in children from 3 to 17 years old and Videofluoroscopy, mostly representing the swallowing process of the patient, as useful techniques. Although both techniques use video tapping, the main difference is that the second uses X-ray-based technology. Complications are rare and these techniques are performance rapidly.

Magnetic Resonance imaging (MRI) is a non-invasive technique that investigates soft tissue. It could be used in the dental field to screen adenoid hypertrophy, but the limitations include the cost and the fact that the conventional MRIs are not ideal for dental investigations due to the high mineral content of teeth (enamel 90% and dentin 50%) and its water constitution reduce the signal of MRI pulses.[36]

Computer tomography, another indirect and non-invasive tool, has high sensitivity and specificity (more than 90%) for adenoid screening and investigation however, limitations include the scope, the amount of radiation dose and the cost of CTs.[37] These factors in addition to the inability of most dentists to interpret CT imaging limit its application in the dental field.

The current reference standard for adenoid hypertrophy diagnosis is Nasopharyngoscopy (NP).

1.5.1 Nasopharyngoscopy

NP consists of digital video clips obtained from a flexible or rigid fiberoptic endoscope. The endoscope passes through the nose providing an excellent view of the adenoid and adjacent structures.[38] NP advantages are numerous. The flexibility of the tube allows the examiner to evaluate several anatomical areas and the patient to tolerate the examination by only using a topic anesthetic application – 4% xylocaine solution mixed ½ with a 0.1% xylometazoline decongestant – sprayed using an atomizer. Also, the video is captured by a camera and could be stored and reviewed for further analysis.

A grading system to evaluate the video images was elaborated and validated in 2006 by Parikh et al[38]. This system consists of evaluating the relationship between the adenoids and the adjacent structures; vomer, soft palate, torus tubaris and choanae (during inspiration). (Figure 1) The OHNS physician evaluates the proposed structures and provides a grade of the obstruction as demonstrated in Figure 1.2.

NP advantages compared to the conventional 2D images are related to the non-exposure to radiation by following the ALARA (As Low As Reasonable Achievable) principle. Other advantages include that the video image is representative of all three planes from an anatomical view (possibility to move the camera) and the reduced patient management time while using videos (15-30 seconds).

Sleep endoscopy is a modality of nasoendoscopy where the patient is examined while sleeping or submitted to a drug-induced sleeping on an OSA patient.

1.5.2 Lateral Radiograph

The two-dimensional lateral cephalometric radiograph was traditionally selected as the tool to screen the size of the adenoid by orthodontists.[7] The advantage of the conventional lateral cephalogram is that it can easily be interpreted while assessing the adenoids; it is deemed reproducible and has a relative low cost.[39] This imaging modality easily represents the relationship between the soft tissue palate and adenoids. The limitation is that it considers a single plane of view. To further complicate matters, the view can be altered if, during the respiration cycle, the patient's head and palate change positions.[40]

The routine access of lateral cephalograms by orthodontists for orthodontic diagnostics makes them a radiographic reference for airway screening and assessment.[7] However, the images can be limited or inaccurate. This downside occurs when the obstruction is caused solely by the lateral adenoid growth and when the choanae opens medially.[38] Also, the size of the adenoids or the airway space is not accurately displayed in this type of view due to superimposition of craniofacial structures.[39]

1.5.3 Cone-Beam Computer Tomography

The advent of CBCT provides clinicians with the opportunity to assess simultaneously cross-sectional areas and volumetric regions of the upper airway in multiple planes, coronal, axial and sagittal.[41,42] Even though the CBCT is not usually indicated to visualize of soft-tissue, the contrast between the air and any other structures create contrast allowing the segmentation of the required area.[39] The quantification of the 3D morphology of the upper airway area by CBCT scans could substitute the conventional assessment with 2D and support the patient's referral to an OHNS.

In addition, a study suggested that CBCT and medical CT without contrast imaging in a coronal reconstruction as the best tool to visualize nasal septum deviation.[43]

In this regard, three-dimensional CBCT diagnosis can certainly be considered a useful imaging method for upper airway, when properly indicated, as it refines the image definition and diagnostic accuracy when compared to traditional two-dimensional imaging.[23,39,44]

1.5.4 Comparison between diagnostic techniques

A systematic review addressed the accuracy of diagnostic tests for adenoid hypertrophy. The main concern was to find alternate screenings tests because the nasopharyngoscopy is out of the scope of dentistry. The CT and the videofluoroscopy had the best sensitivity (92% - 100%) and specificity respectively. The conventional and most common method used by dentists, the lateral cephalometric presented a good sensitivity (86%) however, the specificity was 41%.[37]

Ysunga et al[45] compared the two techniques to visualize the adenoids hypertrophy, the lateral cephalometric and video fluoroscopy. Their results showed 95% of agreement between same raters from both techniques; however the sensitivity (100%) and specificity (90%) of results were higher in video fluoroscopy images. The suggestion of using video fluoroscopy could be a reliable alternate to cases where patient management/cooperation is a concern.

Other authors[33] validated the Videonasopharyngoscopy and compared it to the reference standard, the polysomnography, for OSAS and syndromic patients. The technique showed 87% sensitivity and 100% specificity on a sample of 52 patients with confirmed OSAS in a variety of levels. The PPV value of 84% and a NPV of 100% indicated OSAS. The study presented the videonasopharyngoscopy as a reliable and accurate alternate to the PSG.

Also, the statistical agreement/accuracy was excellent when a research group compared the diagnosis from the conventional lateral radiograph and the direct view produced by video; it was obtained using a Kappa test value of 0.83.[38] The downside could be related to the quality of the imaging, which is inferior to the direct view through endoscope and child cooperation while using just a topical anaesthesia.

CBCT and Lateral cephalometric capability and reliability were also tested.[7] Their conclusion reaffirmed the initial screening function of the lateral skull imaging when the CBCT imaging is not available. Limitations in comparing lateral cephalometric and CBCT imaging might be related to the position of the patients in each technique, upright and supine respectively.[39] The latter was improved with the patient sitting in upright position in the new versions of the machine.

1.6 Airway management

1.6.1 Role of the Otorhinolaryngology and Head and Neck Surgery (OHNS)

Pediatric sleep-disordered breathing caused by adenoid hypertrophy are addressed primarily by medical or surgical procedures based on the severity of each case. Intranasal steroids, topic decongestants address, allergenic control could help this patients. However, the effects of SDB during periods of facial growth have to be controlled or stopped.[39] Advanced obstruction of upper airway is addressed, in majority, by adenoidectomy and tonsillectomy.

The lymphoid tissue could decrease its size after the adolescent phase (after 14 years of age). In fact, airflow resistance should be not limited just to obstruction (size) of airway; but also to airway shape.[39] Specific Pediatric guidelines classify and impose treatment to each level and patient's condition.[46,47]

1.6.2 Role of the Dentist on the Airway Management

Two-dimensional (2D) lateral radiographs have been over the years the tool applied by dentists to assess adenoid hypertrophy in their patients.[48] This useful sagittal imaging is however not accurate compared to the 3D imaging. Although a representative image could be obtained, the axial plane is not accessible on the lateral cephalogram and the measurements have limitations related to assessment of a complex tridimensional structure with a 2D view.[49] An option for the dental practitioner could be refer the patient to the physician to assess the airway space by the Computer Tomography image.[14] However, with the advent of CBCT, the dentist could access the area with a large field of view (FOV) using a credible tool.

1.7 Treatment methods

1.7.1 Non surgical methods

Intranasal corticosteroids (INS) spray and saline spray that may reduce the inflammation from external irritants or allergenic.[50] Allergy tests and orientation of allergenic trigger avoidance educate the patient and parents. As well, adenoid hypertrophy management could be done by antibiotic therapy if there is acute infection. Patients who do not respond have to follow combined therapy. The first line systemic antibiotic for adenotonsillitis is penicillin (acute streptococcus infection) for a long-term period to eradicate of the bacteria.[2] However, this is not the type of hypertrophy your study focuses on.

1.7.2 Adenotonsillectomy

Adenotonsillectomy is the most common treatment choice of the treatments of recurrent tonsillitis and pediatric OSA patients with evidence of adenotonsillar hypertrophy causing SDB/OSA. This is a very safe operation where a minor period of hospitalization and low complication rates are the main characteristics.[30] It is indicated for treatment on patients with adenotonsillar hypertrophy and confirmed diagnosis by PSG presenting moderate (5-10) or severe (more then 10) Apnea–Hypopnea Index or Apnoea–Hypopnoea Index (AHI). This is an index used to indicate the severity of sleep apnea. Others indications of adenotonsillectomy in OSA patients are linked to recurrent tonsillitis, reasons of infection and association with morbidities such as obesity.[30] In some cases as obesity patients are treated with continuous pressure Continuous positive airway pressure (CPAP) ventilators with mild air pressure to keep the airway opened. Adenotonsillectomy is solely indicated if the patients present with one or more indication in their history, evidences in the physical examination and confirmation by a specific test, if suspicious after the two first steps.[46] (Table 1)

Regarding the surgical technique, a tonsillectomy could be done with or without an adenoidectomy. Many different techniques to remove tonsils and adenoids have been proposed.[51] The improvement of these techniques aims to decrease the rates of hospitalization and complications during recover of anaesthesia or/and during the two weeks after surgery.

The complications of the surgery are rare and the most serious of them is the haemorrhage, around 4.5% of the total rate of post operative complications.[52] Two types of postoperative haemorrhage that could happen: the first related to the first 24 hours of recovery, and the second one, occurring after 24 hours of surgery. One study showed that patients with recurrent tonsillitis patients have an increased risk of postoperative bleeding episodes (haemorrhage) compared to OSA patients.[52] De Luca Canto et al systematically reviewed the post-operatory complications after tonsillectomies.[47] Their results showed complications were five times higher in OSA children (OR=4.9). The most frequent complications were respiratory complications as post obstructive pulmonary edema (9.4%), followed by secondary haemorrhage (2.6%). The first complication in linked to OSA children and the second to non-OSA children.

1.8 Statement of the problem

Adenoid hypertrophy is relatively common and may cause partial or total upper airway obstruction. The body responds normally by increasing breathing through the mouth mainly during sleep, but can also happen during the day. Sleep-disordered breathing may affect general and craniofacial growth, cognitive development and physical posture of individuals affected by it. Due to its prevalence and overall health impact significant upper airway obstruction is considered a public health concern. Early detection in children and adolescents could prevent the further consequences of this disease. Several methods to screen the adenoids have been proposed. Most of them are out of the practice scope of dentists and dental specialists. Dentists have an early opportunity to assess related areas while using imaging to plan different dental patients' treatments. If they can screen for mouth breathing or disturbing-sleep tendencies, they may be able to refer these patients for a thorough investigation by the OHNS. The surgical excision of the adenoids is the last option for the patients who present an advanced and severe hypertrophy. Steps to early detection of upper airway dysfunction should be investigated. By evaluating/screening incidental findings on the upper airway area via CBCT reconstructions, specifically adenoid hypertrophy, the orthodontists and oral maxillofacial radiologists could prevent future dysfunctions and developmental deficiencies.

1.8.1 Objectives

Our study has three specific goals:

1. Determine the accuracy and reliability of orthodontists is in screening for adenoid hypertrophy using CBCT imaging as compared to the diagnosis made by an OHNS using nasopharyngoscopy (NP).

2. Determine the accuracy and reliability of oral maxillofacial radiologists is in screening for adenoid hypertrophy using CBCT imaging as compared to the diagnosis made by an OHNS using NP.

3. Determine the capability of common automated commercial imaging software in determining volume and minimal cross-sectional area as it correlates to different levels of obstruction of adenoid hypertrophy obstruction determined by a nasopharyngoscopy diagnosis made by an OHNS.

1.8.2 Hypotheses

The ***first objective*** of this study was to determine how reliable and accurate are Orthodontists in screening for adenoid hypertrophy analysing CBCT imaging. (Part I)

First hypothesis:

H_o= Orthodontists are not reliable in screening adenoid hypertrophy using CBCT imaging.

H_a= Orthodontists are reliable in screening adenoid hypertrophy using CBCT imaging as

Second hypothesis:

H_o= Orthodontists are inaccurate in screening adenoid hypertrophy using CBCT imaging as compared to the diagnosis made by an OHNS.

H_a= Orthodontists are accurate in screening adenoid hypertrophy using CBCT imaging as compared to the diagnosis made by an OHNS.

The ***second objective*** was to evaluate the reliability and accuracy of Oral Maxillofacial Radiologists in screening adenoid hypertrophy by using CBCT imaging. (Part II)

First hypothesis:

H_o= Oral maxillofacial radiologists are not reliable in screening adenoid hypertrophy using CBCT imaging.

H_a= Oral Maxillofacial radiologists are reliable in screening adenoid hypertrophy using CBCT imaging as compared to the diagnosis.

Second hypothesis:

H_o= Oral maxillofacial radiologists are inaccurate in screening adenoid hypertrophy using CBCT imaging as compared to the diagnosis made by an OHNS.

H_a= Oral Maxillofacial radiologists are accurate in screening adenoid hypertrophy using CBCT imaging as compared to the diagnosis made by an OHNS.

The ***third objective*** was to evaluate the effectiveness of Dolphin Imaging Software® in determining volume and minimal cross-sectional area in association with the levels of obstruction of adenoids hypertrophy by the reference standard, the Nasopharyngoscopy (Part III)

H_o= There is no correlation between CBCT airway imaging of nasopharyngeal volume and minimal cross-sectional axial area, visualized by commercial software and the nasopharyngoscopy level of obstruction, diagnosis made by an OHNS.

H_a= There is correlation between CBCT airway imaging of nasopharyngeal volume and minimal cross-sectional area, visualized by commercial software and the nasopharyngoscopy level of obstruction, diagnosis made by an OHNS.

1.9 Figures & Tables

Figure 1.1 – The upper airway space[1]

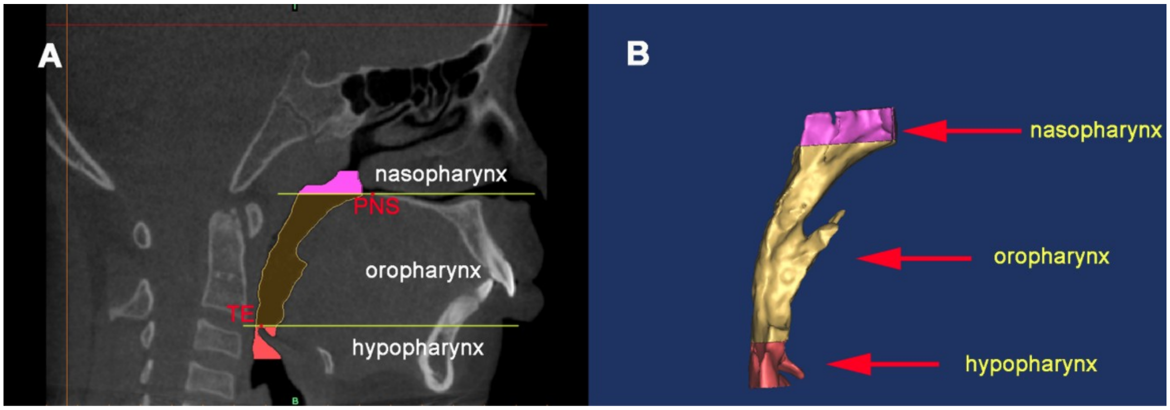

Figure 1.2 – Scammon's diagram[2]

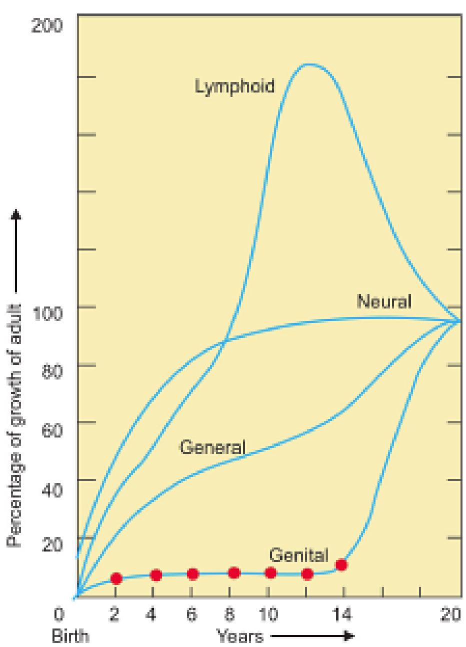

Fig. 2: Scammon's growth curve

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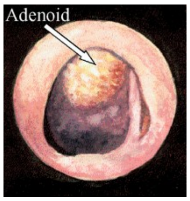
[1]

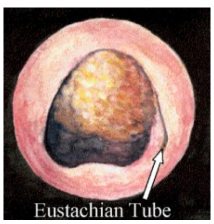
[2] https://books.google.ca/books?id=MsIHCgAAQBAJ&pg=PA10&lpg=PA10&dq=scammon's+growth&source=bl&ots=c8YeHZRtar&sig=VObEMwtfd5a-0n_YcVCVJ91rcoY&hl=en&sa=X&ved=0CE4Q6AEwC2oVChMIxdb2uYu-yAIVViuICh1caw7T#v=onepage&q=scammon's%20growth&f=false

Figure 1.3 Obstruction-adenoid tissue – Grading system[3]

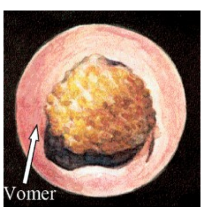
Grade 1: None (0–25% of scarce tissue at rhinopharynx choanal opening); non-obstructive and the adenoid tissues do not contact adjacent tissues.



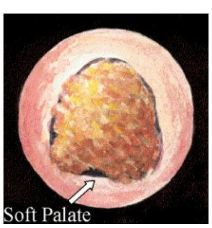
Grade 2: Mild (>25% to maximum 50%). Confined to upper half of the rinopharyngeal cavity. Patent choanae; adenoid tissues in contact with torus tubaris.



Grade 3: Moderate (>50%–75%). Considerable obstruction, free only in inferior area; adenoid tissues in contact with Vomer.



Grade 4: Severe (>75% of choanae). Practically complete obstructed; adenoidal tissue in contact with palate while on rest position



[3] Parikh, S. R., M. Coronel, J. J. Lee and S. M. Brown (2006). "Validation of a new grading system for endoscopic examination of adenoid hypertrophy." Otolaryngol Head Neck Surg 135(5): 684-687.

Table 1.1 – Recommendation of Adenotonsillectomy by American Academy of Otolaryngology – Head and Neck Surgery[4]

History	**Physical Examination**	**Tests** (If abnormality is identified)
1. Four or greater episodes of recurrent purulent rhinorrhea in prior 12 months in a child <12 years of age. One episode should be documented by intranasal examination or diagnostic imaging. 2. Persisting symptoms of adenoiditis after two courses of antibiotic therapy. One course of antibiotics should be with a B-lactamase stable antibiotic for at least two weeks. 3. Sleep disturbance with nasal airway obstruction persisting for at least 3 months. 4. Hyponasal speech. 5. Otitis media with effusion >3 months or associated with additional sets of tubes. 6. Dental malocclusion or orofacial growth disturbance documented by orthodontist or dentist. 7. Cardiopulmonary complications including cor pulmonale, pulmonary hypertension, right ventricular hypertrophy associated with upper airway obstruction. 8. Otitis media with effusion (age 4 or greater).	1. Description of uvula, palate, tonsils, nasal airway, cervical lymph nodes. 2. Evaluation of adenoids by mirror, palpation, nasal endoscopy or imaging only as necessary. 3. Assessment for signs of hypernasal speech or risk factors for postop voice disturbance	1. Coagulation and bleeding evaluation based on personal or family history 2. Radiographs (lateral neck or cephalometric) 3. Sleep tape recording (if documentation of snoring or apnea required) 4. Polysomnography in children at high risk for respiratory compromise

[4] Clinical Practice Guideline: Polysomnography for Sleep-Disordered Breathing Prior to Tonsillectomy in Children, Otolaryngology- Head and Neck Surgery, XX(X) 1-15 http://oto.sagepub.com/content/early/2011/06/02/0194599811409837.full.pdf+html

Chapter 2: The accuracy and reliability of Cone-Beam Computerized Tomography for Diagnosis of Adenoid Hypertrophy among Orthodontists

2.1 Introduction

Among children and adolescents one of the most common causes of an obstructed upper airway is the hypertrophy of adenoids and/or tonsils[53], which can lead to the development of sleep-disordered breathing [54] and, in severe cases, obstructive sleep apnoea (OSA)[10,45]. Neurocognitive impairment, and behavioural effects such as attention deficit hyperactivity disorder and aggression[55] have been linked to Sleep-disordered Breathing (SBD).

The initial diagnosis of upper airway dysfunction is primarily based on medical history, as well as consideration of patients and parents' complaints.[6] Signs and symptoms may include chronic snoring, breathing interruption during sleep, delayed growth, tendency to fall asleep during the day, behavioural difficulties and/or chronic runny nose.[10] To supplement the initial assessment, the otolaryngologists – the Ear, Nose and Throat specialists (OHNS) may execute direct visualization of the area through nasopharyngoscopy (NP).

The advent of CBCT, with its lower ionizing radiation dosage as compared to the conventional computer tomography (CT), has provided clinicians with the opportunity in three dimensionally (3D) assess the upper airway.[41] In this regard, 3D CBCT diagnosis can certainly be considered a useful imaging method, when properly indicated, as it refines the image definition and diagnostic accuracy when compared to traditional two-dimensional imaging.[42]

A previous study[18] proposed using CBCT imaging to screen for adenoidal hypertrophy when CBCT images were already indicated for other reasons. Strong sensitivity (88%) and specificity (93%) was reported, supporting the ability of this type of 3D imaging as a reliable tool for adenoid hypertrophy screening. However, the number of evaluators was small and all of them had a moderate to high comfort level manipulating CBCT images.

Therefore, a 2-fold study was designed: (1) Primarily this study aimed to evaluate the reliability of agreement between orthodontists, with various degrees of CBCT manipulation comfort, in classifying adenoid hypertrophy through CBCT generated images, and (2) to determine how accurate and reliable are orthodontists are, with various degrees of CBCT manipulation comfort, in screening for adenoid hypertrophy using CBCT imaging as compared to the reference standard diagnosis, a NP by an Otolaryngologist – Head and Neck surgery (OHNS).

2.2 Materials and Methods

This cross-sectional study protocol ethical approval was granted from the Research Ethics Board at the University of Alberta - Pro00043684. (Appendix A)

This research is closely linked to a research project[56] previously approved by the Research Ethics Board: CBCT Imaging for Diagnosis of Upper Airway Dysfunction - Pro0020649.

2.2.1 Sample Selection Process

The CBCT sample was consecutively evaluated patients from a multidisciplinary airway management clinic. The CBCT population and the methodology follow a previously reported study.[18] Following the ALARA principle (As Low As Reasonable Achievable)[57,58] CBCT scans were not specifically taken to evaluate adenoids, but due to more complex craniofacial patterns common in children with a high likelihood of OSA.[57]

The selection criteria were children and adolescents 6 to 16 years old with a referral based on obstructive upper airway concerns. CBCTs of individuals with previous treatment of upper airway dysfunction or sleep disorders, patients with documented syndromic craniofacial disorders (e.g. cleft palate), and/or previous orthodontic treatment were not used in this study.

All subjects had the CBCT performed by a radiology technician, and a pediatric OHNS completed the NP. Both were obtained within two hours of each other. The CBCT was taken with an iCAT scanner (Imaging Sciences International, Hatfield, Pennsylvania, PA). The same technician following a protocol-imaging algorithm acquired for all images.

The NP was performed following the protocol established by the American Academy of Allergy. Subsequently, the same OHNS analyzed the NP of each patient and the adenoid size was classified in a 4-point scale based on its obstruction level.[33] The severity of adenoid hypertrophy was graded by a validated method[38]: grade 1 (up to 25% of obstruction); grade 2 (25% to 50%); grade 3 (50% to 75%) and grade 4 (more than 75%). (Appendix D)

2.2.2 Orthodontists Randomized Selection

The complete list of boarded-certified orthodontists (34 specialists) of a Canadian city was considered for sample size calculation. A final sample size of 13 orthodontists' evaluators was determined to be representative, based on a confidence level of 95% and power calculation of 80%. (Figure 2.3) The number of 10 scans was established on a time-base of a 30 minutes evaluation for each participant. The entire CBCT pool of 39 patients were stratified by grades of NP and randomized by statistician. The stratified sampling was representative of the disease spectrum, a pre-established distribution was determined as follows: 2 patients classified by the OHNS as Grade 1, 3 patients Grade 2, 3 patients Grade 3 and 2 patients grade 4. The latter aimed to evenly distribute the obstruction grades. The participating orthodontists utilized a visual analysis of the upper airway obstruction as depicted from CBCT reconstructions, all limited to the area of the adenoids. Software is needed to visualize the digital imaging and communication in medicine (DICOM). InVivo Dental viewer software (Anatomage, San Jose, CA), specifically the "Lay Egg" function was used and the DICOM data was made anonymous. The evaluators only had access solely to the CBCT reconstructed images and were blinded to any other patient information.

Evaluators were consecutively recruited based on a randomized list until the necessary sample size was achieved. Prospective evaluators were contacted by e-mail. Orthodontists consenting to participate received an information package and informed consent by email and it was discussed verbally prior to them signing. (Appendix B & C) All participants had the opportunity to ask technical questions about the viewer software and had access to a previously published visual guideline for evaluating adenoid size. (Appendix D)

The principal investigator was present during all evaluations. Participants received instructions how to manipulate the software prior to beginning orienting them how to access and evaluate the images. The OHNS classification of the adenoid hypertrophy[38] was also verbally described. Evaluators were asked to classify the adenoid size, as mild (grade 1 = <25% obstruction); moderate (grade 2 = 25 -50% obstruction); advanced (grade 3 = 50 -75% obstruction) or severe (grade 4 = >75% obstruction). A CBCT reporting template was completed and sealed in an envelope. (Appendix E)

2.2.3 Statistical Analysis

The statistical Package for the Social Sciences SPSS (version 23, IBM, Armonk, NY) was used for data analysis. Reliability between orthodontists and accuracy of evaluations against the NP were investigated with the Intraclass Correlation Coefficient (ICC) and Kappa statistics. The (ICC) test was used to evaluate the inter-observer classification of adenoid size on the 4-point scale, testing the reliability of assessments between the evaluators. ICC was also used to access the accuracy of orthodontists' classification against the NP. Agreement was classified according to the following ICC values: excellent > 0.9; good = 0.75 - 0.9; moderate = 0.5 – 0.75; poor < 0.50.[59] *P*-values less than (or < 0.05) 0.05 indicated a statistical significance. The accuracy of a dichotomous diagnosis "diseased" vs. "healthy" was evaluated with Kappa statistics. The grades

1 and 2 were renamed as healthy and 3 and 4 as unhealthy. The level of agreement reflected by Kappa was considered as excellent above 0.9; good when it was between 0.75 and 0.9; moderate in the range of 0.5 – 0.75 and poor when less than (or < 0.5) 0.5[60] Intra-observer reliability was previously investigated in an earlier study.[18]

2.3 Results

The CBCT population was based on a stratified random sampling of 10 large-field CBCT volumes and was selected following this distribution: 2 subjects NP grade 1; 3 NP grade 2; 3 NP grade 3 and 2 subjects NP grade 4. The distribution showed a heterogeneous sample composed of different levels of obstruction.

Fourteen Royal College of Dentists of Canada (RCDC) board certified orthodontists (13 was the sample size required) practicing in the same Canadian city participated in this study. All participants used the same computer to prevent performance bias.[61] The participant's evaluation of adenoid size followed a similar classification as the reference standard OHNS via NP. The mean time spent by the orthodontists was 12:02 minutes (SD± 3:49). The answer sheet was placed in an envelope and a third person transferred the data to an Excel file. The data was checked carefully and outliers were verified.

2.3.1 Reliability of measurements

The ICC was used to evaluate inter-examiner reliability. No clinically relevant discrepancies were found, showing high reliability between examiners (Table 2.1); consistency was excellent (ICC=0.941, CI 95% = 0.882-0.984, P<0.001). Overall, the differences in evaluation CBCT evaluation between the 14 different orthodontists were statistically insignificant.

2.3.1 Reliability of CBCT compared with the reference standard (Nasopharyngoscopy)

The orthodontist's evaluation against the reference standard had poor accuracy, (ICC_{mean}= 0.39; ICC_{range} = 0.00 - 0.74). Figure 2.1 presents the ICC results from each orthodontist against the NP. For a second inter-operator reliability analysis, different analysis perspective, we use the "statistical mode" (the value that appears more often on visual analysis data/the most frequently occurring number found in a set of numbers). The purpose of this data transformation was to limit the influence of possible outliers. In this scenario, the results presented a moderate agreement between orthodontists and NP grades, ICC=0.753 CI 95% (0.119, 0.937). (Table 2.1)

Thereafter a Kappa test was applied to evaluate the clinical determination of healthy (grade 1 & 2) vs. diseased (grade 3 & 4). Dichotomous data representing healthy and unhealthy patients were analyzed individually; each orthodontist evaluation and NP's results (accuracy) is presented by Figure 2.2. The average values were still poor, K_{mean}= 0.44 and K_{range}= 0.20 – 0.80. However, when analyzing the "mode" values (again, to limit the influence of outliers), the Kappa results increased, as the accuracy was good, K= 0.80 with SE of kappa = 0.186, P_{all}= 0.90 ($P_{yes/healthy}$ = 0.90 and $P_{no/unhealthy}$ = 0.88). The asymptotic Delta Δ= 0.90 represented a chance of rightness of 50%. (Appendix F)

2.4 Discussion

Since adenoid hypertrophy is the most common cause of pediatric sleep apnea,[62,63] early screening for adenoid hypertrophy should be encouraged when upper airway dysfunction is suspected. If a dental practitioner could assess the nasopharyngeal area, they may be able to refer the patient for timely management potentially preventing any associated craniofacial consequences.[64] The main objective of this study was to evaluate a sample of orthodontists' accuracy and reliability of assessing adenoid size using CBCTs. This study advanced previous investigations[18] by including a larger sample of orthodontists with a wider range of CBCT experience to more accurately reflect the average clinician's diagnostic capability in private practice.

Different radiographic imaging modalities may be used to estimate the adenoid size and/or obstruction of the upper airway. Magnetic resonance imaging (MRI) reproduces accurately reproduces the sizes of the adenoid hypertrophy[65], but the required time and cost are disadvantages.[66] Specifically within the dental scope, two-dimensional (2D) lateral radiography is one of the tools readily available to complete an initial assessment.[66-68] Traditional 2D sagittal imaging is partially useful and not as accurate as 3D imaging.[39] Although a partial view of the nasopharynx could be obtained, the axial plane is not accessible on 2D lateral cephalograms.[43] A systematic review addressed this topic, stating that 2D images are useful for adenoid size determination, but deficient in represent the surrounding nasopharyngeal space.[69]

In several scenarios, CBCT has improved image definition and diagnostic accuracy in comparison to conventional 2D imaging.[44] CBCT volumetric data can be reoriented and different algorithms allow the clinician to realign and assess the patients in a variety of views and planes.[70] Therefore, 3D CBCT diagnosis could certainly be, if available, one useful tool, or part of the preferred imaging method for this specific diagnosis area.

A previous study[18] evaluating 3 orthodontists with substantial CBCT training found high agreement – clinically meaningful - between CBCT imaging and NP diagnosis. Our results, considering a larger sample size of practitioners, partially confirmed this finding. The orthodontists' assessments were highly reliable, being consistent between evaluators (inter-observer ICC >0.90). However, the orthodontists' accuracy against the NP results was poor (ICC_{mean}= 0.39 and ICC_{range}= 0.00 - 0.74). Furthermore the orthodontists' ability to discriminate between healthy or diseased was similar to what would be expected by simple chance – a poor outcome (kappa = 50%).

A likely reason for the substantial discrepancy in the diagnosis accuracy between this study and the previous study[18] is how the CBCT images were reviewed. We observed in this study that some of the participants frequently based their assessment oNPy on the first sagittal view presented by the viewer; few adjusted the contrast or moved the slice position during the evaluation, failing to explore the entire reconstruction. This apparent systematic error could be inherent from decades of using the traditional lateral view of the skull cephalograms. Or it could be due to the operators' lack of familiarity with CBCT imaging and under-utilization of the several software tools available. Either hypothesis could indeed explain the low accuracy. Some participating orthodontists even emphasized their experience with CBCT as user-unfriendly and preferred to evaluate airway space on a 2D lateral view of the skull. Lastly, evaluators participating in this study may not be entirely reflective of clinical practice. Some participants were initially reluctant, but later accepted to participate, due to the fact that they not routinely evaluate CBCT images themselves in clinical practice. Only one orthodontist declined participation stating that it was due to inexperience with 3D imaging; whereas others who did not participate did not provide specific reasons for not participating. If we may have actually considered those that declined to participate due to lack of comfort with the technology, then the results may actually turn poorer.

For this study, ICC and Kappa means were presented by in addition to individual assessments. The orthodontists' number 2, 4 and 11 could be considered outliers due to their poor performance. (Appendix F) When data transformations were applied to limit the impact of outliers, the accuracy of the orthodontists' CBCT assessment improved to acceptable (mode ICC = 75%, mode kappa = 80%), although though not exceptional as reported previously[18]. This finding is not unexpected since the previous study only evaluated one "expert" practitioner. In this sense, the current study agrees with others: orthodontists lacking experience in CBCT imaging and 3D anatomic landmarks could jeopardize the results.[39,49,71] Having stated that the fact is that the current practitioner pool does mainly include "non-experts" and that is where these findings acquire relevance.

2.4.1 Clinical Significance

This study assessed the accuracy and reliability of adenoid assessment using CBCT as performed by orthodontists compared to the reference standard NP. If orthodontists are instructed to evaluate the adenoids hypertrophy on available scans, they could support their referral to the family doctor or OHNS. Our findings suggest clinical orthodontists should exercise caution while evaluating CBCT images themselves ($ICC_{mean} = 0.39$). Poor to fair diagnostic accuracy should be expected from orthodontists with average to low CBCT interpretative skills. Furthermore, clinical orthodontists appear to be prone to consistent and systematic errors in their evaluation process (ICC = 0.94). Our findings do not de-value the inherent accuracy of the CBCT imaging tool nor do they discredit previous studies[18]. Instead this current study draws attention to how critical the operator's subjective evaluation may be in final diagnostic accuracy.

2.4.2 Limitations

The generated DICOM views could be a confounding factor when evaluating the upper airway area. There are several software viewers available in the dental market; our selection of the viewer software was based on its availability and popularity. However, to limit this potential performance bias all participants used the same viewer and computer.

Even when all the images were obtained by the same technician, the need of a protocol for obtaining the images and managing patients has to be emphasized to prevent distortions based on respiration time and movement of the of patients' position.[72] This limitation is inherent to all CBCT scan-based studies.

The participants of this study used a 4-point scale to categorize the levels of obstruction. An underlying phenomenon of participants preferring not to select extremes in these types of scales, has been previously discussed.[73] The potential impact of this remains unknown.

Even though the required sample size was obtained, we met with certain reluctance from some orthodontists while inviting them to participate. The most common argument was the lack of ability and experience on evaluating 3D images. This should be considered as this potentially means that the sample of participating orthodontists may indeed have above average CBCT management skills.

Different levels of CBCT expertise may impact its diagnostic/screening accuracy.

2.5 Conclusion

Participating orthodontists showed excellent inter-examiner reliability – that is consistency between evaluators. However, large variability with poor agreement of the adenoid obstruction degree compared to the NP (reference standard) demonstrated clinical orthodontists had poor diagnostic accuracy. Together these findings suggest orthodontists were making consistent and systematic errors in their evaluation process.

2.6 Figures & Tables

Figure 2.1 – Inter-reliability analysis between each orthodontist and NP

	Intraclass Correlation	Confidence interval 95%	
	ICC	Lower Bond	Upper Bond
Orthodontist 1	0.65	0.65	0.90
Orthodontist 2	0.13	0.00	0.63
Orthodontist 3	0.67	0.17	0.90
Orthodontist 4	0.11	0.00	0.00
Orthodontist 5	0.00	0.00	0.61
Orthodontist 6	0.50	0.00	0.84
Orthodontist 7	0.73	0.21	0.92
Orthodontist 8	0.34	0.00	0.77
Orthodontist 9	0.41	0.00	0.81
Orthodontist 10	0.56	0.00	0.80
Orthodontist 11	0.10	0.00	0.68
Orthodontist 12	0.60	0.63	0.88
Orthodontist 13	0.30	0.00	0.75
Orthodontist 14	0.54	0.00	0.86

ICC: Two-way mixed effects model
Negative ICC numbers are be presented as "0"
P Values are not representative in correlation tests

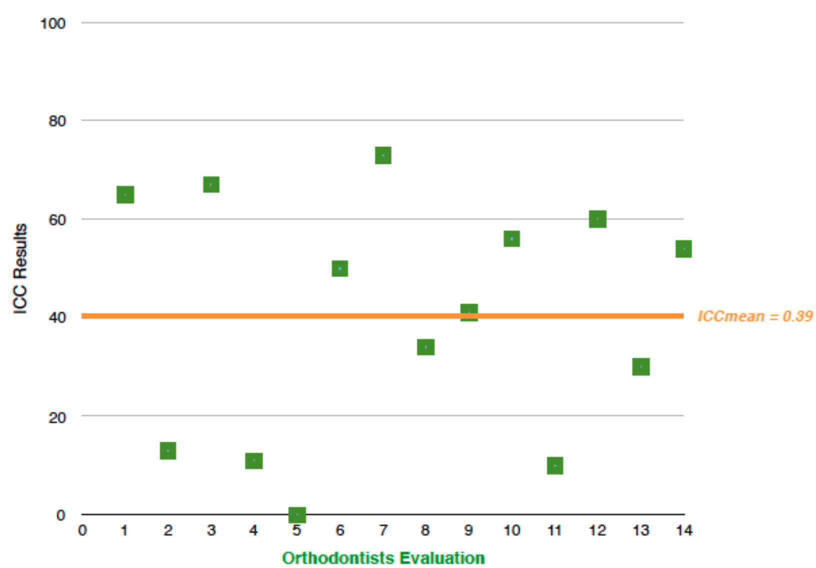


Figure 2.2 - Accuracy of orthodontists against NP (dichotomous data)

	Kappa test	Standardized Error
	Agreement	
Orthodontist 1	0.60	0.25
Orthodontist 2	0.20	0.28
Orthodontist 3	0.80	0.18
Orthodontist 4	0.20	0.31
Orthodontist 5	0.20	0.28
Orthodontist 6	0.40	0.23
Orthodontist 7	0.60	0.25
Orthodontist 8	0.40	0.28
Orthodontist 9	0.40	0.28
Orthodontist 10	0.40	0.28
Orthodontist 11	0.40	0.28
Orthodontist 12	0.80	0.18
Orthodontist 13	0.20	0.28
Orthodontist 14	0.60	0.25

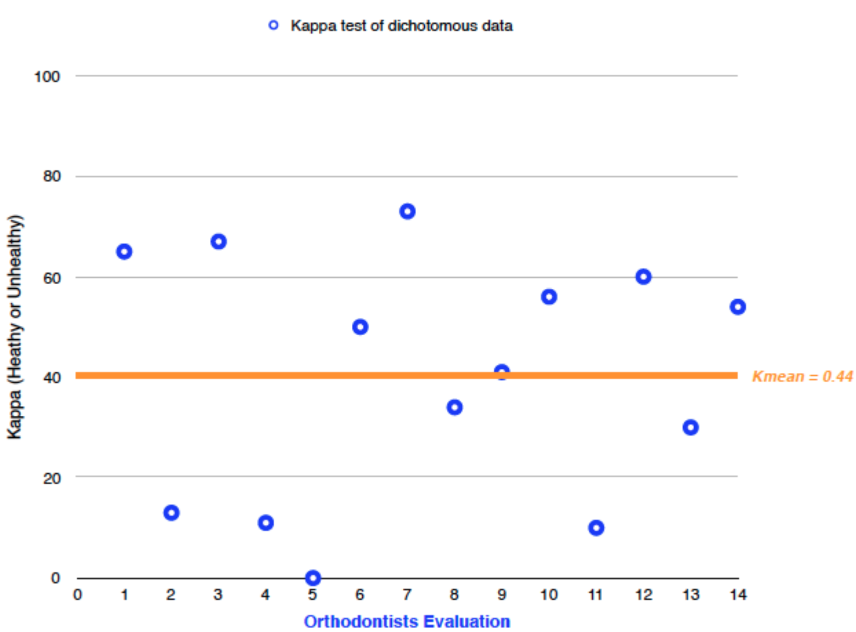


Figure 2.3 – Sample size calculation for orthodontists[5]

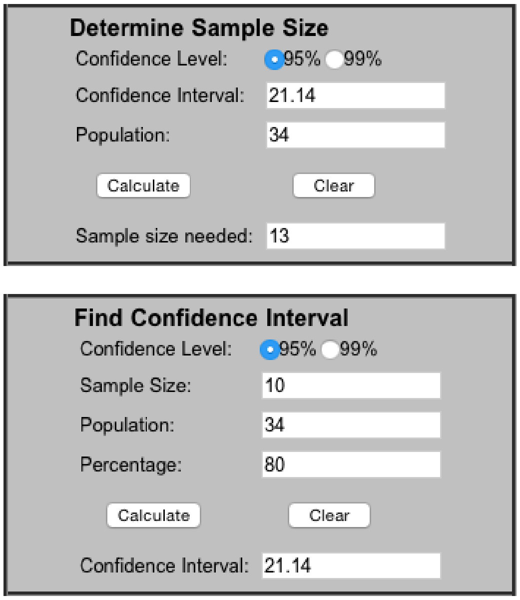


Table 2.1 - Intra-Operators reliability & Orthodontists Accuracy against NP

	Intraclass Correlation	Confidence interval 95%		Degree of Freedom
		Lower Bond	Upper Bond	
Reliability test				
Orthodontists Inter-reliability	0.94	0.88	0.98	9
Accuracy tests				
Mode* vs. OHNS	0.75	0.12	0.94	9
Average ICC#	**Mean**	**Minimum**	**Maximum**	**Std. Deviation**
All orthodontist against OHNS	0.39	0.00	0.74	0.23
Average Kappa#	**Mean**	**Minimum**	**Maximum**	**Std. Deviation**
All orthodontist against OHNS	0.44	0.20	0.80	0.21

ICC: Two-way mixed effects model - Consistency
*Orthodontists' mode of 14 evaluations compared with Nasopharyngoscopy.
Average calculated from data of each evaluator presented in Figure 1

[5] Creative Research Systems web site consulted on Jan 9, 2015: http://www.surveysystem.com/sscalc.htm

Chapter 3: Reliability and Accuracy of Oral Maxillofacial Radiologists when evaluating Cone-Beam Computer Tomography imaging for Adenoid Hypertrophy screening: A comparison with Nasopharyngoscopy

3.1 Introduction

Among the first structures from our immune system that protect us from foreign bodies are adenoids and tonsils. These lymphoid tissues are constantly exposed to antigens coming from allergic diseases, passive smoking or with the food.[69,74] The body reaction to these constant irritants could cause recurrent episodes of localized upper respiratory inflammation processes.[6]

The diagnosis of upper airway obstruction is primarily made on the basis of a medical history, associated with a chief complaint, either from patients and/or parents. The adenoids are strategically located superiorly and posteriorly in the nasopharynx. If the determination of an upper airway obstruction remains non-conclusive after the clinical assessment, direct visualization of adenoid becomes mandatory. Nasopharyngoscopy is the reference standard tool for adenoidal direct examination, being a non-invasive and radiation-free technique that facilitates the assessment of adults and children without sedation.

In the medical[38] and dental[7] fields, two-dimensional skull radiograph was traditionally elected as the adenoid size-screening tool. However, superimposition of structures due to being a static view (evaluation on a single-plane view) and limited to two space planes does not allow for an accurate reflection of the craniofacial lymphoid tissues.[38,39] Specifically in dentistry, the Cone-Beam Computer Tomography (CBCT) has provided the opportunity to assess simultaneously, the cross-sectional area and volumetric portrayal of the upper airway with refined image definition and improved diagnostic accuracy, not available before with two-dimensional technology.[41,42]

With this technology Oral Maxillofacial Radiologists (OMFR) and Orthodontists have the opportunity to analyze 3-dimensional reconstructions of complexes cases of children at opportune times in their craniofacial growth.[75]

Recently, the use of available CBCT imaging for secondary upper airway analysis was investigated. One study reported a high prevalence (42.3%) of incidental findings related to airway, specifically on the naso-oropharyngeal area, in a pool of large-field CBCT scans from orthodontic patients.[75] This elevated incidence should be considered carefully as it raises the possibility of CBCT being a reliable tool for upper airway abnormalities screening.[76] More specifically, a second study validated the assessment of available CBCT imaging as a tool for adenoidal enlargement screening.[18] Two orthodontists and one OMFR assessed CBCT imaging assessed the reconstructions and it was concluded that their sensitivity was 88% and their specificity was 93% in detecting adenoidal hypertrophy.[18] It could be argued that the fact that only one OMFR was involved and this specialist is part of a research team assessing upper airway problems among a referred pediatric population may not necessarily represent the OMFR community.

Knowing that the previous limited sample size could have bias the results and that OMFRs are the dental specialists responsible for the identification and interpretation of incidental findings coming from CBCT images, the aim of this study was to determine how accurate and reliable are a more representative sample of Oral Maxillofacial Radiologists in screening for adenoid hypertrophy using available CBCT imaging as compared to the reference standard diagnosis - Nasopharyngoscopy.

3.2 Materials and Methods

This retrospective study protocol was revised and approval granted by the Research

Ethics Board at the University of Alberta Pro00043684. (Appendix G)

3.2.1 CBCT sample

No CBCT scans were taken for the purpose of the present study. The CBCT sample was collected prospectively from examined patients at the Multidisciplinary Airway Clinic of a Faculty of Medicine & Dentistry, and image assessment for the current study performed retrospectively. CBCT imaging was acquired for orthodontic diagnosis and treatment planning due to complex craniofacial development common to children with airway obstruction.[75]

The only inclusion criterion for the available images was age (children from 6 to 16 years old). Scans of individuals with previous treatment of upper airway dysfunction or sleep disorders, patients with documented syndromic craniofacial disorders (e.g. cleft palate) and previous orthodontic treatment were excluded. The eligible group consisted of thirty-nine subjects and the age of the patients examined from 6.3 to 15.8 years, the mean age 11.5 (SD ± 2.8). It was selected from a pool of consecutive patient files previously examined at the airway clinic.[18]

All subjects had the CBCT and Nasopharyngoscopy (NP) obtained at the same day. The CBCT imaging replaced the conventional orthodontic records imaging composed by lateral cephalometric, panoramic and posteroanterior cephalogram, by simultaneously providing physicians with additional meaningful information. The CBCT protocol was carried out by the same technician using the same scan I-Cat Classic (iCat Imaging Sciences International, Hatfield, US) at 110kV, 6,19mAs, with a 12-inch field of view, 300μm voxel, and 8.9 sec scan time with the patient in upright position in maximum intercuspation. The NP was performed as established by the American Academy of Allergy's protocol.[45] Subsequently, an Ear Nose Throat Specialist, an OHNS, analyzed the NP of each patient and the adenoid size was classified in a 4-point scale based on its obstruction[45]. The severity of adenoid hypertrophy was graded by a validated method[38]: Grade 1 (up to 25% of obstruction); Grade 2 (25% to 50%); Grade 3 (50% to 75%) and Grade 4 (more than 75%). (Appendix D)

3.2.2 Randomization of Patient Data

The CBCT and NP data of selected patients were assessed and the OHNS diagnostic collected. The number of 10 images was determined by time-estimation of 30 minutes evaluation. Specifically for this study, the CBCT images were selected and a randomized list generated by computer. Patients classified in specific different adenoids hypertrophy levels were chosen to warrant the heterogeneity of obstruction. Two patients classified as Grade 1 by OHNS, 3 patients Grade 2, 3 patients Grade 3 and 2 patients grade 4 composed the sample of 10 images. The goal of the stratified random sample was to obtain a heterogeneous sample composed of different levels of obstruction.

3.2.3 Recruitment of Oral Maxillofacial Radiologists

Due to fairly small number of certified OMFRs in North America (Canada and US) all OMFRs were listed. OMFRs were prospective recruited; a convenient sample size of participants was based on the maximum number of acceptance until a defined date (September 15, 2015) and invited by e-mail. A positive answer was followed up with an information letter and the consent form that had to be sent back to the researcher. (Appendix H & I) Each OMFR had the opportunity to ask technical questions about the viewer software by direct e-mail to the principal researcher. The made anonymous DICOM data was sent via a secure and time-sensitive drop box accompanied with the cheat sheet (Appendix D) clarifying the grades of obstruction and a CBCT report form (Appendix E). The evaluation had to occur in a one-time visualization of the images. The evaluation took place at their office and computer however, all used the same CBCT viewer and had access to the same tools and slices. After the form was completed it was sent to the researcher by an anonymous e-mail service and a third person transferred the answers to an Excel file.

The specialists participating in this study applied visual analysis using CBCT large field-of- view of upper airway obstruction, limited to the adenoids area. All OMFRs evaluated the DICOM reconstructed via the same viewer software (InVivo Dental viewer software - Anatomage, San Jose, CA) in an attempt to eliminate logistical issues and prevent biases.[61] The OMFRs participants were blinded to any other information from the patients.

The adenoids hypertrophy obstruction grades were detailed to assure the participants understand the criteria. The adenoids hypertrophy was classified by the participants of this study as mild (Grade 1 if less than 25%); moderate (Grade 2 if 25 -50%); advanced (Grade 3 if 50 - 75%) or severe reflecting the Grade 4 representing more than 75% of hypertrophy, presented in Appendix D.

3.2.3 Statistical Analysis

The statistical Package for the Social Sciences (version 23; SPSS, Chicago, III) was used for data analysis. The Intraclass Correlation Coefficient (ICC) was applied to evaluate the inter-observer reliability of the evaluators and the accuracy of the classification against the Nasopharyngoscopy graded by the OHNS - the reference standard. ICC was interpreted as follows: 0-0.2 indicating poor agreement: 0.3-0.4 = fair agreement; 0.5-0.6 = moderate agreement; 0.7-0.8 = strong agreement; and more than 0.8 indicated almost perfect agreement.[77] A Kappa test was applied in an attempt to justify and analyze the large variation in the confidence interval (CI) reliability/accuracy results and link the results with the clinical relevance about disease and healthy diagnosis. The level of agreement reflected by Kappa was considered as excellent above 0.9; good when it was between 0.75 and 0.9; moderate in the range of 0.5 – 0.75 and poor when bellow 0.5.[60] *P*-values bellow 0.05 indicated statistical significance.

3.3 Results

Number of OMFRs invited by e-mail was 45 with a positive response of 14 (response rate of 31%). Table 3.1 presents the results from inter-observer reliability and accuracy against NP by both tests, ICC and Kappa. The average and standard error of ICC are shown in this table. In addition, each OMFR had their evaluation agreement calculated as per ICC and Kappa. (Figures 3.1 & 3.2) The reliability of the evaluators was strong (ICC=0.79), with a relatively small CI (0.63,0.93) variation. Thereafter reliability between examiners against the NP results (accuracy as compared with the reference standard) was tested. In general, the average was moderate ICC_{mean}= 0.65 and ICC_{range}= (0.12-0.81). An ICC result of each OMFR is presented at Figure 3.1. When comparing the "statistical mode", the value that appears the most, the average accuracy of OMFRs was very good, ICC_{mean}= 0.81 (0.43-0.94). To investigate the large variation on the confidence interval in both tests, we applied Kappa test on the dichotomous data. The 4-point scale grade was transformed in a binary diagnosis; the evaluation/patient was grouped as "health" (grades 1 and 2 of obstruction) and "unhealthy" (grades 3 and 4) for adenoids hypertrophy. In average, the kappa (K) results demonstrated a good agreement between the OMFR and NP, K_{mean}= 0.83 and K_{range}= 0.38-1.00. In addition, individual Kappa tests of each evaluator confirmed these results. (Figure 3.2)

3.4 Discussion

It has been suggested that CBCT provides more information than previous radiographic imaging.[78] While analyzing CBCT imaging a thorough understanding of the structures, shape and anatomic landmarks of the upper airway is required.[79] Even though the absorbed doses from oral and maxillofacial radiology procedures are usually low, only no exposure to radiographs can be regarded as completely free of risk.[80]

The secondary use of CBCT for upper airway analysis has opened the discussion about the impact of incidental findings in complex patient's treatment. Three-dimensional imaging is still not the standard of care in all-dental application; however, the evaluation of all irradiated head and neck structures is mandatory when requested. This study addresses the capability of a sample of Oral Maxillofacial Radiologists in evaluating CBCT images for adenoids hypertrophy screening.

The number of OMFRs in North America is small. In fact, the Canadian Association of Oral Maxillofacial Radiologists (CAOMR) is composed of a list of 27 active members (http://caomr.org/caomr/membership/list), while the American Academy of Oral Maxillofacial Radiology represents 103 certified specialists in USA (http://www.abomr.org). This number does include the effective number of active and inactive ORMFs. A sample size of 14 participants reached more than 10% of the effective radiologists in North America, and a significant number based on global similar survey parameters. The evaluator's profile ranged from newer to experienced specialists. Our sample of raters is considered homogeneous due to the fact that they all need to be boarded-certified in North America to participate in this study. However, it has to be noted that our evaluators were not specifically calibrated for this study. Our aim was to determine reliability of secondary analysis of CBCT imaging from isolated practitioners. A careful calibration could raise the reliability of evaluators.[42,81] Also, it has to be considered that evaluators not trained and inexperienced with the 3-D technology could jeopardize the results.

The accuracy between the OMFR and NP represented a good agreement, when analyzing the average of ICC. Most of the evaluators had a strong accuracy against NP, however 3 evaluators (OMRF #1, #7 and #9) presented very low ICC numbers and a larger CI. (Appendix J) A certified oral & maxillofacial radiologist (N.A.) and the principal researcher (C.P.P.) analyzed the answers of these 3 raters in an attempt to better understand the disagreement-in answers. They were generally between the grades 2 and 3, representing the adenoid hypertrophy ranging from 26 and 74%; however, the extremes were well classified. As well, the results become more accurate if the evaluators could use a descriptive of the adenoids size and relation with anatomic landmarks in axial and sagittal view as the NP grades are based on.

The dichotomous data analyzed by Kappa correlation appears to compensate for the relatively abrupt classification between the levels of hypertrophy and agrees with a previous published study.[18] When renaming mild and moderate as healthy and severe and advanced as unhealthy, the agreement was stronger. The same 3 evaluators kept the low agreement; however, the Kappa coefficient was above 0.8 for 10 of 14 raters (71%), demonstrating an excellent agreement with NP. (Figure 3.2) Several factors may have an impact on the final Kappa values. First, the four-point scale could lead to confusion. It may mean that an alternate method with a 2-point scale level of obstruction could have better represented adenoids obstruction levels. In general terms the evaluators were very consistent and the dichotomous data accuracy (compared to the NP) achieved a "substantial" agreement. Secondly, previous authors discussed the subjectivity of NP results.[82] The actual reference standard to grade adenoids hypertrophy depends on the patient tolerance and the ability of the evaluator to capture a reliable video. Even the most experienced expert Otolaryngologist could misinterpret the axial and sagittal airway imaging.

3.4.1 Clinical Significance

This study assessed adenoid visualization with CBCT against the diagnosis made by the OHNS (Grade of adenoid obstruction). An early and accurate diagnosis and management of adenoid hypertrophy using CBCT image should not replace the reference standard, the NP, and the indication of the imaging shouldn't be solely based in the screening of these structures. However, if the detection and referral is made at the right time then some of the potential craniofacial growth and development consequences may be avoided. As well, some of the already present effects may normalize and/or may favour physiological and harmonious development of bone and dental structures.[64]

3.4.2 Limitations of the study

Due to the referrals to the Upper Airway Clinic being made by suspicion of upper airway dysfunction, the subject's sample may not be reflective from the general population because the patients were recruited from an airway clinic The results of our study should only be extrapolated to children aged 6 to 16 years old.

Intra-reliability of evaluators (ORMF and OHNS) was not assessed on this study, a convenient shortcoming due to the fact that specialists were not in-person evaluations and to secure blindness of process (results and patient identity).

Our study has a susceptible bias due to the selection of a convenient evaluator-sample size; however, a very good number of ORMF was attained based on the limited number of specialists in this field and specifically selected based on the "certified in North America" criterion.

3.5 Conclusions

When compared to the reference standard – Nasopharyngoscopy, the accuracy of Oral Maxillofacial Radiologists to classify adenoid hypertrophy on 4-point scale was moderate to strong and improved when the adenoid hypertrophy was classified dichotomously as healthy/unhealthy. Oral and maxillofacial radiologists were reliable and accurate in screening adenoid hypertrophy using CBCTs.

3.6 Figures & Tables

Figure 3.1 - Accuracy analysis between each ORMF and NP

	Intraclass Correlation	Confidence interval 95%	
		Lower Bond	Upper Bond
OMFR 1	0.406	-0.225	0.807
OMFR 2	0.799	0.396	0.945
OMFR 3	0.813	0.411	0.950
OMFR 4	0.789	0.351	0.943
OMFR 5	0.646	0.045	0.900
OMFR 6	0.670	0.093	0.907
OMFR 7	0.447	0.000	0.826
OMFR 8	0.633	0.081	0.893
OMFR 9	0.124	0.124	0.915
OMFR 10	0.776	0.321	0.939
OMFR 11	0.775	0.324	0.939
OMFR 12	0.780	0.368	0.940
OMFR 13	0.763	0.315	0.935
OMFR 14	0.789	0.351	0.943

ICC: Two-way mixed effects model; inter-reliability/accuracy against Nasopharyngoscopy.

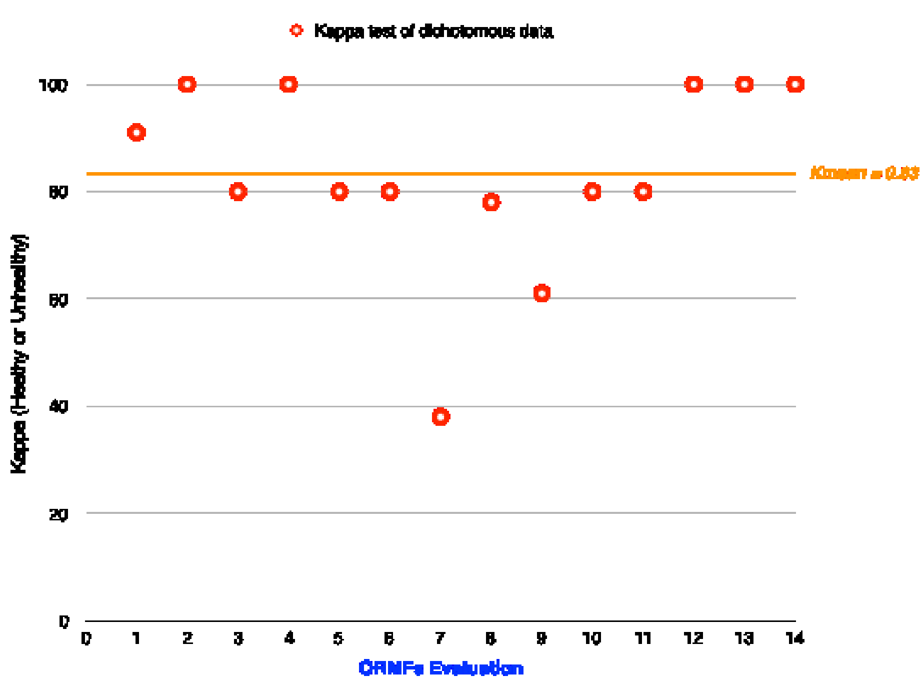


Figure 3.2 – Accuracy of OMFR while evaluating dichotomous against NP

	Kappa	Standardized Error
OMFR 1	0.910	0.288
OMFR 2	1.000	0.000
OMFR 3	0.800	0.186
OMFR 4	1.000	0.000
OMFR 5	0.800	0.186
OMFR 6	0.800	0.186
OMFR 7	0.378	0.300
OMFR 8	0.783	0.201
OMFR 9	0.615	0.225
OMFR 10	0.800	0.186
OMFR 11	0.800	0.186
OMFR 12	1.000	0.000
OMFR 13	1.000	0.000
OMFR 14	1.000	0.000

Kappa test of dichotomous data
Grades 1 and 2 of NP = Healthy patients (1)
Grades 3 and 4 of NP = Unhealthy patients (2)

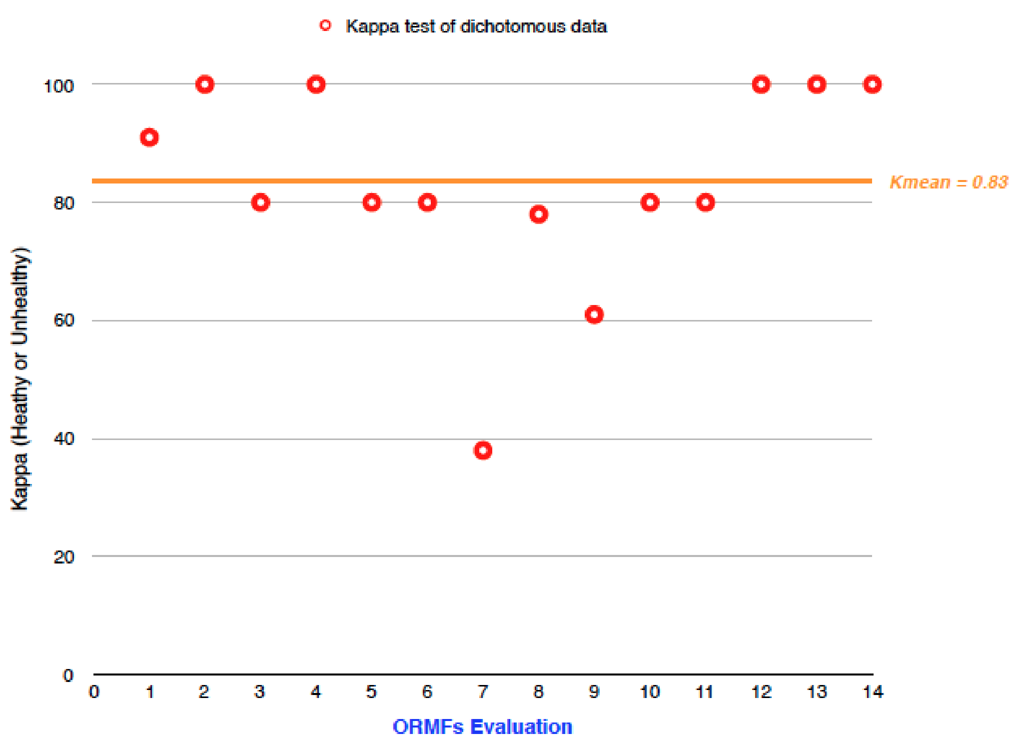


Table 3.1 - Intra-examiner reliability & accuracy analysis

	Intraclass Correlation	Confidence interval 95%		Degree of Freedom
		Lower Bond	Upper Bond	
Reliability test				
ORMF Inter-reliability	0.79	0.63	0.93	9
Accuracy tests				
Mode* vs. OHNS	0.81	0.43	0.94	9
Average ICC#	**Mean**	**Minimum**	**Maximum**	**Std. Deviation**
All OMFRs against OHNS	0.65	0.12	0.81	0.20
Average Kappa#	**Mean**	**Minimum**	**Maximum**	**Std. Deviation**
All OMFRs against OHNS	0.83	0.37	1.00	0.17

ICC: Two-way mixed effects model
*Orthodontists' mode of 14 evaluations compared with Nasopharyngoscopy.
Average calculated from data of each evaluator presented in Figures 1 & 2

Chapter 4: Correlation of volumetric and cross-sectional measurements generated from a CBCT automatic segmentation and 3D reconstruction for evaluating adenoid hypertrophy determined by OHNS

4.1 Introduction

One of the most common causes of an upper airway dysfunction in children and adolescents is adenoid and/or tonsils hypertrophy. They can hypertrophy significantly as part of an immune response potentially causing a partial or total airway obstruction.[53] In such cases, adenotonsillar hypertrophy is considered as an important risk factor for obstructive sleep apnea development.[10,14,45]

The diagnosis of obstructive dysfunction in the upper airway is primarily made on the basis of a medical history, as well as evaluation of physical findings.[6] Chronic snoring, breathing interruption during sleep, diminishing growth rate, tendency to fall asleep during the day, behavioural difficulties and/or a chronic runny nose are common factors associated with it.[10] An indicative medical history with associated physical findings will support an imaging request to provide a definitive diagnosis. In such cases, nasopharyngoscopy (NP) is considered the reference standard of imaging, being a "non-invasive" and radiation-free technique that facilitates the assessment of the adenoids without sedation.

Among dental professionals, two-dimensional lateral skull radiograph has been the traditional tool to screen for adenoid hypertrophy.[38] The advent of CBCT imaging has expanded the screening capability of the upper airway area by providing the opportunity to assess simultaneously cross-sectional areas and volumetric portrayals. 3D imaging compensates the downside of 2D views, by refining the image definition, eliminating structural superimpositions, and improving the overall diagnostic accuracy.[23,41,42,44,69] Simultaneously, CBCT is starting to be the imaging tool of choice for diagnosis and treatment planning of moderate to complex orthodontic cases.[41] However the high percentage of incidental findings in airway area (42.3%) has raised the attention of researches.[75,76]

Several software companies have developed specific applications to analyze and display the Digital Imaging and Communications in Medicine (DICOM) reconstructions of complex airway space and anatomy.[23] Some available craniofacial reconstruction softwares propose new technology to replace the time-demanding manual segmentation of the upper airway space in 3D reconstructions. These softwares are designed offer to automatically or semi-automatically do the upper airway CBCT segmentation demanding limited or without operator control and knowledge of anatomy while transforming the data into a 3D volume.[72]

A previous study questioned the accuracy of Dolphin in this regard as they found that observer's effects influenced the segmentation/volume when the method was not standardized and numbers compared with manual segmentation.[83] To the best of our knowledge, no study has correlated so far the volume and minimal cross-sectional airway area calculated from these softwares with the correlation of the reference standard assessment through nasopharyngoscopy so far. Therefore the aim of this study is two-fold: (1) To test the reliability of CBCT volumetric and cross-sectional area measurements of the nasopharynx using Dolphin; (2) To test the correlation of CBCT volumetric and cross-sectional area measurements of the nasopharynx, using Dolphin, with a definitive nasopharyngoscopy-supported adenoid hypertrophy diagnosis.

4.2 Material and Methods

This retrospective study protocol was approved by the Research Ethics Board at the University of Alberta - Pro00044649. (Appendix G)

4.2.1 The Study Sample

Our sample consisted of CBCT imaging from thirty-nine subjects with ages between 6.3 and 15.8 years of age (mean 11.5 years ± 2.8). This prospective sample was selected from an available pool of patients' records from the Upper Airway Clinic at the University of Alberta. Consecutive examined patients were previously selected as explained in a previous study.[18] No additional CBCT was taken for this specific study, following the ALARA (as low as reasonable achievable) principle and the standard of care of the American[57] and European[58] guidelines.

The inclusion criteria were: (1) Children from 6 to 16 years old and (2) whose chief complaint and reason for referral were based on significant upper airway concerns. Those individuals who had (1) previous active treatment of upper airway dysfunction or sleep disorders, (2) previous orthodontic treatment were excluded and (3) developmental craniofacial disorders as syndromes and cleft palate.

All subjects had the CBCT and NP obtained during a two-hour appointment. The same technician using the same scan parameters followed a CBCT imaging protocol. The images were taken using an ICat Classic (Cone beam 3-D Dental Imaging System, Imaging Sciences International, Hatfield, PA) at 110kV, 6,19mAs, with a customized height field of view maximum12-inch, 300µm voxel, and 8.9 sec scan time with the patient in upright position in maximum intercuspation. Images were stored in DICOM format.

Subsequently, an Otolaryngologist - Head and Neck Surgeon (OHNS) analysed the NP of each patient and the adenoid size was classified in a 4-point scale based on its obstruction[45]. The severity of adenoid hypertrophy was graded by this validated method: Grade 1 (up to 25% of obstruction); Grade 2 (25% to 50%); Grade 3 (50% to 75%) and Grade 4 (more than 75%).

(Appendix D) The NP was performed following the American Academy of Allergy's protocol.[45]

The entire CBCT sample was assessed to verify reliability of third-party reconstruction softwares to read DICOM on different anatomical planes (axial, coronal and sagittal). Our study applied analysis of upper airway obstruction, limited to the adenoidal area, selecting the reconstruction software by convenience: Dolphin 3D software (Version 11.7 Premium, Dolphin Imaging & Management Solutions, Chatsworth, CA). Our choice of software was justified by the fact that Dolphin is the most commonly used reconstruction software for CBCT imaging in North America.[84]

4.2.2 The Measurement protocol

We applied a standardized protocol[81,85] to reposition the images according to head position orientation to minimize errors while limiting the landmarks and calculating the volume areas. It had been confirmed that most of the programs in use have limitations in measuring curvilinear areas.[49]

We applied the Dolphin head positioning tools and the same researcher (CPP) oriented all images as follows:

1. Frontal view, the axial plane crossed the right and left orbital points;
2. Lateral view, the coronal plane perpendicular to the Frankfort horizontal plane (FH) and coincident with the axial plane.[81] The FH plane was constructed from the right to left porions in the external auditory meatus and the right and left orbitale.[86]
3. Axial view was based on the Posterior Nasal Spine (PNS) point located on the frontal view in a vertical axis crossing with the nasofrontozygomatic plane.[86]

The Appendix K (Figure 1) represents the head-orientation standardized sequence.

The segmentation method was validated, described and tested for validity by Palomino et al.[85] For evaluation of the nasopharynx limited to the adenoids area, landmark points/limits for segmentation were located in the posterior nasal spine (PNS), vomer posterior (VP), horizontal extension point VP and vertical extension point ENP (VA), Uvula[87] and Basion (Ba). Landmark location details for each point can be found in Table 4.1.

The representation of the sagittal plane was amplified four times for better visualization of the area. The ideal slice to start the landmark identification was the one that clearly showed the distal cortical of the posterior portion of the Vomer. The reference points were identified in the sagittal plane.

The delimitation of the adenoid area was defined by the junction of PNS, VP, Ba and a plane passing through the Uvula point as localized in the coronal view. This plan crossed two perpendiculars, one originated at the PNS anteriorly and the other posteriorly at the Basion point. This 5-junction area forms a pentagon. The "pentagon area" represents the nasopharynx; the PV point limits it superiorly and inferiorly by the Uvula plane. The adenoid area, which is our region of interest, was visualized inside this "pentagon area" on the sagittal view of 3D reconstructions created by the third-party software. (Figure 4.1a)

The Uvula point was identified at the coronal view, and then the evaluators used a seed point specifically for this purpose. The seed point thereafter showed the Uvula inferior limit when the operator changed the view. The Uvula plane was based on the sagittal view and crossed the PV and PNS perpendiculars.

To determine the area contrast sensibility, two reference points ("seed points" – specific tool of Dolphin 3D) were placed in the middle of the airway space inside the projected pentagon. Thereafter, the area to be measured was filled out (pink color). This delimitation represents the densities of airway and should not invade the airway space and structures around in any of the planes.[83] The determination of the "sensibility" number on Dolphin® followed the same criteria for all reconstructions. (Figure 4.1b presenting the seed points of Dolphin)

After previous calibration of raters (described in the following section), the volume was quantified in cubic millimetres. To delimit the minimal transversal area section (delimited on the airway space of the nasopharynx), Dolphin offered two limiting lines presented in Figure 4.2. Using these two lines that limit the desired slices, the evaluator defined the position of the upper and lower limits, and the automatic tool of the software produced a yellow cut representing the most restricted area and generates that area in square millimetres. Figure 4.3 provides another view from the minimal cross-sectional area delimited by Dolphin.

4.2.3 The evaluators' calibration and effective measurements

The operators were oriented, trained and calibrated to assess the adenoid/upper airway area using CBCT scans not included in this study sample. An Intraclass Correlation Coefficient test (ICC) was applied to evaluate the intra-operator calibration until a high level of consistency was achieved with an ICC of 0.969 (CI 95% (0.948, 0.983) $P<0.001$). The training took place until adequate agreement of 5 images (different from the study sample), measured in two consecutive trials, presented intra-reliability above an ICC= 0.90, representing a very good agreement between raters.

The sample measurements followed a randomized order, generated by a statistician, for each one of the trials. All measurements were completed by the same evaluators and repeated two times under identical conditions, within a 1-week interval. The evaluators did not have access to their previous measurement when participating in the second trial. In addition, the raters were blinded for any other information from the patients' records.

4.2.4 Statistical Analysis

The statistical Package for the Social Sciences (version 22; SPSS, IBM, Armonk, NY) was used for data analysis. The ICC test was applied to evaluate the consistency/ intra-observer reliability, the inter-observer reliability (accuracy between evaluators). Reliability was ranked according to the ICC value. The level of agreement reflected by the ICC was considered as follows: 0-0.2 indicating poor agreement: 0.3-0.4= fair agreement; 0.5-0.6= moderate agreement; 0.7-0.8= strong agreement; and more than 0.8 indicated almost perfect agreement.[77] The Spearman's rank correlation coefficient (Spearman's rho = ρ) measured the statistical dependence of the non-parametric variables, representing the association of the volume and minimum cross-sectional area with Nasopharyngoscopy - reference standard. The values of the correlation were interpreted following the Cohen's 1998 convention to interpret effect size [88]: a correlation coefficient of 0.10 - 0.30 is thought to represent a weak or small association; a correlation coefficient of 0.31- 0.49 is considered a moderate correlation; and a correlation coefficient of 0.50 or larger is thought to represent a strong or large correlation.

In addition, a Discriminate Analysis (DA) explored the data, the NP grades were renamed into dichotomous data as healthy (Grades 1 and 2 of NP) and unhealthy (Grades 3 and 4 of NP). The discriminate analysis performs a multivariate test of differences between groups aiming to predict a classification between volume and MCA on two groups of patients (Health adenoids and Unhealthy adenoids). The Canonical discriminant functions (*r*) of groups were analyzed via Wilks' lambda (*L*) testing equality of groups (maximum value 1) and Eigenvalues (*A)* testing the potential of discrimination (the larger the Eigenvalue is, the greater the amount of variance shared the linear combination of variables, ideal value 0). The Standardized Canonical Coefficient (*D*) ranks the importance of each variable. Chi-square and discriminate function were interpreted via DA.

Finally, ROC analysis established the cut off points for Volume and MCA, from these numbers, sensitivity, specificity, predictive positive values (PPV), negative predictive values (NPV) and likelihood ratio (LR) will be discussed. PPV and NPV are population dependent statistics directly related to disease prevalence. To increase the reliability of adenoid prevalence number, the average of published prevalence on studies with population matching our age-range were established at 31.4%. (REF)

P-values < 0.05 indicated statistical significance.

4.3 Results

The final sample consisted of 38 subjects, 16 girls and 22 boys; one subject was later excluded due to radiopaque object interfering in the measurement of landmarks. The age of the patients examined ranged from 6.3 to 15.8 years old; the mean age was 12.3 (SD ± 2.8 years). The distribution of selected cases showed a heterogeneous sample composed of different levels of obstruction.

The researchers oriented and limited the anatomical points on Dolphin following a randomized sequence (by statistician) on the different trials; the software calculated the volume of the most constricted area automatically. The data was checked carefully and outliers verified. All evaluations were completed by the same raters and re-assessed two times. The ICC was used to detect systemic intra-examiner errors.

The consistency of evaluators between the two trials in Dolphin 3D for volume and minimal cross-sectional area was excellent for the principal evaluator, ICC=0.975 CI 95% (0.951, 0.987) and ICC= 0.840 CI (0.693, 0.917) respectively. The inter-operator reliability for volume followed the constant pattern (ICC=0.975 CI 0.952, 0.987) and was good, ICC=0.701 CI 95% (0.448, 0.849), for minimal cross-sectional area, the latter with a large confidence interval. Table 4.2 presents the consistency and agreement between raters. Overall, the differences in evaluation when comparing the two different trials and evaluators were considered insignificant.

Since high correlation was found in all trials, we selected only one of the trials from the first evaluator to be associated with the reference standard - NP. The mean volume of the nasopharynx was 6990.91 ± 2845.49 mm^3. The minimal area = 50.71 ± 30.42 mm^2. Detailed numbers are presented in the Table 4.3.

An average number of measurements were analyzed; the descriptive showed a skewed (asymmetric) data and was not normally distributed. Due to the significant standard deviation variation, a Spearman's rho was applied to investigate correlations between variables. For volume, the correlation between the Dolphin® segmented volume and the NP was weak and not significant with a negative trend (ρ = -0.222). The association between minimal cross-sectional area and the NP was also weak and not significant, but with a positive trend (ρ = 0.192). Table 4.4 and Figures 4.4a & 4.4b represent these associations w.

The addition of DA confirmed that the prediction of volume and minimal cross-sectional areas with the adenoid size based on NP grades was weak. (Appendix K, Sequence 1) The three assumptions before running DA were checked: normality of data (violated), equality of variance-covariance within groups (showed unequal variance for both outcomes) and low multicollinearity of the variances (violated, higher than 0.8).[6] The descriptive analysis of the dichotomous data showed considerable overlap between the variables, Healthy/Volume $_{mean}$ = 7246.37 SD ± 2995.70 and Healthy/MCA $_{mean}$ =50.39 SD ± 38.37 and Unhealthy/Volume $_{mean}$ = 6193.72 SD ± 3165.11 and Unhealthy/MCA $_{mean}$ =56.94 SD ± 56.94. The Canonical discriminant functions of groups were analyzed via Wilks' lambda (L) showing non-statistical significance and equality of groups, L_{VOLUME} = 0.974 P = 0.329 and L_{MCA} = 0.946 P = 0.160. The Eigenvalues (A) were very low, A = 0.143 (with Canonical correlation (r) = 0.345), representing low potential of discrimination between groups. The values of the standardized Canonical discriminant function coefficient were -0.855 and 0.993 for volume and MCA respectively, meant that the groups differ

[6] Original Lab website accessed on Oct 28, 2015: http://www.origiNPNPab.com/doc/Origin-Help/Discriminant-Analysis

considerably on that variable. The Chi-square tested the significance of L, $X^2 = 4.678$ $P = 0.96$, the low value demonstrated that group differences between diseased vs. non-diseased patients could not be classified in this data. Finally, due to the fact that the data was not normally distributed, unequal variance, and non-linearity for both outcomes (Volume and MCA), most of the Discriminant Analysis assumptions were violated and thus DA was not carried out. The Scatter plot showcases the attempt of running the Discriminate Analysis (Figure 4.5), where the overlap is seeing on most of the data.

The evaluations were transformed into clinically relevant binary diagnoses of diseased vs. non-diseased based through a ROC analysis, which generated cut off values for volumes (cut off: 7028 mm^3) and MCA (cut off: 49.75 mm^2) measurements. The volume measurements achieved sensitivity values of 66% and specificity values of 43%. For MCA, sensitivity of 50% and specificity of 46% were demonstrated. The Positive predictive values (PPV) and negative predictive values (NPV) were calculated based on the adenoid hypertrophy prevalence of 31.4%. Volume measurements PPV 53% and NPV 47%, and MCA numbers of PPV 62% and NPV 38% were found. The positive LR of volume (+LR= 1.6) and MCA (+LR= 0.9), as well the negative LR for volume (-LR= 1.5) and MCA (-LR= 1.0) demonstrated the very small usefulness of the test. (Appendix K, Tables ROC Analysis)

4.4 Discussion

In this study, we focused on the reliability and effectiveness in using volumetric and cross-sectional area measurements using commercial software to indicate adenoid hypertrophy associated with nasopharyngeal obstruction. The Dolphin 3D software® values for volume and minimal area of the adenoidal region have not been previously correlated against the results of the reference standard diagnosis - NP.

Two-dimensional lateral radiograph has traditionally been the tool applied by dentists and some physicians to assess upper airway obstructions.[38,48] This traditional 2D imaging is useful, but not as accurate as 3D imaging.[39] Although the most important perspective, a mid-sagittal view, could be generated the axial plane is not accessible on lateral cephalograms.[43]

CBCT 3D views refine image definition and diagnostic accuracy not available before with 2D technology.[39,44] A literature review suggested that CBCT also provides a lower cost, easily accessible/manipulation and relatively low ionizing radiation doses for evaluation of craniofacial structures compared to the conventional medical Computer Tomography.[14,44,89] Published articles on airway findings via CBCT images showed that some related aspects have not been completely elucidated because of the lack of a reliable CBCT protocol.[72] The need for a reliable protocol could prevent distortions based on a snapshot of the respiration cycle and sensibility to patients' head position alterations.[72]

Orthodontists have the opportunity of seeing patients during their active craniofacial development phase and the advent of CBCT has increased the number of upper airway incidental findings.[76] However, in this study we are not indicating the prescription of the CBCT imaging solely for adenoidal area screening.

A previous study[18] evaluated the agreement between the adenoid hypertrophy diagnosis by CBCT imaging and NP - the reference standard for upper airway assessment. Their assessment evaluated the upper airway area by applying both tools (CBCT and NP) and validated the use of CBCT for adenoid hypertrophy screening by orthodontists with an adequate level of CBCT imaging management. A recent study presented strong agreement between Oral Maxillofacial Radiologists evaluation of adenoids via CBCT and NP results, suggesting again the analysis of 3D imaging for screening of upper airway dysfunction.[90]

The current study convincingly demonstrated that the operators were consistent. The results of our study demonstrated a high-reliability index (ICC > 0.90) confirming that volume and MCA measurements of Dolphin commercial software were similar and reliable when calibrated operators applied the same method. This study agreed with others[48,83] that this technology presented high intra and inter-reliability between operators. The implication of this finding is that any differences in the imaging analysis cannot simply be attributed to operator error.

Regarding the measurements, volume presented a non-significant association with the OHNS-determined diagnosis. The MCA measurements also did not present any significant association with the NP grades of obstruction. The poor accuracy of this automatic software in representing volumes has been previously discussed in others studies. El and Palomo[91] compared oropharynx volume provided from three commercial software (Dolphin, InVivo and OnDemand3D) and values from manual segmentation. Our results demonstrated that automated airway reconstructions with the DICOM viewers were reliable, but not accurate suggesting systematic errors in the automatic measurements. Our results are consistent with findings from De Walter et al[83] who found not accurate numbers provided by Dolphin, a 42% of discrepancy between automated segmentation of upper airway volume and manual segmentation

A negative trend was expected on the cross-sectional area measurements; it suggests that the higher value of the minimal area, the lower the NP grade (higher obstructed level, less free airway space). However, the data extracted from the automated measurements presented a weak association of 3.7% (variability coefficient) with the NP grades of obstruction and an almost zero correlation

In the present study we tested the reliability and efficacy of Dolphin 3D against NP using the analyses generated by two trained and experienced evaluators. Others studies assessed the experience of the evaluator and agreed that oral maxillofacial radiologists and orthodontists adequately trained in CBCT imaging are precise enough for diagnosis using CBCT generated reconstructions. [37,42] The problem lies in casual users that trust on the values provided by automated softwares and possible “cut off” values representing airway obstruction. These factors will depend on patients’ airway anatomy and shape.

The sensitivity / specificity of CBCT imaging for evaluating adenoid hypertrophy of volume (66% and 43%) and MCA (50% and 46%) were poor, justifying the suggestion of non-applicability of the measurements for volume and cross-sectional area provided by Dolphin. The clinical implication of the volume-test could be interpreted as the chance of a patient with positive test will truly has the disease in 62% (1 in 1.4 patients with negative results will be disease free). As well, the minimal cross-sectional area provided by Dolphin will be probable 53% true if the patient actually has the adenoid hypertrophy, the same as chance. The likelihood ratio of both numbers shows a rarely useful method of testing for adenoids hypertrophy.

Previous studies discussed the volume information provided by software,[42,71,91] as the projection of the volume solely does not necessarily represent the areas of actual constrictions. Our data revealed a large variation of airway volume (mm^3) in patients presenting the same grades of obstruction (NP). Figures 4.6a and 4.6b shows that the inverse is also true, patients with different NP grades varying the airway volume considerably. Additionally, upper airway volumetric increases do not automatically imply improvement in breathing function.[7]

The selected software offers the possibility to find the minimal area, and this could be challenging.[42] Our evaluators found that the most restricted area could vary according to the position of the bars (two red dotted lines) that the software provides for limiting the area. It seems that the most restricted area will always be coincident with the lower limit; other authors mentioned the same finding.[42] Despite using a standardized method and controlled for associated bias, we still found defining the automatic delimited minimal area to be unreliable, as is showcased by the large standard deviations. As well, the minimal axial area provided by Dolphin showed almost the same square millimeters for patients having less than 25% and more than 75% of adenoid hypertrophy that is obstructing the airway space (Figures 4.7a and 4.7b). The inverse was also true, the minimal cross-sectional area less than $50mm^2$ in patients with adenoids without hypertrophy or presenting more than 75% of hypertrophy. Therefore the clinicians should not rely solely on the final square millimeter "minimal axial area" presented by the software. Our study associated volume and the most restricted area with the NP generated obstruction grade, and we found a weak correlation (less than 9%).

The limitations detected on the volume and MCA area brought our attention to the fact that the involved operators were remarkably calibrated, and even then a high variation in the results was noted. Previous studies mentioned the limitations of software performing measurements in curvilinear regions, specifically the nasopharyngeal region.[49,86] Nevertheless the MCA represented by Dolphin could be a strong tool to support patient education. The airway tools should be used with caution by clinicians who are not calibrated and those who do not follow a standardized method to locate the landmarks.[18] Dolphin 3D imaging tools related to volume and the minimal area could be acceptable for the screening of structures, patient education and to support referral to physicians, but not likely for prediction of treatment and diagnosis of adenoid hypertrophy.

4.4.1 Clinical significance

This study assessed the upper airway volume and MCA, and correlated these measurements against NP (degree of obstruction due to adenoid hypertrophy). The clinician should not automatically associate the CBCT volumetric and minimal cross-sectional area with healthy and unhealthy patients. We propose that automated software could be solely applied as an educational tool; the outcome numbers of volume and MCA were not accurate, effective and capable to support the clinician diagnosis in airway dysfunction.

4.4.2 Limitations

Airway volume could be influenced by several factors: patient age and weight, head posture, face height, anteroposterior jaw relationship and stage of breathing/respiration cycle. The scan time could interfere with the imaging's quality, as the scanning duration may affect the uvula and soft palate position while swallowing; as well the head position affects the stability of the patient and respiration cycle.[81,92]

The Dolphin automatic reconstruction tool offers an area contrast sensitivity tool based on "seed points", but it is limited to the coronal and axial planes. However, the operator needs to certify that the lateral wall of the pharynx is included in all lateral projections. After conducting the anatomic delimitation and filling it in with "seed points", the entire airway space is outlined automatically. Once again the operator needs to re-check the airway delimitation in all visualization planes, to make sure that the area outlined has been totally filled in. As slices will favour the ideal mapping of structures, it is important that the operators be experienced and that they have an excellent knowledge of 3D anatomy for a reliable and accurate delimitation of the airway space. An inexperienced or untrained operator, as well the automated delimitation of software could jeopardize the results.

4.5 Conclusions

Health professionals should not only rely on CBCT volumetric and cross-sectional measurements produced by Dolphin software to assess upper airway constriction related to adenoid hypertrophy. Dolphin software is reliable, but volume and cross-sectional area measurements were not accurate – they did not reflect the actual nasopharyngeal constriction as assessed via nasopharyngoscopy by an OHNS. Referrals from dentists to OHNS specialists should rely on clinical symptoms and potential airway constrictions as depicted in multi-planer CBCT 3D reconstructions rather than automated measurements of volume and the minimal area generated from Dolphin.

4.6 Figures & Tables

Figure 4.1a. Delimitation of the upper airway area ("pentagon area")

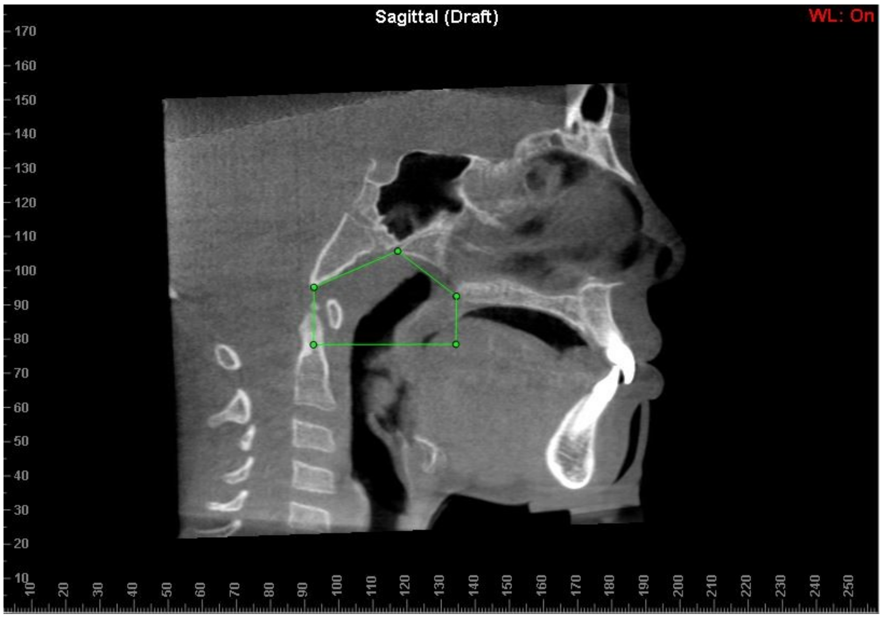


Figure 4.1b – Seed points delimiting airway volume

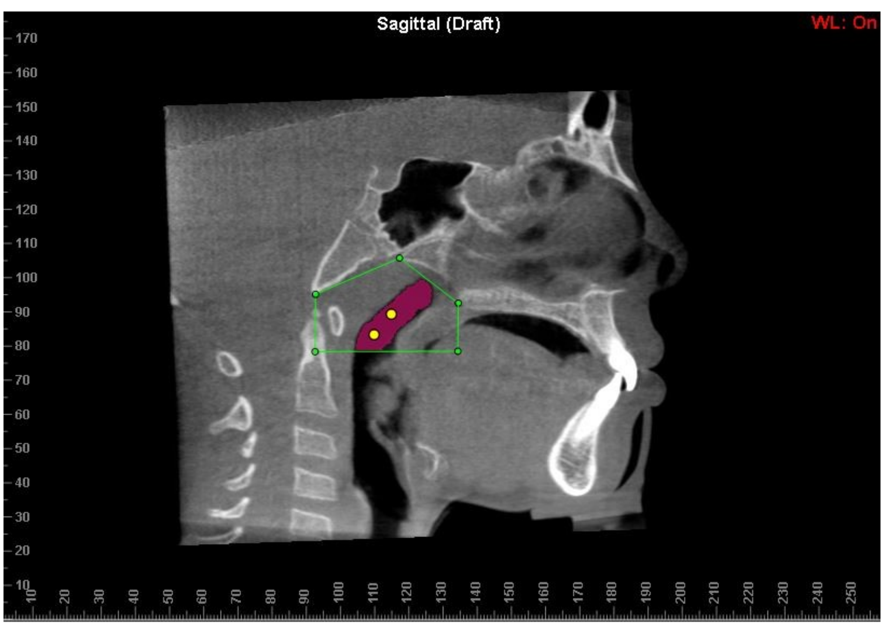


Figure 4.2 - Dolphin bars (red lines) for limiting area

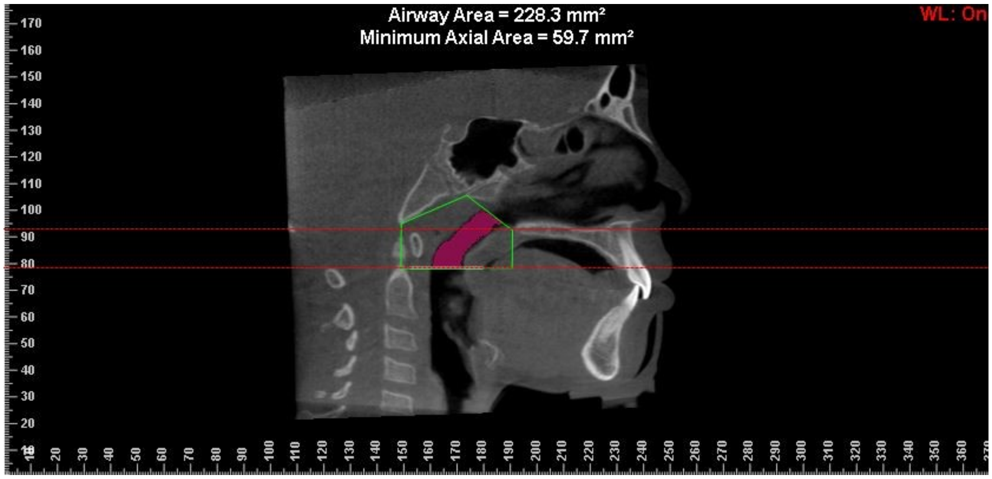


Figure 4.3 - Delimited minimal cross-sectional area

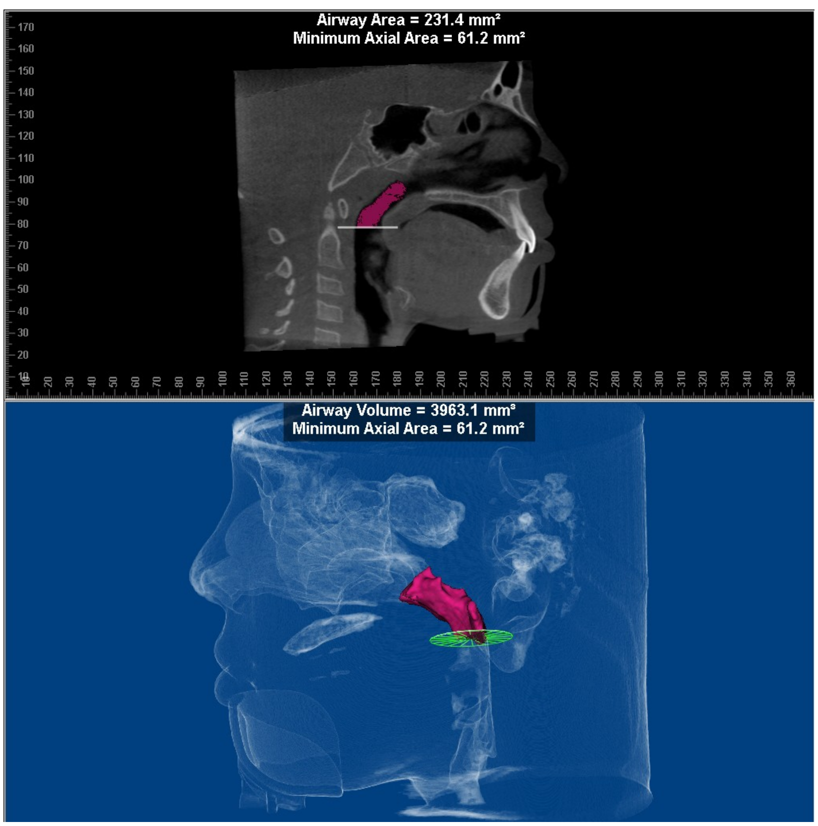
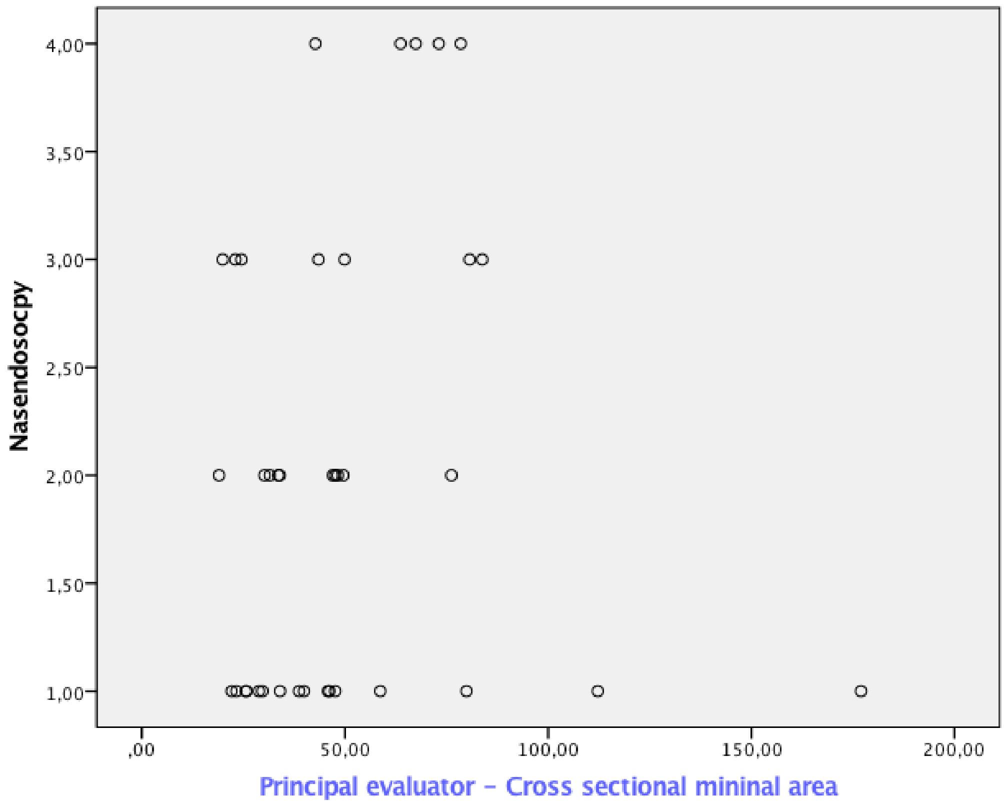


Figure 4.4a – Cross-Sectional area vs. Nasopharyngoscopy grades



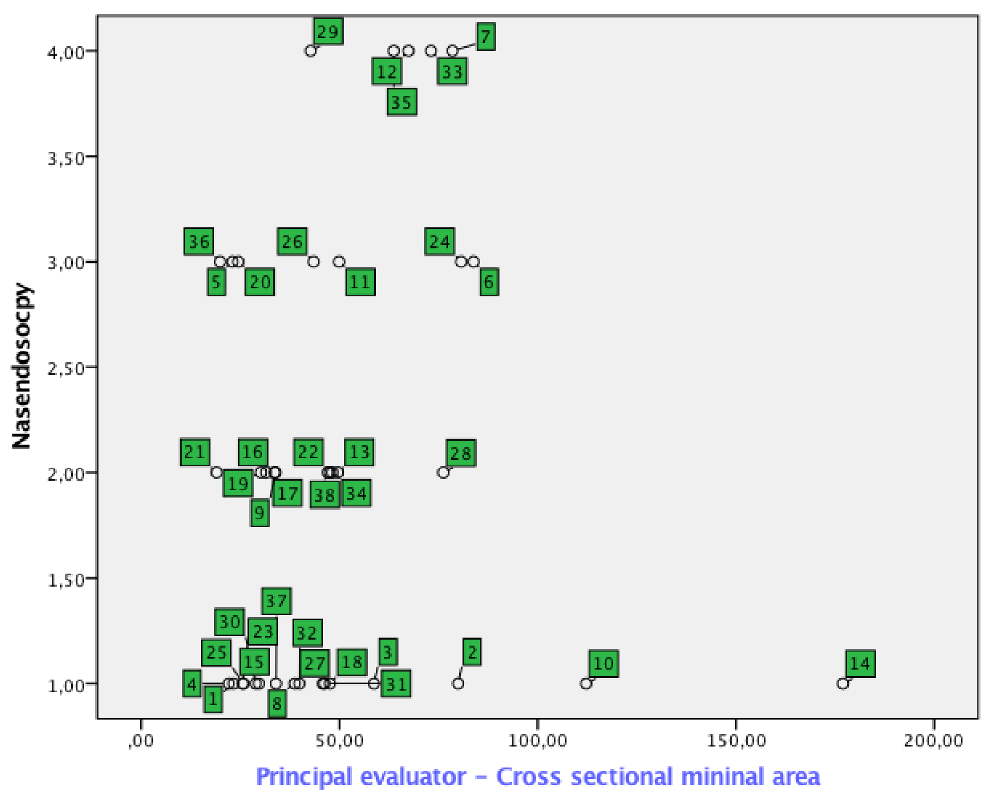


Figure 4.4b – Volume vs. Nasopharyngoscopy grades

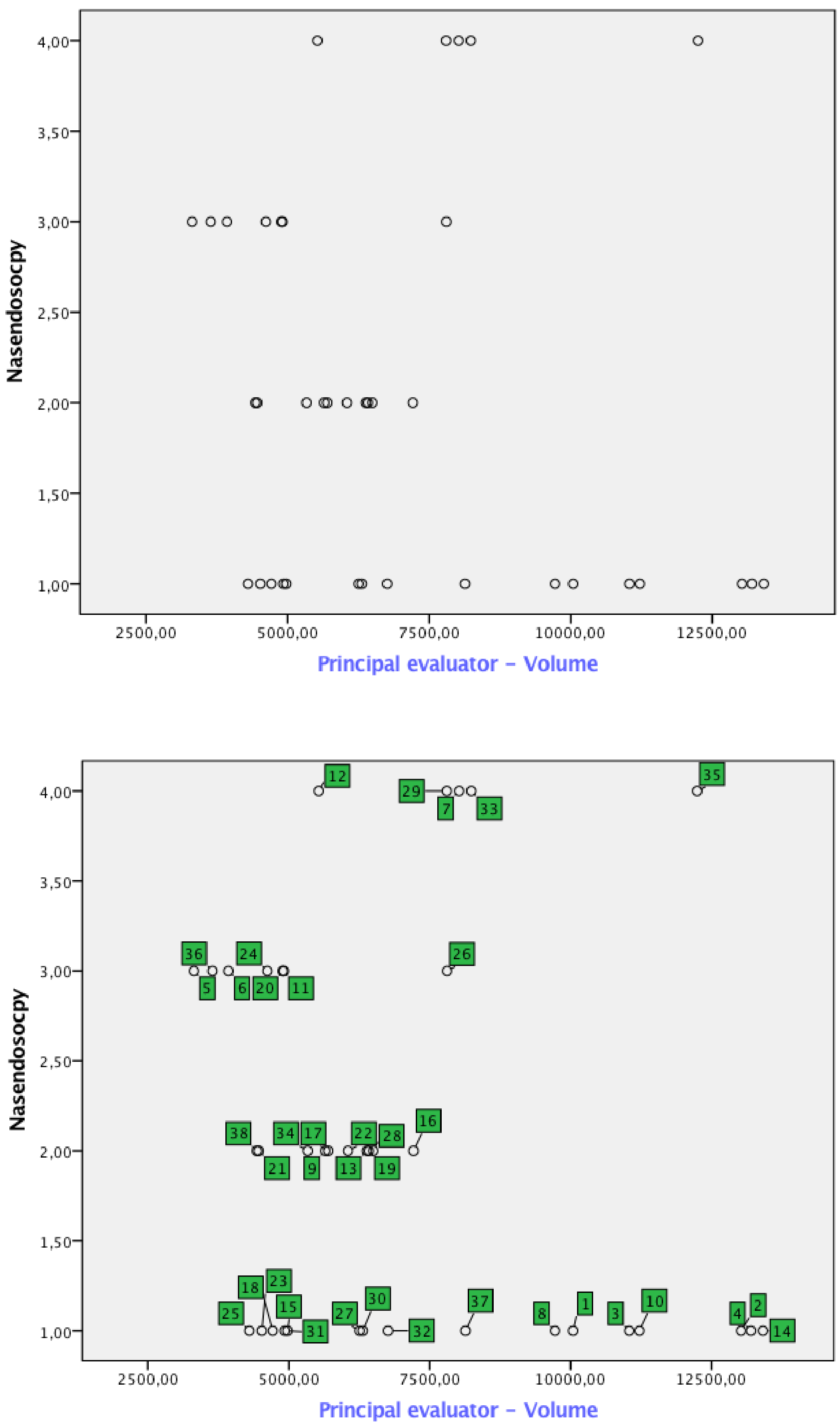
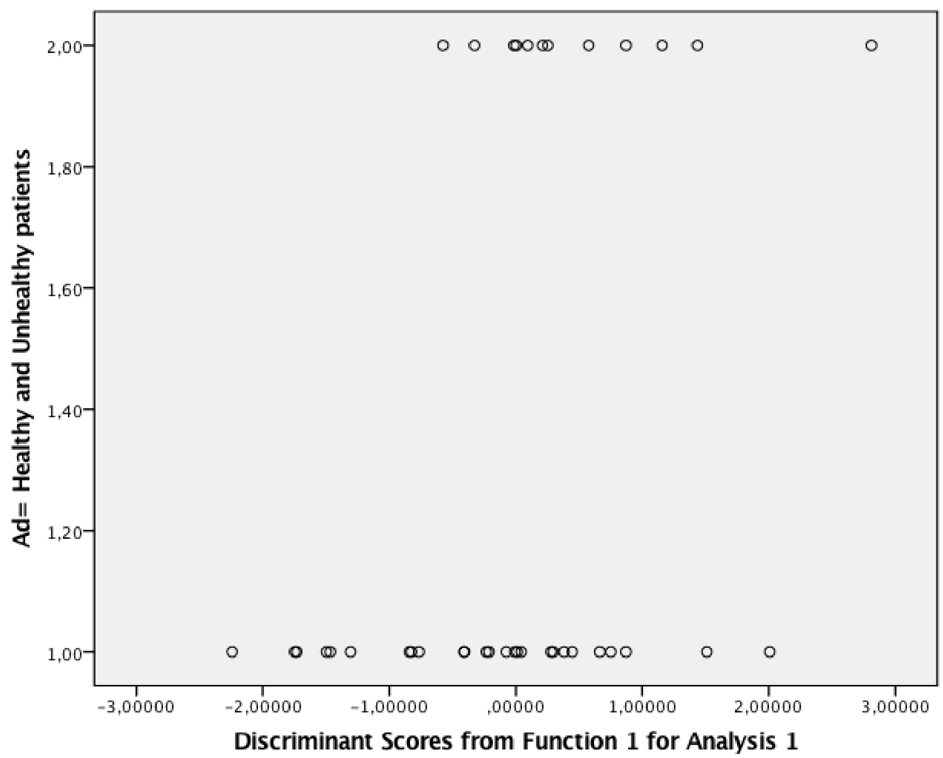


Figure 4.5 - Scatter-plot of Discriminant Analysis & Boxplots of groups



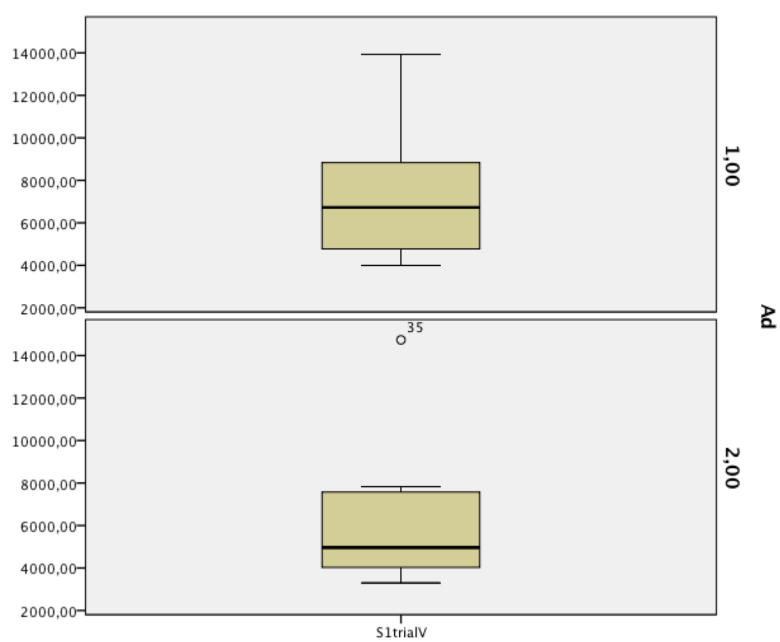


Figure 4.6a - Volume measurements of a patient NP grade 4

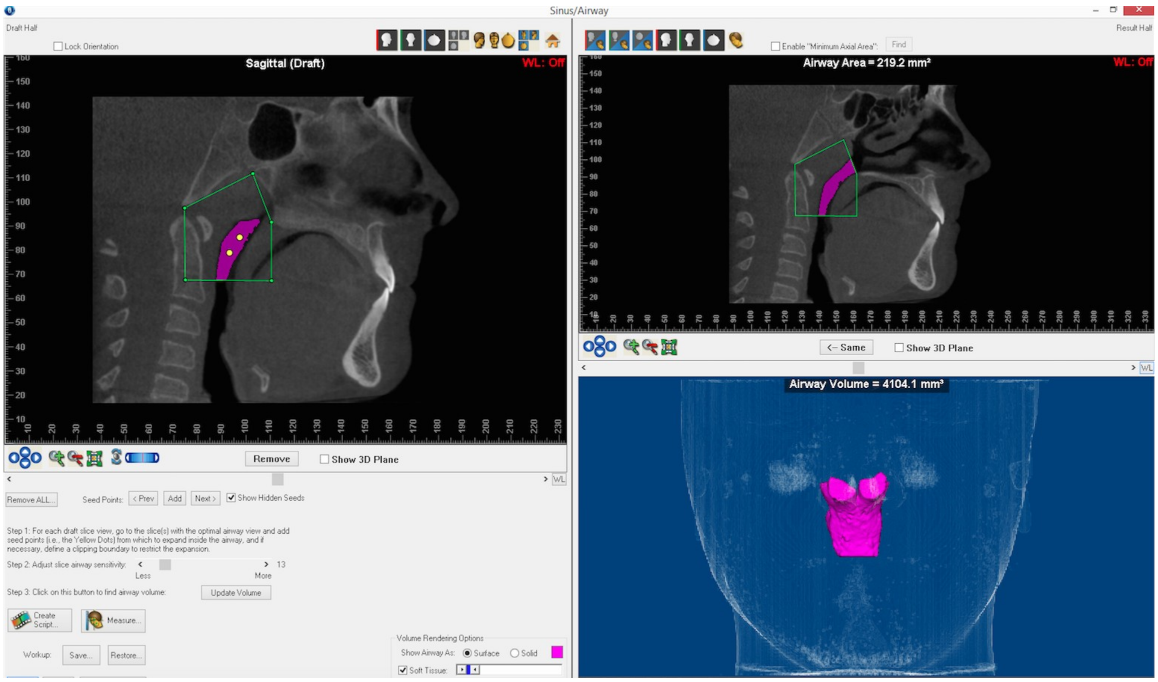


Figure 4.6b - Volume measurements of a patient NP grade 1

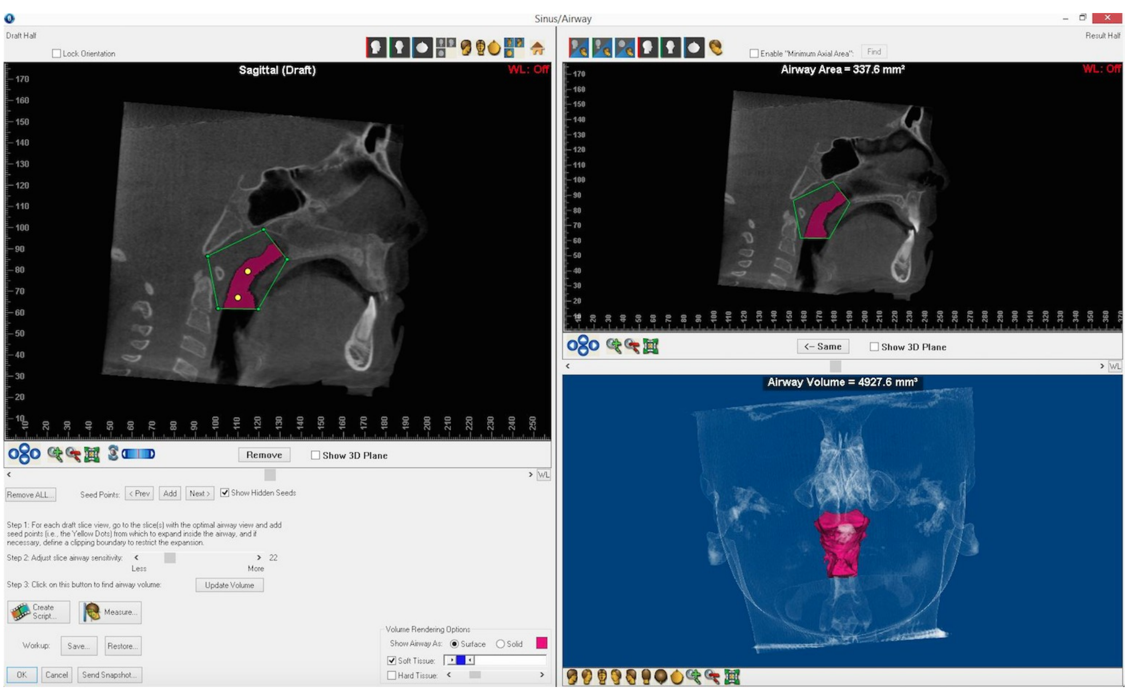


Figure 4.7a – Minimal Cross-Sectional Area on a NP grade 1

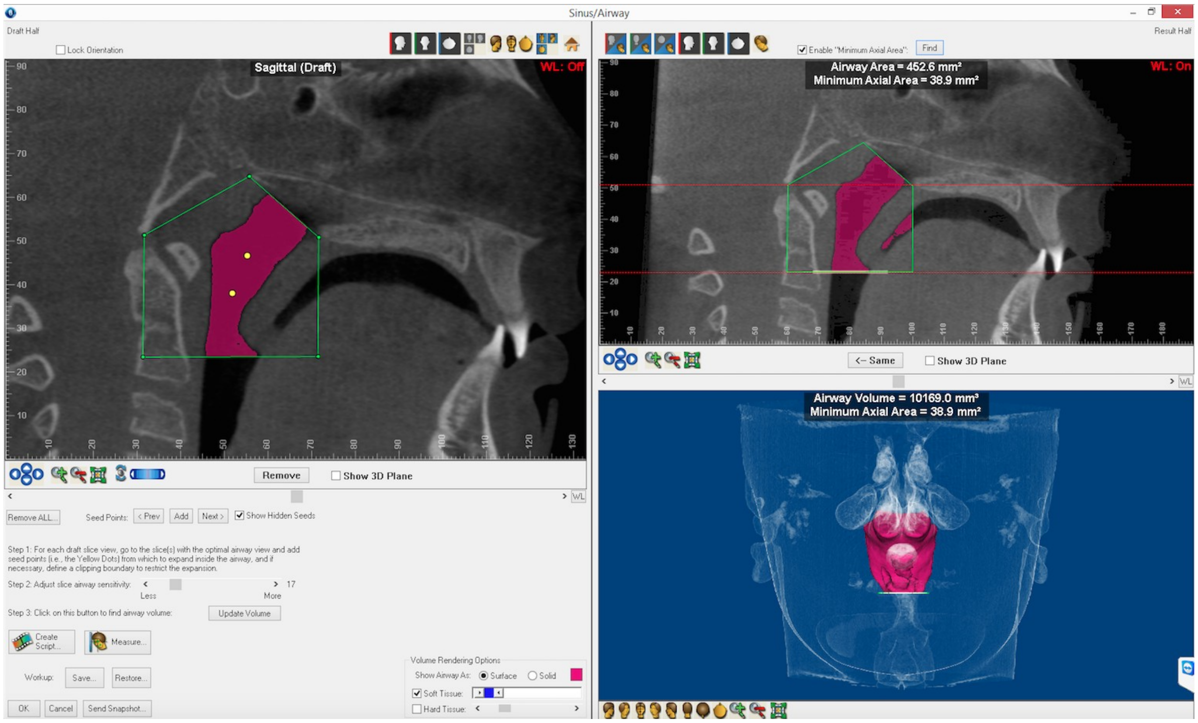


Figure 4.7b – Minimal Cross-Sectional Area on a patient NP grade 4

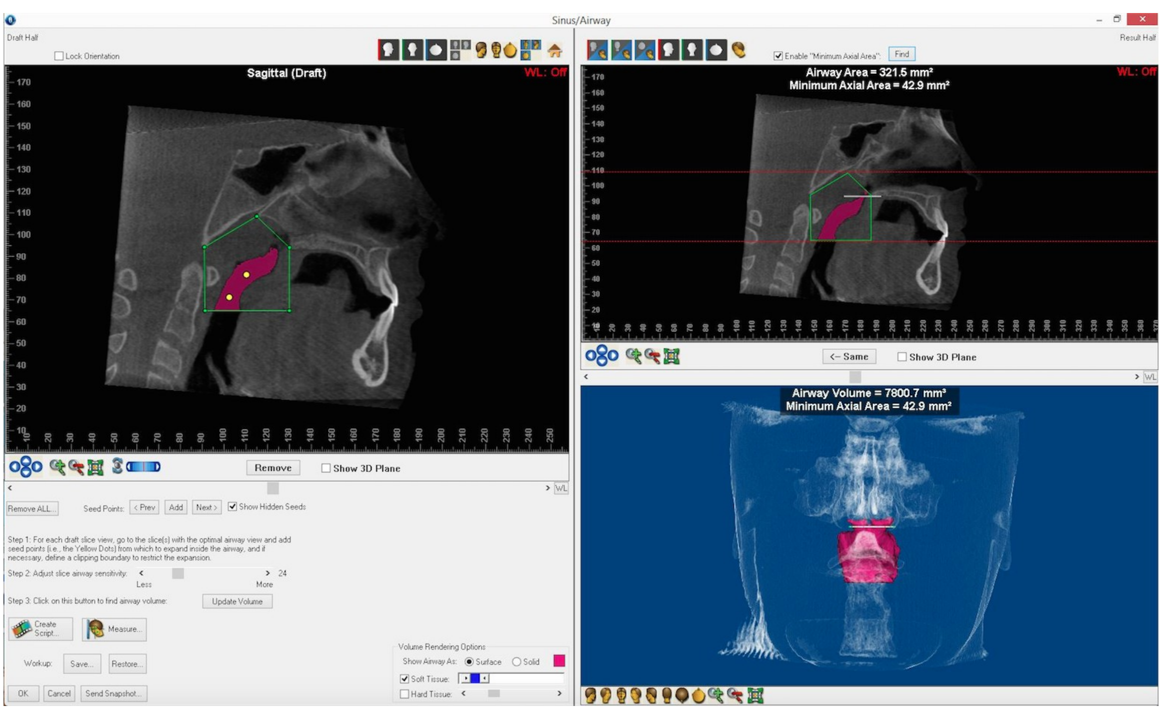


Table 4.1 - Landmarks adopted as reference for the airway space measurements[85,93]

PNS	Posterior Nasal Spine: the most posterior point of the posterior palatal bone and the floor of the nose cavity, in the mid-sagittal median point;
VP	Vomer Posterior: the most posterior portion of the vomer bone;
BA	Basion: the most anterior-inferior portion in the margin of the foramen magnum, in the mid-sagittal plane;
Uv	Uvula: The inferior limit of uvula in the coronal view

Table 4.2 - Intra- and Inter- operator reliability analysis*

	Intraclass Correlation	**Confidence interval 95%**		**Degree of Freedom**
		Lower Bond	Upper Bond	
Intra-operator Volume	0.999	0.995	0.999	37
Intra-operator Minimal area	0.840	0.693	0.917	37
Inter-operators Volume	0.975	0.952	0.987	37
Inter-operators Minimal Cross-sectional area	0.710	0.448	0.849	37

*Two evaluators, each one measured 2 times within 2-week interval.

Table 4.3 - Descriptive average on Volume and Minimal Cross-sectional Area measurements

	Dolphin 3D	**Variation**		**Standard deviation**
	Measurements	Minimum	Maximum	
Average Volume	6990.91	3316.20	13411,50	2845.49
Average Minimal area	50.07	19	177	30.42

Table 4.4 – Correlation of Dolphin Volume / Minimal Area and NP

	Spearmam Rank's Correlation	**N***	**Significance** (2 – tailed)
Dolphin 3D Volume mm^3	- 0.222	38	0.180
Dolphin 3D area mm^2	0.192	38	0.247

*sample size

Chapter 5: Conclusions

5.1 Evaluation of Hypotheses and Study Results

For the ***first objective***, the primary null hypothesis was rejected and the alternative hypothesis accepted; the secondary null hypothesis was accepted and the alternative hypothesis rejected The orthodontists, if trained in CBCT analysis, are not accurate, but reliable in screening adenoid hypertrophy as compared to the OHNS diagnosis.

For the ***second objective***, both primary and secondary null hypotheses were rejected and the alternatives hypotheses accepted. The Oral Maxillofacial Radiologists are accurate and reliable in screening adenoid hypertrophy using CBCT imaging if compared to the reference standard diagnosis provided by the OHNS and NP.

At last, for the ***third objective***, the null hypothesis was accepted and the alternative hypothesis was rejected. The values of volume and minimal cross-sectional area produced by Dolphin are weak to be correlated with the Nasopharyngoscopy grades of obstruction.

Findings of the studies

***Part I (Chapter II)* –** Although CBCT is a reliable and accurate tool to screen adenoid hypertrophy, different levels of CBCT expertise can have an impact in its accuracy. Participating private practitioner orthodontists showed excellent inter-examiner reliability (ICC = 0.94) between themselves; however, large variability with poor accuracy on the adenoid obstruction degree (ICC_{mean} = 0.39 and $Kappa_{mean}$ = 0.44) compared to NP (reference standard) was noted.

***Part II (Chapter III)* –** Oral Maxillofacial Radiologists are strongly consistent when evaluating adenoid hypertrophy on 3D imaging (ICC = 0.80). When compared to the reference standard – nasopharyngoscopy, the accuracy of Oral Maxillofacial Radiologists to classify adenoid hypertrophy on 4-point scale was moderate to strong (ICC_{mean} = 0.70) and improved ($Kappa_{mean}$ = 0.77) when the adenoid hypertrophy was classified dichotomously as healthy/unhealthy

Part III (Chapter IV) – An experienced dentist should not rely solely on Dolphin semi-automatic tools to assess the upper airway obstruction using CBCT imaging. Dolphin software is reliable but not capable of reconstruct an accurate imaging to correlate the volume and minimal cross-sectional area and Nasopharyngoscopy to screen adenoid hypertrophy. Referrals from dentists to Otolaryngology specialists could rely in CBCT reconstructions, but not on measurements of volume and minimal area calculated semi-automatically from Dolphin software airway section. These airway 3D reconstructions should support patient education and the demand/referral of an earlier intervention in children from 6 to 16 years old presenting airway dysfunction if the obstruction is detected.

5.2 Clinical implications of the studies

This three-part study assessed by radiographic imaging the upper airway area and compared the final "diagnosis" against the diagnosis made by the OHNS (grade of adenoid obstruction). Considering the emerging use of CBCT by orthodontists and oral radiologists, an early and accurate diagnosis and management of adenoid hypertrophy and upper airway dysfunction, if properly treated, can reduce airway obstruction and decrease mouth-breathing tendencies.[64] It is not proposed that the CBCT image will replace the reference standard, the Nasolagyngoscopy, and the indication of the imaging shouldn't be based just on screening of the nasopharynx. Adenoid hypertrophy screening is suggested by evaluation of available CBCT imaging from complexes orthodontic cases, as a secondary investigation.[90] However, if the detection and referral is made at the right time then some of the potential craniofacial growth and development consequences may be avoided.[64] Also, the prevention of the sleep-disordered breathing could improve the quality of life of these patients.[22] As well, an early intervention on a patients' airway may normalize and/or may favour physiological and harmonious development of bone and dental structures.

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Appendices

A. Ethics Approval - HERO Pro00043684 for chapters 2 and 3

Approval Form

Date: November 28, 2013 Study ID: Pro00043684

Principal Investigator: Carlos Flores Mir

Study Title: Reliability of Cone-bean Computerized Tomography (CBCT) imaging for diagnosis of adenoid hypertrophy and deviated nasal septum among oral maxillofacial radiologists and orthodontists.

Approval Expiry Date: November 27, 2014

Sponsor/Funding Agency: Rayburn McIntyre Funds

RSO-Managed Funding: Project ID Project Title Speed Code Other Information

There are no items to display

Thank you for submitting the above study to the Health Research Ethics Board - Health Panel . Your application, including revisions received November 14, 2013, has been reviewed and approved on behalf of the committee.

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. It has been determined that a portion of the research described in the ethics application is a retrospective chart review for which subject consent for access to personally identifiable health information would not be reasonable, feasible or practical. Subject consent therefore is not required for access to personally identifiable health information described in the ethics application. In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (November 27, 2014), you will have to re-submit an ethics application.

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

https://remo.ualberta.ca/REMO/Doc/0/6QANDEJGGEI4B78I...1 of 2 2015-10-30, 3:10 PM

Covenant Health approvals should be directed to (780) 735-2274.

Sincerely,

Carol Boliek, Ph.D.

Associate Chair, Health Research Ethics Board - Health Panel

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

https://remo.ualberta.ca/REMO/Doc/0/6QANDEJGGEI4B78I...

B. Information letter for Orthodontists

UNIVERSITY OF ALBERTA

Study Information

Dear Potential Participant,

As an Orthodontist established in Edmonton, you have been contacted via e-mail to participate in a proposed study. You are been asked to take part in a research designed to evaluate consistency in reporting findings from CBCT imaging. More specifically our research question is investigating those findings as related to adenoid hypertrophy in CBCT imaging.

Purpose of the study:

Specifically, we hope to accomplish the following:

> To evaluate the reliability of the CBCTs in diagnosing/screening adenoid hypertrophy compared to the actual reference standard, the nasoendoscopy.

Please take a moment to read the following information.

1) Your participation is voluntary.
2) You will be asked to provide radiographic reports for 10 large field of view CBCT images. Those reports will be only focused on the adenoids.
3) You will be only permitted to view the multi-planar and 3-D reconstructed views only. No other information from the patient's will be available.
4) Your responses will remain anonymous and interpretation documents will not contain personal identifiers.
5) This study has received ethics approval from the HREB-Health Panel the University of Alberta, Edmonton, Canada.
6) Once you have submitted the interpretation documents, they will become property of the University of Alberta and cannot be returned to you due to lack of personal identifiers on it.

Please contact either my supervisor or myself by the following means should you choose to participate or if you have any questions or concerns (Email: cppereir@ualberta.ca or carlosflores@ualberta.ca). **Further information will be provided if you choose to participate.**

Sincerely,

Camila Pachêco, DDS, MSc Candidate (University of Alberta)
Graduate Student - Investigator
613 7908795

C. Informed Consent for Orthodontists

UNIVERSITY OF ALBERTA

CONSENT TO PARTICIPATE IN RESEARCH

The reliability of Cone-bean Computerized Tomography (CBCT) for Diagnosis of Adenoid Hypertrophy.

You are asked to participate in a research study by the Department of Dentistry at the University of Alberta. You have been asked to participate in this study because you are an Orthodontist practicing in Edmonton, AB Canada. Your participation in this study is entirely voluntary. You should read the information below, and ask questions about anything you do not understand, before deciding whether or not to participate.

Identification of the Investigators

If you have any questions about the research, please contact any of the investigators listed below:

Project Supervisor: Dr. Carlos Flores-Mir…………………………….. carlosflores@ualberta.ca

Master's Student: Camila Pachêco Pereira…………..…………………cppereir@ualberta.ca

Purpose of Study & Research Question

Research Question: Is it reliable to use CBCT imaging for diagnosis of adenoids hypertrophy in comparison to the Nasoendoscopy results?

Procedures

If you volunteer to participate in this study, these procedures will be involved:

- CBCT will be presented in our own notebook.
- The participant will review the series of 10 provided CBCTs.
- A separate radiographic report for all 10 CBCT images will be provided.
- You will be asked to report only on findings related to adenoid hypertrophy (as mild, moderate, advanced or severe obstruction of upper airways) identified in each CBCT image.
- Your reports will be sent back to the investigators by anonymous e-mail or a blinded envelope. The reports will be blinded, non-identified, and received by a third person on a sealed envelope.

Privacy and Confidentiality

No personal information about you, or provided by you during this research, will be disclosed to others. When/if the results of the research are published or discussed in conferences, no information will be included that would reveal your identity. Collected data will only be used for this thesis project. Collected information will be stored in an encrypted and password protected computer inside the Department of Dentistry (ECHA - 5th Floor). Data will be stored for a time period of 5 years.

Direct Benefit or Risk of Participation

Involvement will not directly benefit participants, but the findings will help us gain an improved insight into what findings are reported consistently or not by other colleagues. No risks of participation are expected.

Participation and Withdrawal

Your participation in this research is entirely VOLUNTARY. If you choose not to participate, that will not affect your relationship with the University of Alberta. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice. If you have any questions regarding your rights as a research subject, you may contact the University of Alberta's Research ethics office at (780) 492-2615.

Title: The reliability of Cone-Bean Computerized Tomography (CBCT) in diagnosing Adenoid Hypertrophy.

Principal Investigator(s): Camila Pachêco Pereira (Master's Student), Dr. Carlos Flores-Mir (Supervisor)

Phone Number(s): 613 7908795 or 780 492-7409, respectively.

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and/or discuss this study?	☐	☐
Do you understand that you are free to withdraw from the study at any time, without having to give a reason?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐

How was this study explained to you?

____

I agree to take part in this study: YES ☐ NO ☐

Signature of Participant ____

(Printed Name) ____

Date:________________________

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

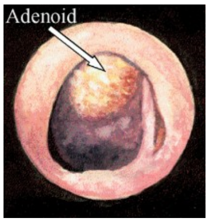
Signature of Investigator or Designee _________________________ Date __________

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT

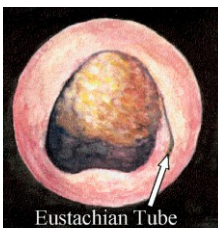
D. Cheat Sheet for participants

Obstruction of Adenoid tissue - Grade System for Endoscopic Examination[7]

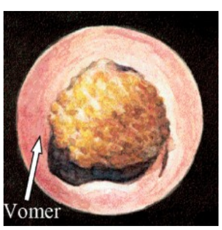
Grade 1: None (0–25% of scarce tissue at rhinopharynx choanal opening); non-obstructive and the adenoid tissues do not contact adjacent tissues.



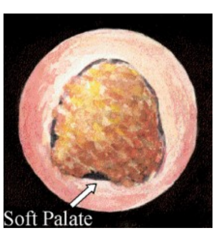
Grade 2: Mild (>25% to maximum 50%). Confined to upper half of the rinopharyngeal cavity. patent choanae; adenoid tissues in contact with torus tubaris.



Grade 3: Moderate (>50%–75%). Considerable obstruction, free only in inferior area; adenoid tissues in contact with Vomer.



Grade 4: Severe (>75% of choanae). Practically complete obstructed; adenoidal tissue in contact with palate while on rest position



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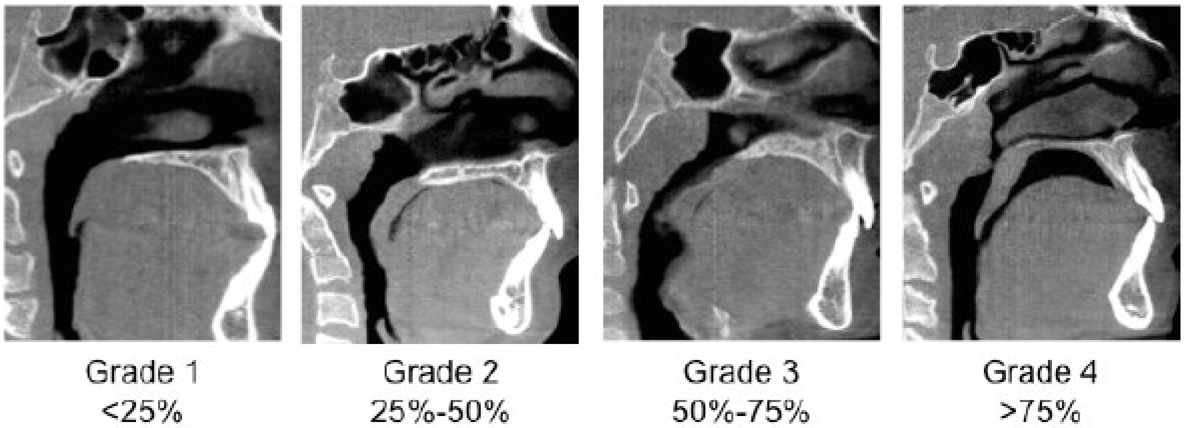
[7] Parikh SR, Coronel M, Lee JJ, Brown SM. Validation of a new grading system for endoscopic examination of adenoid hypertrophy. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology.* 2006;135(5):684-687.

Grade system used for evaluation of CBCT – mid-sagittal slice[8]



For this specific project:

Grade 1 = **Mild** obstruction

Grade 2 = **Moderate** obstruction

Grade 3 = **Advanced** obstruction

Grade 4 = **Severe** obstruction

Thank you for your participation!

Camila Pachêco-Pereira

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[8] Major MP. *Accuracy and Reliability of CBCT imaging for Assessing Adenoid Hypertrophy*: School of Dentistry, University of Alberta; 2013.

E. Adenoids Evaluation Template

CBCT findings related to Adenoids Hypertrophy

Dear participant, please check only one option for each patient.

Patient 1: ( ) Mild ( ) Moderate ( ) Advanced ( ) Severe

Patient 2: ( ) Mild ( ) Moderate ( ) Advanced ( ) Severe

Patient 3: ( ) Mild ( ) Moderate ( ) Advanced ( ) Severe

Patient 4: ( ) Mild ( ) Moderate ( ) Advanced ( ) Severe

Patient 5: ( ) Mild ( ) Moderate ( ) Advanced ( ) Severe

Patient 6: ( ) Mild ( ) Moderate ( ) Advanced ( ) Severe

Patient 7: ( ) Mild ( ) Moderate ( ) Advanced ( ) Severe

Patient 8: ( ) Mild ( ) Moderate ( ) Advanced ( ) Severe

Patient 9: ( ) Mild ( ) Moderate ( ) Advanced ( ) Severe

Patient 10: ( ) Mild ( ) Moderate ( ) Advanced ( ) Severe

We appreciate your participation in this study, please send this report to the following anonymous e-mail: cbctfindings@gmail.com

Camila Pachêco Pereira

F. Complimentary data analysis from Chapter 2

Figure 1a: Nasopharyngoscopy/OHNS against Statistical "Mode"

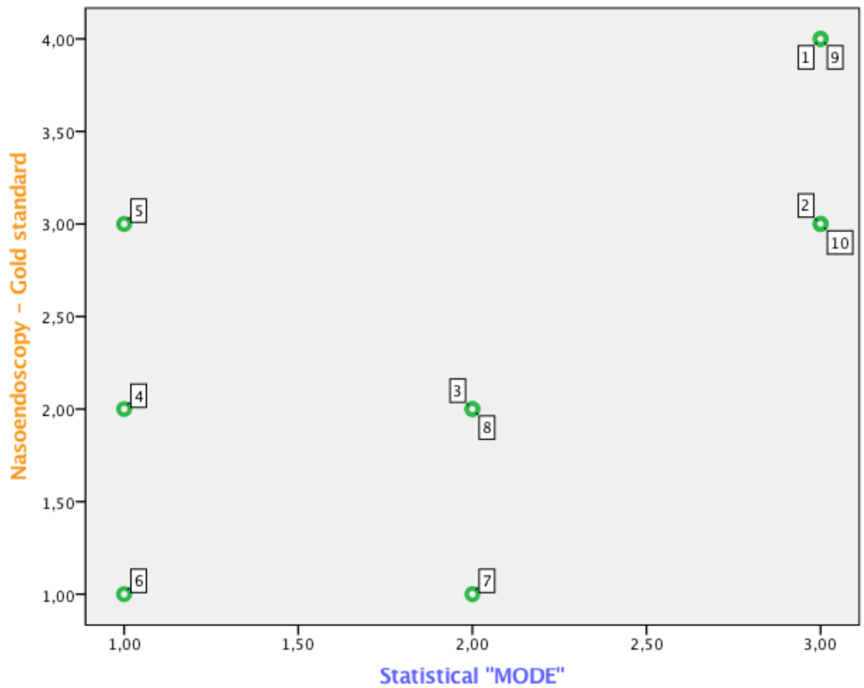
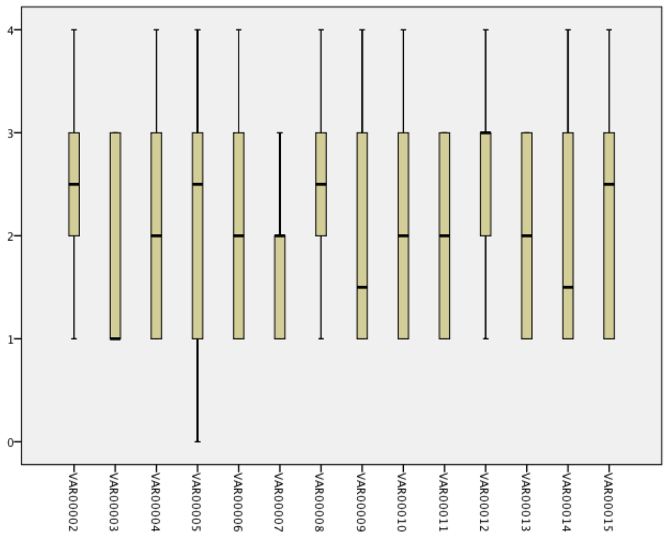


Table 2- Kappa test results of dichotomous data ("statistical mode" vs. reference standard)

"Mode vs. Reference"	Healthy	Unhealthy (no)	Total
Yes	5	0	5
No	1	4	5
Total	6	4	0

Grades 1 and 2 of NP= Healthy patients
Grades 3 and 4= Unhealthy patients

Figure 2 - Outliers and Normality of the distribution



G. Ethics Approval – HERO Pro00044649 for Chapter 4

Approval Form

Date: January 31, 2014 Study ID: Pro00044649

Principal Investigator: Carlos Flores Mir

Study Title: Imaging software validity to determine nasopharynx lumen when using CBCT data in comparison to an OHNS assessment

Approval Expiry

Date: January 30, 2015

Sponsor/Funding

Agency: McIntyre Orthodontic Funds

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

The Health Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. It has been determined that the research described in the ethics application is a retrospective records review for which subject consent for access to personally identifiable health information would not be reasonable, feasible or practical. Subject consent therefore is not required for access to personally identifiable health information described in the ethics application. In order to comply with the Health Information Act, a copy of the approval form is being sent to the Office of the

Information and Privacy Commissioner.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date (January 30, 2015), you will have to re-submit an ethics application.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research.

Enquiries regarding Alberta Health approvals should be directed to (780) 407-604. Enquiries regarding Covenant Health approvals should be directed to (780) 735-2274.

Sincerely,

Anthony S. Joyce, Ph.D.

Chair, Health Research Ethics Board - Health Panel

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

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H. Letter of Information for OMFRs

UNIVERSITY OF ALBERTA

Study Information

Dear Potential Participant,

As an Oral Maxillofacial Radiologists boarded-certified in North America, you have been contacted via e-mail to participate in a proposed study. You are been asked to take part in a research designed to evaluate consistency in reporting findings from CBCT imaging. More specifically our research question is investigating those findings as related to adenoid hypertrophy in CBCT imaging.

Purpose of the study:

Specifically, we hope to accomplish the following:

> To evaluate the reliability of the CBCTs in diagnosing/screening adenoid hypertrophy compared to the actual reference standard, the nasoendoscopy.

Please take a moment to read the following information.

1) Your participation is voluntary.
2) You will be asked to provide radiographic reports for 10 large field of view CBCT images. Those reports will be only focused on the adenoids.
3) You will be only permitted to view the multi-planar and 3-D reconstructed views only. No other information from the patient's will be available.
4) Your responses will remain anonymous and interpretation documents will not contain personal identifiers.
5) This study has received ethics approval from the HREB-Health Panel the University of Alberta, Edmonton, Canada.
6) Once you have submitted the interpretation documents, they will become property of the University of Alberta and cannot be returned to you due to lack of personal identifiers on it.

Please contact either my supervisor or myself by the following means should you choose to participate or if you have any questions or concerns (Email: cppereir@ualberta.ca or carlosflores@ualberta.ca). **Further information will be provided if you choose to participate.**

Sincerely,

Camila Pachêco, DDS, MSc Candidate (University of Alberta)
Graduate Student - Investigator
613 7908795

I. Informed Consent for OMFRs

UNIVERSITY OF ALBERTA

CONSENT TO PARTICIPATE IN RESEARCH

The reliability of Cone-bean Computerized Tomography (CBCT) for Diagnosis of Adenoid Hypertrophy.

You are asked to participate in a research study by the Department of Dentistry at the University of Alberta. You have been asked to participate in this study because you are an Oral Maxillofacial Radiologist boarded-certified in North America. Your participation in this study is entirely voluntary. You should read the information below, and ask questions about anything you do not understand, before deciding whether or not to participate.

Identification of the Investigators

If you have any questions about the research, please contact any of the investigators listed below:

Project Supervisor: Dr. Carlos Flores-Mir…………………………….. carlosflores@ualberta.ca

Master's Student: Camila Pachêco Pereira…………..…………………cppereir@ualberta.ca

Purpose of Study & Research Question

Research Question: Is it reliable to use CBCT imaging for diagnosis of adenoids hypertrophy in comparison to the Nasoendoscopy results?

Procedures

If you volunteer to participate in this study, these procedures will be involved:

- CBCT will be presented in our own notebook.
- The participant will review the series of 10 provided CBCTs.
- A separate radiographic report for all 10 CBCT images will be provided.
- You will be asked to report only on findings related to adenoid hypertrophy (as mild, moderate, advanced or severe obstruction of upper airways) identified in each CBCT image.
- Your reports will be sent back to the investigators by anonymous e-mail or a blinded envelope. The reports will be blinded, non-identified, and received by a third person on a sealed envelope.

Privacy and Confidentiality

No personal information about you, or provided by you during this research, will be disclosed to others. When/if the results of the research are published or discussed in conferences, no information will be included that would reveal your identity. Collected data will only be used for this thesis project. Collected information will be stored in an encrypted and password protected computer inside the Department of Dentistry (ECHA - 5th Floor). Data will be stored for a time period of 5 years.

Direct Benefit or Risk of Participation

Involvement will not directly benefit participants, but the findings will help us gain an improved insight into what findings are reported consistently or not by other colleagues. No risks of participation are expected.

Participation and Withdrawal

Your participation in this research is entirely VOLUNTARY. If you choose not to participate, that will not affect your relationship with the University of Alberta. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice. If you have any questions regarding your rights as a research subject, you may contact the University of Alberta's Research ethics office at (780) 492-2615.

Title: The reliability of Cone-Bean Computerized Tomography (CBCT) in diagnosing Adenoid Hypertrophy.

Principal Investigator(s): Camila Pachêco Pereira (Master's Student), Dr. Carlos Flores-Mir (Supervisor)

Phone Number(s): 613 7908795 or 780 492-7409, respectively.

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and/or discuss this study?	☐	☐
Do you understand that you are free to withdraw from the study at any time, without having to give a reason?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐

How was this study explained to you?

____

I agree to take part in this study: YES ☐ NO ☐

Signature of Participant ____

(Printed Name) ____

Date:______________________________

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee ________________________________ Date __________

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT

J. Complimentary data analysis from Chapter 3

Figure 1 - OMFR #1 vs. NP

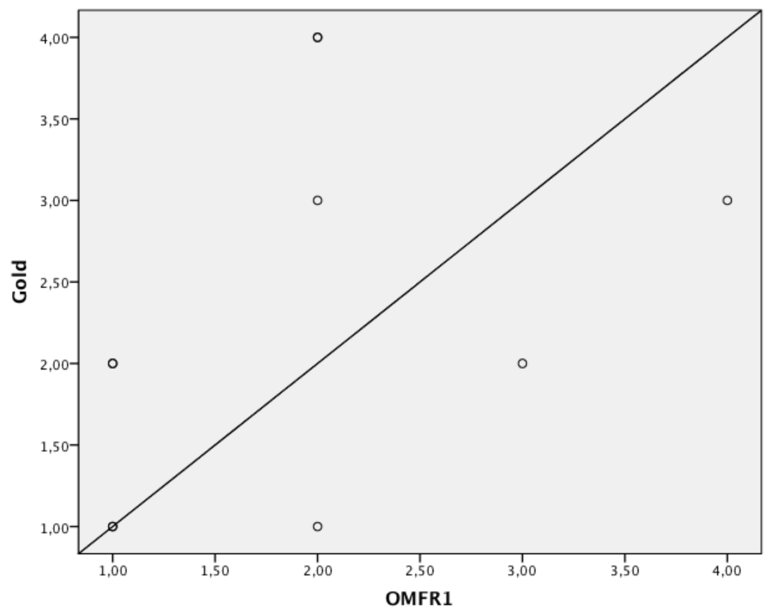


Figure 2 - OMFR #7 vs. NP

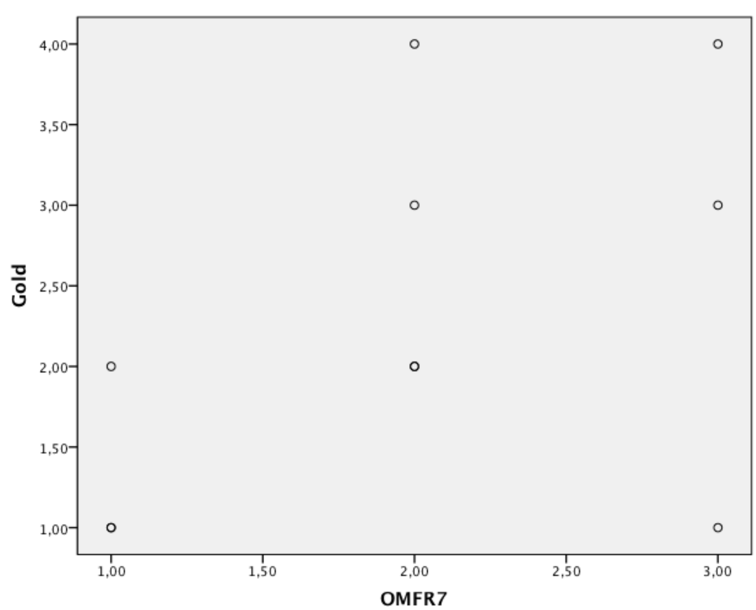
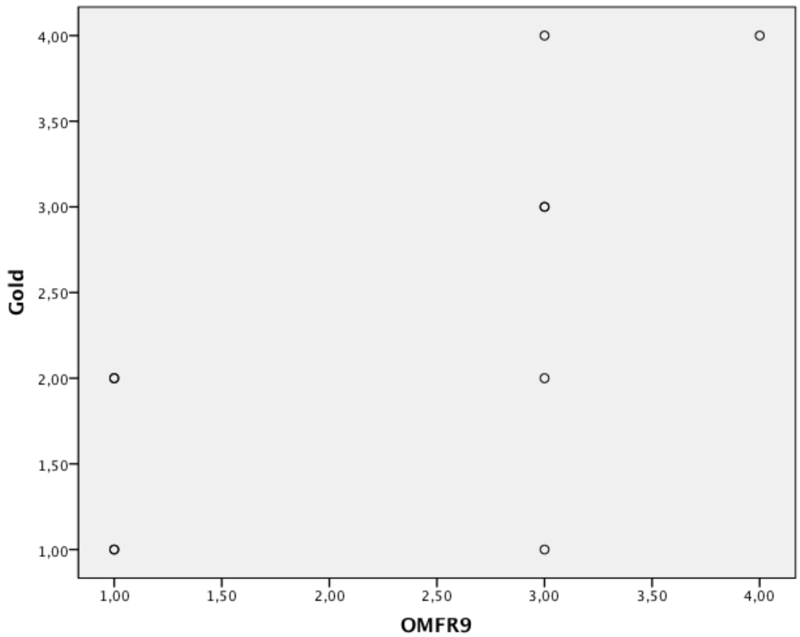


Figure 3 - OMFR #9 vs. NP



K. Complimentary data analysis from Chapter 4

Figure 1 – Dolphin representation of head-orientation standardized sequence

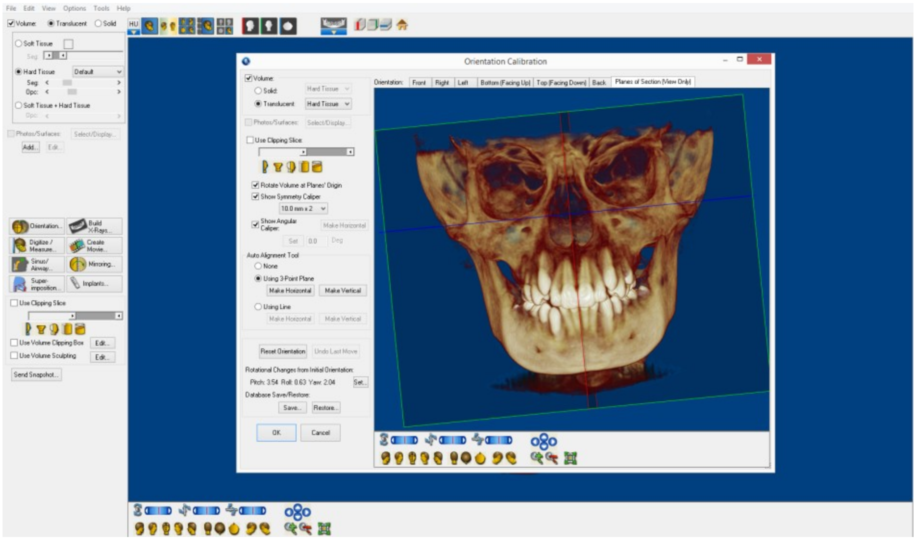
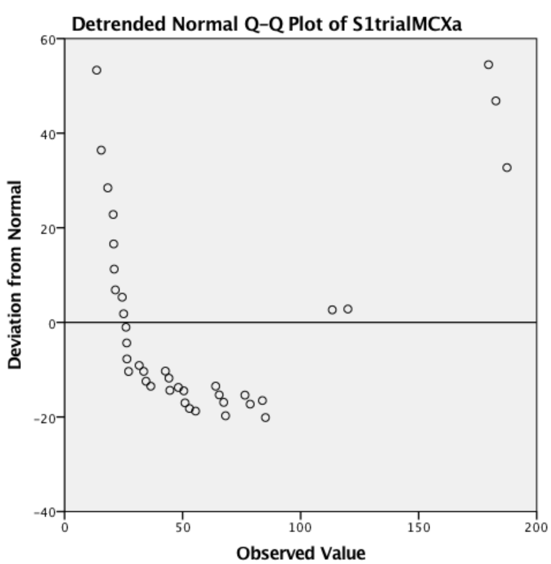


Figure 1. Tridimensional view from the 3 planes: axial, coronal and mid-sagittal. Head orientation and landmarks on 3D images. Lateral view right and left: the coronal plan needs to passing by the porion points crossing the Frankfurt plan; Frontal View, the axial plane should pass by the orbitary cephalometric points, distinguished from the mid-sagittal plane.

Sequence 1 - Discriminant Analysis

Assumptions:

1) Data is not normal distributed (violated the 1st assumption)



Descriptive Statistics for Volume and Minimal Cross-Sectional area

	N	Minimum	Maximum	Mean	Std. Deviation
S1trialV	38	3293.70	14738.10	6913.9605	3047.60271
S1trialMCXa	38	13.60	187.40	57.4816	45.50578
Ad	38	1.00	2.00	1.3158	0.47107
Valid N (listwise)	38				

Adenoids groups: 1=Healthy (Grades 1 and 2) and 2=Unhealthy (Grades 3 and 4)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1,00	26	46.4	68.4	68.4
	2,00	12	21.4	31.6	100.0
	Total	38	67.9	100.0	
Missing	System	18	32.1		
Total		56	100.0		

Group Statistics for Healthy and Unhealthy

				Valid N (listwise)	
Ad		Mean	Std. Deviation	Unweighted	Weighted
1,00	S1trialV	7246.3769	2995.70563	26	26.000
	S1trialMCXa	50.3923	38.37488	26	26.000
2,00	S1trialV	6193.7250	3165.11454	12	12.000
	S1trialMCXa	72.8417	56.94098	12	12.000
Total	S1trialV	6913.9605	3047.60271	38	38.000
	S1trialMCXa	57.4816	45.50578	38	38.000

.

2) Equality of Groups (high – violated)

Tests of Equality of Group Means

	Wilks' Lambda	F	df1	df2	Sig.
S1trialV	0974	0979	1	36	0.329
S1trialMCXa	0946	2.055	1	36	0.160

0

Summary of Canonical Discriminant Functions

Eigenvalues

Function	Eigenvalue	% of Variance	Cumulative %	Canonical Correlation
1	0.143[a]	100.0	100.0	0.354

a. First 1 canonical discriminant functions were used in the analysis.

Wilks' Lambda

Test of Function(s)	Wilks' Lambda	Chi-square	df	Sig.
1	0.875	4.678	2	0.096

Standardized Canonical Discriminant Function Coefficients

	Function
	1
S1trialV	-0.855
S1trialMCXa	0.993

Canonical Discriminant Function Coefficients

	Function
	1
S1trialV	0.000
S1trialMCXa	0.022
(Constant)	0.667

Unstandardized coefficients

DISCRIMINANT ANALYSIS

Group Statistics

Ad		Mean	Std. Deviation	Valid N (listwise)	
				Unweighted	Weighted
1,00	S1trialV	7246.3769	2995.70563	26	26.000
	S1trialMCXa	50.3923	38.37488	26	26.000
2,00	S1trialV	6193.7250	3165.11454	12	12.000
	S1trialMCXa	72.8417	56.94098	12	12.000
Total	S1trialV	6913.9605	3047.60271	38	38.000
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Tests of Equality of Group Means

	Wilks' Lambda	F	df1	df2	Sig.
S1trialV	0.974	0.979	1	36	0.329
S1trialMCXa	0.946	2.055	1	36	0.160

Pooled Within-Groups Matrices [a]

		S1trialV	S1trialMCXa
Covariance	S1trialV	9293159.912	57714.177
	S1trialMCXa	57714.177	2013.356

The covariance matrix has 36 degrees of freedom.

Classification Results [a,c]

		Ad	Predicted Group Membership		Total
			1,00	2,00	
Original	Count	1,00	24	2	26
		2,00	9	3	12
	%	1,00	92.3	7.7	100.0
		2,00	75.0	25.0	100.0
Cross-validated [b]	Count	1,00	23	3	26
		2,00	10	2	12
	%	1,00	88.5	11.5	100.0
		2,00	83.3	16.7	100.0

a. 71,1% of original grouped cases correctly classified.

b. Cross validation is done only for those cases in the analysis. In cross validation, each case is classified by the functions derived from all cases other than that case.

c. 65,8% of cross-validated grouped cases correctly classified.

Main graph showing the results of DA

Huge overlap between groups – not possible to establish a discriminate score between groups

Tables – ROC analysis

Table: 2x2 table of Nasopharyngoscopy for adenoid hypertrophy vs. Volume

	NL (+) Adenoids Hypertrophy	NE (-)
Volume test (+)	8	15
Volume test (-)	4	11

Table: 2x2 table of Nasopharyngoscopy for adenoid hypertrophy vs. MCA

	NL (+) Adenoids Hypertrophy	NE (-)
Volume test (+)	6	14
Volume test (-)	6	12

Table: Sensitivity, Specificity, LR, PPV and NPV of Volume and MCA provided by Dolphin

	Sensitivity	Specificty	+ LR	- LR	PPV	NPV
Volume by Dolphin	0,66	0,43	1.6	1.5	0,53	0,47
MCA by Dolphin	0,5	0,46	0.9	1.0	0,62	0,38
LR = Likelihood ratio PPV = Positive Predictive Value NPV = Negative Predictive Value Prevalence of adenoid hypertrophy = 31.7%						