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Incidental Calcifications s of the Head and Neck on CBCT scans

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A mini-thesis submitted to the Faculty of Dentistry, University of the Western Cape, in partial fulfilment of the requirements for the degree Magister Scientiae in the Department of Diagnostics and Radiology, Faculty of Dentistry, University of the Western Cape

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KEYWORDS

Calcification

Carotid artery calcifications

Clinical significance

Cone-beam computed tomography

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Maxillofacial

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ABSTRACT

Introduction: One of the most notable additions to the dental imaging armamentarium is the introduction of cone-beam computed tomography (CBCT) scanning in general dental practices. The multi-planar functionality of CBCT allows for accurate localization of structures and pathology and hence minimizes the risk of overlapping of structure images, inherent in conventional two-dimensional radiographs. Additionally, the large image volume acquired in a CBCT scan means that more structures are viewable. Consequently, the chance of finding incidental findings (IFs) is increased. An IF could be defined as any asymptomatic entity/condition/presentation/region that draws the attention of a reporting clinician, with no clinical presentations prior to the primary exam. IFs occur extracranially and intracranially. Idiopathic, dystrophic, or metastatic calcification can affect head and neck structures and also be encountered as incidental findings. They may have little to no clinical significance, require monitoring, or may be of such clinical significance that they require referral to a medical specialist.

Aim: To evaluate incidental head and neck calcifications on CBCT records of a Western Cape Province population.

Methods: 350 archived CBCT records were assessed in a minimum of 2 orthogonal planes for the presence of incidental calcifications, using the OnDemand3D™ Dental software program.

Results: A total of 239 patients out of 350 had incidental calcifications (ICs) (68%). The total number of ICs was 523. This translates to an average of 1.49 incidental calcification per patient. The total number of single calcifications was 163 (31.17%) and multiple calcifications were found to occur 360 times (68.83%). Of the 523 incidental calcifications, 130 were found intracranially (24.86%) and 393 were found extracranially (75.14%). 40 calcifications were located centrally (7.65%), 324 were found bilaterally (61.95%), 80 were found unilaterally on the right (15.30%), and 79 were found unilaterally on the left (15.11%). There were 427 ICs that required no follow-up (81.64%), 18 that required monitoring (3.44%) and 78 that required referral to a medical physician for further follow-up (14.91%).

Conclusion: The current study aimed to evaluate ICs in head and neck full FOV CBCT scans of a South African population. 68% of the studied sample had incidental calcifications. There is a positive association between an increase in age and the possibility of having an incidental calcification. The majority of ICs require no treatment (81.64%), 3.44% require monitoring

and 14.91% require follow-up or referral due to clinical significance. It is the prerogative of the requesting clinician to advise patients of the possibility of encountering ICs and their clinical significance, before image-taking, so as to ensure adherence to the principle of informed consent and patient autonomy.

DECLARATION

I declare that Incidental Calcifications of the Head and Neck on CBCT Scans is my own work, that it has not been submitted before for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged as complete references.

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Signed: Leila Ebrahim

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&

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DEDICATION

This work is dedicated to two individuals whom I treasure as my professional mentors:

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ABBREVIATIONS

ALARA:	As Low as Reasonably Achievable
CBCT:	Cone-beam computed tomography
CCAA:	Calcified carotid artery arteriosclerosis
CCAC:	Common carotid artery calcification
CPC:	Choroid plexus calcification
CTC:	Calcified triticeous cartilage
CSC:	Calcified stylohyoid chain
CSTC:	Calcified superior horn of thyroid cartilage
ECAC:	External carotid artery calcification
EICAC:	Extracranial carotid artery calcification
FOV:	Field of view
HCC:	Habenular commissure calcification
HU:	Hounsfield unit
ICs:	Incidental calcifications
IFs:	Incidental findings
IICAC:	Intracranial carotid artery calcification
ILC:	Interclinoid ligament calcification
LHS:	Left hand side
MAA:	Medial artery arteriosclerosis
MIP:	Maximum intensity projection
OMFR:	Oral and maxillofacial radiology/radiologist
PGC:	Pineal gland calcification
PLC:	Petroclinoid ligament calcification
RHS:	Right hand side
STROBE:	Strengthening the Reporting of Observational Studies in Epidemiology
TMJ:	Temporomandibular joint
VAC:	Vertebral artery calcification
2D:	Two-dimensional
3D:	Three-dimensional

µSv: Micro-sieverts

GLOSSARY

Artifact: discrepancy between the attenuation co-efficient of the subject and the reconstructed visual image.

Attenuation co-efficient: a measure of the penetrability of a material by x-ray photons.

Bone window: grey-level mapping that is useful for the visualization of bony structures.

Gold standard: the benchmark, used to characterize the procedure that is the best in the genre.

Hounsfield unit: quantitative measurement used in computed tomography to express radio-density of imaged material, named after Sir Godfrey Hounsfield.

Incidentaloma: incidentally found entity that is not related to the primary indication for imaging.

Noise: variability in the image that is an undesired change in pixel values that can lead to difficulties in diagnostic characterisation.

Scatter radiation: secondary radiation that occurs when the incident x-ray beam photons interact with an object and their paths are altered (scattered).

Soft tissue window: grey-level mapping that is useful for the visualization of soft tissue structures, allowing for superior visualization of soft tissues.

Voxel: in 3D computer graphics, any element that defines a point in 3D-space; CBCT voxels are isotropic meaning they are equal in all dimensions.

CHAPTER 1: INTRODUCTION

Imaging techniques in dentistry have seen rapid advancements in a relatively short period of time. One of the most notable additions to the imaging armamentarium is the introduction of the cone-beam computed tomography (CBCT) modality in general dental practices. CBCT machines and software programmes provide scans with multiplanar imaging options with precision and high resolution (Dief *et al.*, 2019), at a lower radiation dose and shorter acquisition time than that of conventional CT machines (Bayrak *et al.*, 2019). The resultant scan may be viewed in a three-dimensional (3D) volumetric format as well as in axial, coronal, sagittal and oblique sagittal slices. This multiplanar functionality allows for accurate localization of structures and pathology, thus minimizing the risk of overlapping of structure images, inherent in conventional two-dimensional radiographs.

The large image volume acquired in a CBCT scan means that an abundance of structures are viewable. Consequently, the chance of uncovering incidental findings (IFs) is increased. CBCT scans offer information about structures of the head and neck, both intracranial and extracranial including dentoalveolar, base of skull and cervical spine areas and are not just limited to the teeth and their supporting structures. An IF could be defined as any asymptomatic entity/condition/presentation/region that draws the attention of a reporting clinician, with no clinical presentations prior to the primary exam (Dief *et al.*, 2019; Khalifa and Felemban., 2021). IFs occur extracranially and intracranially. Idiopathic, dystrophic, or metastatic calcification can affect head and neck structures and also be encountered incidentally. These calcifications may have little to no clinical significance, require monitoring, or may be of such clinical significance that they require referral to a medical specialist.

Systematic reviews on the prevalence of IFs found that overall, the frequency of IFs was high (24.6-94.3%) although the actual prevalence of threatening IFs was low. (Edwards *et al.*, 2013; Dief *et al.*, 2019, Khalifa and Felemban., 2021). Threatening ICs and their risk of debilitating sequelae have been studied regarding their frequency, prevalence, association with systemic disease and risk of potentially debilitating sequelae (MacDonald *et al.*, 2012; Edwards *et al.*, 2013; Dief *et al.*, 2019; Uys and Mavuso, 2022).

An example of threatening ICs are carotid artery calcifications, a calcification that is often found incidentally but whose association with stroke risk factors is well established (Wells, 2011; MacDonald *et al*., 2012; Dief *et al*., 2019; Uys and Mavuso., 2022).

Therefore, it has become apparent that despite the low occurrence of threatening ICs and given the high frequency of IFs in general, clinicians sending their patients for CBCT scans should be aware of the possible ICs they could encounter and be prepared to report on and disclose them to their patients. A comprehensive study evaluating the frequency and general characteristics of all possible ICs on CBCT scans, that will aid clinicians in identifying these calcifications and possibly act as a guide when deciding on their threat status, would be beneficial.

To the author's knowledge, there have been no studies that incorporated all possible calcifications, intracranial and extracranial, in one comprehensive study.

CHAPTER 2: LITERATURE REVIEW

2.1 The CBCT Imaging Modality, a Brief Summary

Imaging techniques in dentistry have seen rapid advancements in a relatively short period of time. One of the most notable additions to the imaging armamentarium would be the introduction of the CBCT modality in general dental practices. CBCT scans may be used for a wide variety of clinical tasks that include diagnosis, treatment planning and prognosis (Dief *et al.*, 2019; Monsarrat *et al.*, 2019; Uys and Mavuso., 2022).

Development of CBCT for the oral and maxillofacial region followed its introduction for use in angiography in the 1990's (Pauwels *et al.*, 2015). It is so named due to the shape of the x-ray beam that is projected to the detector panel i.e., the beam is cone-shaped in contrast to the fan-shaped beam used in conventional CT machines.

CBCT machines and software programmes provide scans with multiplanar imaging options with precision and high resolution (Dief *et al.*, 2019), at a lower radiation dose and shorter acquisition time than that of conventional CT machines (Bayrak *et al.*, 2019). The resultant scan can therefore be viewed in a 3D volumetric format as well as in axial, coronal, sagittal and oblique sagittal slices. This has been lauded as one of the greatest advantages of CBCT scans over conventional (2D) radiographic techniques (Dief *et al.*, 2019). However, the value of conventional 2D radiographs has not been disputed and still remains the gold standard for dental radiography (Scarfe and Angelopoulos., 2018; Monsarrat *et al.*, 2019). There is less image distortion and structure superimposition on CBCT scans than that found on conventional images (Gunduz *et al.*, 2018).

The acquired scans are suitable for viewing gross anatomical structures, depending on the Field of View (FOV) chosen as well as more detailed structures such as root canal anatomy. Furthermore, they are used for various applications that include pre-implant surgery planning, post-surgery assessment, root canal treatment, localization of impacted teeth, orthodontic screening and treatment progress (to name a few). CBCT software programmes offer a variety of different functions, including nerve tracing, airway segmentation, TMJ reconstruction and 3D reconstruction for digital splint design, besides the normal functions such as measurement, contrast and sharpening tools (Abramovitch and Rice, 2014; Lascala *et al.*, 2014). An interesting function included in most CBCT software programmes is the ability to assess the grey levels of different sites on the scan. This value gives an indication of x-ray attenuation and could therefore be useful in defining anatomical boundaries (e.g. the oropharynx) for segmentation processes (Zimmerman *et al*., 2016; Zimmerman *et al*., 2019) or in assessing the density of bone in order to distinguish or identify any variations that may be indicative of an abnormal phenomenon (Nasim *et al.*, 2018).

There is an abundance of structures potentially viewed in a large FOV, presented in the table below (Table 1), adapted from Monsarrat *et al*., 2019.

Table 1: Table of structures and spaces that may be viewed in a large FOV CBCT volume

Naso-oropharyngeal airway	**Skull base**
Ethmoid sinus	***Anterior***
Inferior, middle, superior meatus	Frontal bone
Pharyngeal tonsils, Fossa of Rosenmüller	Ethmoid bone and cribriform plate
Paranasal sinuses	Middle and superior nasal concha
Maxillary sinus	***Middle***
Frontal sinus	Body and greater wing of sphenoid bone
Sphenoid sinus	Hypophyseal fossa
Temporomandibular joint	Petrous part of temporal bone
Temporal fossa and articular tubercles	Inferior and superior orbital fissure
Mandibular condyle	***Posterior***
Articular space	Clivus
Cervical vertebrae	Occipital bone, condyle
Atlas with anterior and posterior arches	Styloid process of temporal bone
Axis with odontoid process	Carotid canal
Cervical vertebrae	Jugular, magnum, stylomastoid foramina
Outer, middle, and inner ear	**Calvaria**
External auditory meatus	Parietal bone
Malleus, stapes, and incus	Coronal, sagittal, and lambdoid sutures
Cochlea	Bregma, lambda, pterion
Semi-circular canals	**Face skeleton**
Mastoid process of temporal bone	Mandible with mental foramen
Focal calcifications	Maxilla
Tonsils	Hyoid bone
Lymph nodes	Nasal bone
Sinu-nasal	Vomer
Arterial (facial, carotid)	Zygomatic bone
Salivary glands	Palatine bone
Pineal glands	Inferior nasal concha
Hypophysis	Lacrimal bone
Falx cerebri	
Stylohyoid chain	

(Monsarrat et al., 2019)

The CBCT imaging modality is therefore an exciting addition to general and specialist dental practices. Much research has been done in an attempt to fully understand the scope and limitations of this modality. Despite this and given its relative newness and yet increasing frequency of use, new questions are continually being formulated to help fully understand the workings of this radiographic imaging modality.

2.2. Incidental Findings

In any given scan volume, there will be structures present within it that will be unrelated to the primary indication for the scan. These will be normal anatomical structures, variations of normal anatomical structures, benign lesions or even abnormal or pathological changes (Edwards *et al*., 2013). Any finding/s that are discovered upon analysis of a radiographic exam that is/are unrelated to the primary indication for the radiograph has/have been defined as an Incidental Finding/s (IF) (Edwards *et al*., 2013; Zain-Alabdeen *et al.*, 2017; Mutalik *et al*., 2018; Dief *et al.*, 2019). In conclusion, an IF could be defined as any asymptomatic entity/condition/presentation/region that draws the attention of a reporting clinician, with no clinical presentations prior to the primary exam.

The abundance of structures potentially viewed in a full FOV scan (Table 1) carries with it the increased likelihood of findings unrelated to the main indication for the image. The practitioner should therefore be prepared for and have a protocol in place for the analysing and reporting of such findings.

A recent systematic review on IFs in CBCT scans concluded that although the frequency of IFs is high (24.6% - 94.3% of CBCT scans), not all of them require immediate medical intervention (Dief *et al.*, 2019). The frequency of IFs highlights that there is an increased responsibility on the part of the clinician responsible for the scans in analysing and reporting on IFs, as there may be clinical consequences attached to the presence of a certain IF, and if not correctly identified or reported on may in fact result in legal ramifications (MacDonald *et al.*, 2012; Edwards *et al.*, 2014; Dief *et al.*, 2019; Monsarrat *et al.*, 2019).

2.2.1 Types of Incidental Findings in the Head and Neck Region

There have been a few studies exploring the characteristics and prevalence of IFs of the head and neck on CBCT scans. Table 2, below, adapted from a recent systematic review, highlights the most commonly occurring head and neck IFs in the literature (Dief *et al.*, 2019). (Table 2)

Table 2: Table of Possible Incidental Findings of the Head and Neck

AIRWAY FINDINGS	Mucous retention cyst Concha bullosa Sinusitis Deviated septum Nasal/antral polyp
TMJ	Flat condylar margin Condylar degenerative change Condylar erosion Subcondylar cyst Osteophyte Bifid condyle
VERTEBRAL	Degenerative changes
VASCULAR	Calcification of atherosclerotic plaque
SOFT TISSUE CALCIFICATION	Tonsillolith Sialolith Antrolith Ligamentous calcification
DENTOALVEOLAR	Supernumery teeth Idiopathic osteosclerosis Root fragments
ENDODONTIC	Pulp stones Endodontic lesions
THREATENING	Malignancy
PATHOLOGICAL	Cysts

(Dief *et al.*, 2019)

In one systematic review, the three most commonly found IFs were vertebral degenerative changes (0.5- 45.6%), sinusitis or mucosal thickening (7.7- 41.7%) and pineal gland calcification (0.5- 19.2%) (Edwards *et al*., 2013). A more recent review found that less severe IFs were more frequent than more severe IFs (Dief *et al.*, 2019). These authors described IFs such as mucous retention cysts (frequency of 55.1%), sinusitis (frequency of 41.7%) and calcified stylohyoid ligament (frequency of 26.7%) as non-threatening less severe IFs and carotid artery calcifications (frequency ranging between 5.7- 11.6%) as threatening. They concluded that although the frequency of IFs is high (24.6% - 94.3% of CBCT scans), not all of them require immediate intervention or referral to a medical doctor (Dief *et al.*, 2019). The most recent systematic review addressing the nature and clinical significance of IFs on CBCT, found that the percentage of low, moderate and high clinically significant IFs ranged between 43.46-71.1%, 15.6-28.9% and 0.3-31.4% respectively (Khalifa and Felemban., 2021).

2.3. Calcifications

Calcifications of the maxillofacial region may be discovered as IFs on CBCT scans. These may be physiological or pathological. ICs may have little clinical significance, need monitoring, or require medical intervention.

Heterotopic ossification is the formation of bone in the 'wrong' place (Vidavsky *et al*., 2020), that occurs under regulated mineralization pathways. An example of this would be an elongated styloid process. Osteophytes of the TMJ are examples of calcifications that stem from bone remodelling (Singer *et al*., 2021), seen in degenerative joint disease. Calcifications along the stylohyoid or stylomandibular ligaments, or within the pineal gland, have been designated as age-related physiological calcifications (Wells, 2011; Bayrak *et al.*, 2019). Due to the presenting features of abnormal high-density structures on CBCT, and previous studies of incidental calcifications, it was decided for the purpose of this research project to include 'calcified stylohyoid chain', and 'osteophytes of the TMJ' as ICs (Monsarrat *et al*., 2019) .

Pathological calcification occurs when structures become mineralised inappropriately (i.e., in tissues such as muscles, cardiovascular structures, and neural structures) (Vidavsky *et al.,* 2020). This type of calcification is seen in certain benign conditions such as chronic inflammation or injury, as well as in association with more concerning disease processes or conditions. In short, the formation of pathological calcifications occurs under a continuum of different mineralisation pathways (still under current research) which may include dysregulated or completely unregulated mechanisms (Vidavsky *et al*., 2020). Vidavsky *et al* (2020) defined a pathway in biomineralization to 'consist of a coordinated series of events that begins with bound or free ions and ends with the final biomineralized tissue.'

Dystrophic calcification is the calcification that occurs in abnormal tissue, in the presence of ischemia & necrotic tissue, with normal serum calcium and phosphate levels (Wells, 2011). Dystrophic calcification accounts for over 95% of calcifications detected on radiographs (Freire *et al*., 2017).

When there are increased serum calcium or phosphate levels, metastatic calcification occurs. Examples of metastatic calcifications are those that occur in the vascular tissues, kidneys, or corneas (Vidavsky *et al.,* 2020). The formation of metastatic calcifications within the vasculature will be discussed in more detail later on.

Additionally, pathological calcifications may occur in response to external factors such as vitamin D deficient rickets or in association with prosthetic devices such as heart valves (Vidavsky *et al*., 2020). Importantly, is also seen in certain malignant diseases.

Proper knowledge and accurate diagnosis of calcifications may aid clinicians in formulating a holistic treatment plan. This may include either no treatment, further monitoring or even referral to a medical specialist. It has been suggested that early identification could lead to life-saving interventions (Wells, 2011; Edwards *et al*., 2013; Ozdede *et al.*, 2018; Dief *et al.*, 2019; Monsarrat *et al*., 2019; Khalifa and Felemban., 2021; Uys and Mavuso, 2022).

2.3.2 Calcifications of the Head and Neck

Head and neck calcifications can be broadly divided into two main categories, namely intracranial and extracranial calcifications. Intracranial calcifications are any calcification found within the cranium of the skull, and conversely extracranial calcifications occur outside of the cranium. Further, these calcifications can be identified by noting other characteristics such as morphology, specific location and distribution patterns (Altındağ *et al.*, 2017). Although a relatively common occurrence, the exact identification of these characteristics is not an easy task on conventional 2D radiographs. This is due to the superimposition of images of structures in close proximity to each other which are inherent on a planar image (Wells, 2011). CBCT scans therefore offer an immediate advantage in precise localization of calcifications due to their multiplanar functionality (Wells, 2011; Altındağ *et al.*, 2017).

The following is a table of possible calcifications that could be encountered on a head and neck CBCT scan (in no particular order) (adapted from (Wells, 2011; Bayrak *et al.*, 2019; Dief *et al.*, 2019)):

Table 3: Possible Calcifications Encountered on a Head & Neck CBCT Scan

EXTRACRANIAL	INTRACRANIAL
Tonsilloliths	Carotid artery calcification
Sialoliths	Pineal gland calcification
Antroliths	Choroid plexus calcification
Phleboliths	Habenular commissure calcification
Stylohyoid chain calcifications	Dural calcification
Triticeous cartilage	Basal ganglia calcification
Lymph nodes	Petroclinoid ligament calcification
Calcinosis cutis	Interclinoid ligament calcification
Pulp stones	Carotico-clinoid ligament calcification
Osteophytes of the TMJ	Phlebolith
Carotid artery calcifications	
Vertebral ligament calcifications	
Vertebral artery calcifications	

2.3.2.1 Extracranial calcifications

These include threatening and non-threatening calcifications. Dief *et al.,* (2019), in their systematic review reported the frequency of IFs of tonsilloliths to range between 1.3% and 14.3%, sialoliths ranged from 0.4% to 1% and stylohyoid ligament calcification frequency ranged from 3.1% to 26.7%. This review also stated that the frequency of ICs of the carotid artery ranged from 2.0% to 11.6 %, however they did not specify whether this was intracranial or extracranial carotid artery calcifications.

Tonsilloliths are composed mainly of calcium hydroxyapatite and calcium carbonate apatite, and form either due to stasis of saliva in salivary ducts or retention of bacterial debris in the tonsillar crypts and chronic tonsillitis. Tonsilloliths may cause no symptoms or they may cause throat irritation and foul tastes or smells (Wells, 2011). The multiplanar function of CBCT scans may enable the differentiation of tonsil stones from calcified lymph nodes, phleboliths or sialoliths in the same region. When comparing phleboliths to tonsilloliths, the phlebolith shows distinctive and well-defined characteristics (see later) (Uzun *et al.*, 2017).

Sialoliths are aggregates of calcified material found within salivary glands or their associated ductal system. The formation of sialoliths has been linked to salivary pH, stasis of saliva, mucous content of saliva and the gross anatomy of the salivary duct. Sialoliths occur most commonly in the submandibular salivary gland, followed by the parotid gland. They may be asymptomatic or cause pain and swelling and result in a condition known as obstructive sialadenitis (Wells, 2011). Notably, vascular lesions such as haemangiomas with calcium deposits may appear similar to sialoliths and it is therefore important to differentiate the two in order to ensure appropriate therapy. Doppler sonography is an appropriate diagnostic tool for this endeavour (Wells, 2011).

Antroliths are calcified masses found within the paranasal sinuses. They are usually incidental findings and present as a uniform radiopacity (Wells, 2011).

A *phlebolith* is a calcified vascular thrombus usually found in association with a vein not contained in bone (Wells, 2011). They are related to vascular malformations (Alsadah *et al.*, 2020) and haemangiomas. The vascular malformation is thought to cause stagnation of blood flow and resultant calcium deposition (Wells, 2011; Uzun *et al.*, 2017; Alsadah *et al.*, 2020) and stone formation. The mineral content is composed of carbonate-flourohydroxyapatite (Uzun *et al.*, 2017). Radiographically, phleboliths present as multiple well-defined radiopaque lamellated circular lesions and are said to have an "onion-like" appearance (Wells, 2011; Uzun *et al.*, 2017), with adjacent radiolucent and radiopaque rings. Phleboliths that aggravate symptoms of venous malformations such as pain or inflammation may require removal (Uzun *et al.*, 2017). Phleboliths tend to be smaller than sialoliths and calcified lymph nodes but larger than tonsilloliths (Uzun *et al.*, 2017). In addition, when comparing multiple sialoliths to multiple phleboliths, the sialoliths tend to follow the pathway of the salivary duct, while the phleboliths are more randomly arranged (Uzun *et al.*, 2017). When identifying phleboliths, their relation to an associated vascular structure is an important step (Uzun *et al.*, 2017).

A *stylohyoid ligament* longer than 35mm could be considered to be calcified or elongated (Wells, 2011). Twelve patterns of calcification of the stylohyoid complex have been described (Saccomanno *et al.*, 2021), based on the four developmental regions of the complex viz. tympanohyal, stylohyal, ceratohyal and hypohyal components. The exact etiology is unknown and further research in this area is required. A calcified stylohyoid ligament may give rise to symptoms that include facial or throat discomfort, dysphagia, or vertigo, amongst others, and has also been shown to sometimes impinge on the carotid artery. This could have dire consequences as associated with occlusion of any major artery. When there are multiple symptoms present a patient may be diagnosed as having Eagle's Syndrome. This syndrome has many names and variations (Wells, 2011), but underlines the importance of noting any calcification of this ligament and correlating it with the patient's medical history.

The *triticeous cartilage* is found at the level of C3, C4, centrally within the lateral thyrohyoid ligament, and may act as a reinforcement for this ligament (Wells, 2011). When calcified this cartilage may resemble carotid artery calcifications due to its location, especially on a conventional panoramic radiograph. It has been reported that calcified triticeous cartilages show a smooth well-defined ovoid image, compared to the linear image with irregular margins of calcifications in the carotid arteries (Ahmad et al., 2005; Wells, 2011).

The *thyroid cartilage* is the superior cartilage of the larynx and is found immediately below the hyoid bone, at the level of the fourth and fifth cervical vertebrae (Wells, 2011; Sabnis and Mane., 2020). Calcification of the thyroid cartilage is regarded as an aging process i.e. a progressive process, that begins along the posterior inferior margin and inferior horn, generally around the age of 25 (Wells, 2011; Sabnis and Mane 2020). Superior cornu calcification occurs in older age groups and on imaging may be encountered in the same area as the triticeous cartilage or carotid artery calcifications (Wells, 2011). Accurate localization using three-dimensional imaging modalities will aid in differentiation.

Calcified *lymph nodes* may be found incidentally on radiographic images, as singular or multiple well-defined lobulated or "cauliflower-like" radiopacities (Wells, 2011; Uzun *et al.*, 2017). These are regularly found in panoramic radiographs at the angle of the mandible, below the inferior border of the mandible as calcified submandibular lymph nodes, but may also present as calcified cervical, submental or preauricular lymph nodes. When comparing calcified lymph nodes to sialoliths, from which they need to be differentiated, lymph nodes occur commonly in multiples while a sialolith is usually solitary (Wells, 2011). Calcified lymph nodes have been shown to occur in people with tuberculosis, chronic inflammatory disease or even neoplasia and therefore may warrant referral for further diagnostic tests (Missias *et al.*, 2018).

Eustachian tube calcification is a rare incidental finding where accumulation of granules of calcium carbonate and calcium phosphate occur within the intracellular substance of the cartilage of the eustachian tube (Syed *et al.*, 2017). These granules may merge and could lead to decreased nutrient supply to the fibrocartilaginous part (torus tubarius) of the eustachian tube that is attached to the base of the skull (Syed *et al.*, 2017), and runs between the petrous portion of the temporal bone and the greater wing of the sphenoid. In a 2017 study, researchers reported that 70% of incidentally found calcification of the torus tubarius occurred unilaterally while 30% occurred bilaterally, with an overall prevalence of 0.6% (Buch *et al.*, 2017). The authors stated that in their study there was no correlation between calcification of the torus tubarius and common medical conditions and re-iterated that the clinical significance of this condition is still uncertain (Buch *et al.*, 2017). A differential diagnosis of a calcified mass in the middle ear is a tympanolith, a calcified mass that is found within the tympanic cavity and can form from extrinsic or intrinsic cause (Nagalingeswaran *et al.*, 2018). However, it has also been stated that tympanoliths are usually associated with symptoms and cannot therefore be assigned as an incidental finding (Nagalingeswaran *et al.*, 2018).

Osteoma cutis is a benign and rare skin disorder characterized by the formation of bone within the dermis or subcutaneous tissue (Gunduz *et al.*, 2018). It can be asymptomatic and found incidentally on radiographic examination (Duarte *et al.*, 2018). It is classified into primary and secondary types, with an unknown pathogenesis. It presents as multiple small well-defined radiopacities within the superficial soft tissue, a common area being the chin. It is reported to occur more commonly in women than men (Duarte *et al.*, 2018; Gunduz *et al.*, 2018).

Enamel pearls are deposits of enamel generally noted at the bifurcation area of multi-rooted teeth (Rocha *et al.*, 2018) and are considered an incidental finding on conventional panoramic or periapical radiographs. Scant literature exists on the characteristics of enamel pearls as seen on CBCT scans.

Pulp stones are calcified masses that can be detected within the pulp of healthy or diseased pulp chambers and canals (Jannati *et al.*, 2019). In a 2019 meta-analysis on pulp stones the prevalence of pulp stones was calculated to be 36.5%, with a higher rate of occurrence in women than men (Jannati *et al.*, 2019), occurring more often in molars than premolars and more often in maxillary teeth than mandibular teeth (Jannati *et al.*, 2019).The same study noted that the possible association between renal stones and pulp stones continues to be controversial in the literature, and that to date there is insufficient evidence of any correlation between the presence of pulp stones and other systemic diseases, in particular cardiovascular disease (Jannati *et al.*, 2019). Further studies exploring these relationships may be beneficial.

Osteophytes of the TMJ could be considered a calcification and are defined as bony outgrowths covered by fibrocartilage. They are characteristic features of temporomandibular joint degenerative disease (Sadaksharam and Khobre., 2016). In one study investigating the bony changes that can occur in the TMJ, osteophyte formation was the second most common change noted (Shahidi *et al.*, 2018).

2.3.2.2 Intracranial Calcifications

Intracranial calcifications are those found anywhere within the vasculature or parenchyma of the brain (Saade *et al.*, 2019). The association between pathological conditions and radiological phenotyping of calcifications has been documented, e.g. vascular calcifications and their role in stroke, and the presence of basal ganglia calcifications in hypoparathyroidism (Saade *et al.*, 2019). In a 2019 study that retrospectively examined 573 CBCT scans, the prevalence of intracranial calcifications was found to be 33.1% (Bayrak *et al.*, 2019). Intracranial calcifications occur due to the deposition of calcium or iron within the soft tissue of the cranium, and may be physiologic or pathologic (Tepe *et al.*, 2022). Intracranial calcifications could possibly result in clinical issues caused by compression of neighbouring structures. Additionally, they could cause complications during surgery. It therefore becomes important to have some knowledge of the structures that could undergo calcification within the cranium.

One of the most notable of these calcifications would be *carotid artery calcifications*. These may be found extracranially or intracranially but for the purpose of this literature review it will be discussed under intracranial calcifications. Literature has reported extracranial internal carotid artery calcifications (EICAC) to occur as frequently as 60.1% and intracranial internal carotid artery calcifications (IICAC) to have a prevalence between 2.4% and 17% (Mutalik and Tadinada., 2019). In almost all the articles considered for this literature review, calcification of the carotid artery was stated to be a risk indicator of coronary artery disease or stroke (Missias *et al.*, 2018; Monsarrat *et al.*, 2019; Uys and Mavuso, 2022). Both are life-altering and possibly life-ending diseases that at the minimum warrant official documentation and disclosure to the patient. Referral to a medical specialist for further follow-up may be warranted (Wells, 2011; Missias *et al.*, 2018; Mutalik and Tadinada., 2019; Khalifa and Felemban., 2021).

A 2016 study described calcifications of the section of the carotid artery found between the carotid canal and the carotid bifurcation as extracranial (Da Silveira *et al.*, 2016). Specifically, EICAC's are found vertically between the levels of C3 to C5 vertebrae, anterior and lateral to their cervical tubercles, below and medial to the angle of the mandible, posterolateral to the pharyngeal airway space and latero-posterior to the greater cornu of the hyoid bone (Wells, 2011; Da Silveira *et al.*, 2016). Calcifications found between the cavernous portion and the petrous portion of the carotid artery were designated as IICAC's (Da Silveira *et al.*, 2016). The authors described tracing the intracranial carotid artery by following its image "within the petrous portion of the carotid canal in the temporal bone to the lacerum segment. This continued along the adjacent cavernous portion, where the artery ascends toward the posterior clinoid process by the side of the body of the sphenoid bone, and again, curving upward on the medial side of the anterior clinoid process." (Da Silveira *et al.*, 2016). Uys and Mavuso., 2022 also analysed the intracranial carotid artery along its six segments: cervical segment (C1), petrous segment (C2), lacerum segment (C3), cavernous segment (C4), clinoid segment (C5) and ophthalmic segment (C6).

Wells (2011) described carotid artery calcifications on CBCT scans as 'rice-grain', curvilinear, circular, or globular radiopacities situated within the soft tissues of the cervical neck area. IICAC's have been described as having a figure of eight oblique shape (Da Silveira *et al.*, 2016), found anywhere along the course of the intracranial portion of the carotid artery described above.

It is important to note, however, that calcifications may occur in any vascular intracranial arteries and clinicians should not limit themselves to only identifying intracranial carotid artery calcifications. A thorough knowledge of intracranial vasculature and its normal presentation on CBCT images is beneficial.

In a systematic review (2019) of incidental calcifications, *calcification of the pineal gland* was reported to be the second most commonly occurring soft tissue calcification with a frequency between 0.5% and 19.2% (Dief *et al.*, 2019). The pineal gland is an endocrine gland that is part of the epithalamus, found superior to the corpus callosum, inferior to the superior and inferior colliculi, superolateral to the choroid plexus, anterosuperior to the thalamus, anteroinferior to the cerebral aqueduct and peduncle, posterosuperior to the vein of Galen and inferior to the quadrigeminal plate (Patel *et al.*, 2020). Calcifications of the pineal gland have been named Corpora Arenacea or Acervuli and demonstrate a lamellar or globular concentric shape (Gheban *et al*., 2019). Despite the relatively common occurrence of pineal gland calcification, the clinical significance is not fully established, but has possibly showed some correlation with neuro-psychiatric changes in older people (Gheban *et al.*, 2019). Additionally, it has been suggested that if pineal gland calcifications are noted in patients younger than nine years, further investigation is warranted as they may be indicative of a neoplasm (Saade *et al.*, 2019). However, there is lack of consensus in the current literature regarding the clinical significance of pineal gland calcification in children younger than six years of age, with one study suggesting that it is no longer accepted as a pathological calcification in children (Tepe *et al.*, 2022).

Calcification of the choroid plexus (responsible for the production of cerebrospinal fluid) has been reported to be the second most commonly occurring intracranial calcification (Bayrak *et al.*, 2019; Saade *et al.*, 2019) and is noted to be a physiologic or age-related calcification. (Javed and Lui, 2019). Calcifications of the choroid plexus can occur in any of the four ventricles of the brain, however it has been reported to occur most commonly in the atria of the lateral ventricle (Bayrak *et al.*, 2019; Saade *et al.*, 2019), usually as punctate hyper-densities on CT.

The *habenular commissure* is a band of nerve fibres that connects the two habenular nuclei and is situated anterior to the pineal gland. The habenular nuclei play a role in the body's reactions to certain stimuli such as sleep and anxiety (Whitehead *et al.*, 2015; Saade *et al.*, 2019). Habenular commissure calcifications are considered to be of physiologic origin (Whitehead *et al.*, 2015; Saade *et al.*, 2019) and have been reported multiple times as the most commonly occurring intracranial calcification (Bayrak *et al.*, 2019). On CT scans the calcifications show a curvilinear pattern (Saade *et al.*, 2019) and are said to be composed of calcium and magnesium salts (Whitehead *et al.*, 2015).

Dural calcifications are generally considered to be physiologic calcifications (McKinney and McKinney., 2017; Saade *et al.*, 2019) and commonly encountered in the tentorium. They may also be observed in the falx cerebri but it is important to remember that this is a finding also associated with Gorlin-Goltz Syndrome (Nevoid Basal Cell Carcinoma Syndrome) (Al-Jarboua *et al.*, 2019) and therefore, in this instance, would not be classified as an incidental finding.

The *basal ganglia* are a group of neurological structures (nuclei) found deep within the brain. The four nuclei that constitute the basal ganglia are the Corpus Striatum, Globus Pallidus, Subthalamic Nucleus and Substantia Nigra. They are reported to be primarily involved in motor- function but ongoing studies have acknowledged their involvement in non-motor functions involving decision-making and emotions (Simonyan, 2019). It has previously been documented that calcifications present in the basal ganglia occur most commonly in the Globus Pallidus (de Brouwer *et al.*, 2019; Saade *et al.*, 2019). These are normally incidental and carry a low significance (de Brouwer *et al.*, 2019). They usually appear as multiple small punctate hyper densities on CT scans (de Brouwer *et al.*, 2019). The literature details a frequency of occurrence between 1.3% and 29.7% on CT(de Brouwer *et al.*, 2019; Saade *et al.*, 2019).

In addition, there are ligamentous structures that have been reported to have become calcified. The *petroclinoid ligament* has been described as an infolding of the dura mater between the petrosal process and posterior aspect of the dorsum sellae (Bayrak *et al.*, 2019). The literature documents conflicting views on the significance of Petroclinoid ligament calcification with some stating that it should be considered as a normal physiologic calcification, radiographic feature of systemic fluorosis or an anatomical abnormality (Bayrak *et al.*, 2019). It is reported to occur rarely and in a 2019 study had a frequency of 2.7% (Bayrak *et al.*, 2019), while a study of skull base ligament calcifications stated a frequency of 18.3% (Touska *et al.*, 2019). The significance of Petroclinoid ligament calcifications is linked to its proximity to neural structures, particularly the oculomotor nerve (Touska *et al.*, 2019) and it has been suggested that calcification of this ligament could compress this nerve.

The encephali of the dura mater are attached to the skull via the anterior, medial and posterior clinoid processes of the sphenoid bone. The anterior and posterior clinoid processes are attached to each other via the *interclinoid Ligament (ICL)*, while the anterior and middle clinoid processes are connected via the *Carotico-clinoid Ligament* (CCL) (Bayrak *et al.*, 2019). Occasionally these ligaments become calcified and may be observed on CBCT scans (Bayrak *et al.*, 2019), within the middle cranial fossa. The incidence of ICL on CT scans was reported to be between 12% and 35.7%, and that of CCL calcification was between 4% and 11.8% (Touska *et al.*, 2019). These findings correlate to the 2019 study of intracranial calcifications on CBCT scans which stated a frequency of 4.88% for ICL calcification and 3.83% for CCL calcification (Bayrak *et al.*, 2019). Calcifications of these ligaments may have clinical significance during surgery due to their proximity to the cavernous sinus and paraclinoid internal carotid artery (Touska *et al.*, 2019).

Notably, it has been reported that some ICs have been found to be *metastatic disease* processes and should therefore also be a consideration for the clinician (Dief *et al.*, 2019; Saade *et al.*, 2019). Adequate referral protocols should thus be activated to ensure proper and timely management. Finally, it should be mentioned that calcified *phleboliths or lymph nodes* could also be encountered intracranially and carry the same clinical significance as those found in extracranial locations.

2.4 The Importance of Reporting on Incidental Findings

It is the prerogative of the requesting clinician to decide on the FOV required to ensure all necessary structures are present in the scan. The FOV may be small, medium or large, and it is important that the clinician adheres to the principles of ALARA (As Low As Reasonably Achievable) in order to reduce radiation exposure to the patient while achieving a scan that is diagnostically acceptable. Irrespective of the FOV chosen, there will always be structures present that are unrelated to the primary indication for the radiographic examination. As discussed above, these ICs may have little to no clinical significance (e.g., pulp stones) or may be suspicious enough to warrant further tests (in the obvious case of carotid artery calcifications). All the articles reviewed have acknowledged the importance of having all

CBCT scan volumes comprehensively examined, be this by the requesting clinician or qualified Maxillofacial Radiologists. It has been noted that disclosure of certain findings can be anxiety provoking to patients (Wells, 2011; Dief *et al.*, 2019; Monsarrat *et al*., 2019) and so it has been suggested that clinicians familiarize themselves with the most commonly occurring IFs and ICs and their significance in order to make an informed decision on how to relay their findings and possible implications to their patients.

Ultimately, it has been recommended that incidental findings should be anticipated and planned for (Wells, 2011.,MacDonald *et al*., 2012; Dief *et al*., 2019). This should be communicated to the patient in an easy-to-understand manner that is accepted by the patient (Friedler and Bertolami, 2014). This respects the principle of patient autonomy which is central to the patient's right to provide informed consent and make an informed decision regarding their own care (Gallin and Ognibene, 2012).

2.5 Shortcomings in the Literature

To the best of the author's knowledge, to date, there have been no systematic reviews done on studies that have focused primarily on incidental findings of calcifications of the head and neck on CBCT scans. In articles selected for this literature review, researchers have mostly chosen to isolate their studies to either only soft tissue calcifications of the head and neck or have focused on a particular calcification and researched the attributes of that alone.

Most of the studies reviewed in a recent systematic review used scans taken for one specialty of dentistry e.g. orthodontics or implant planning (Dief *et al.*, 2019). This inherently limits these studies as the scans taken for orthodontic planning are commonly of a younger patient demographic, and those taken for implant planning have historically been commonly of an older demographic.

There seems to be a paucity in the current literature in terms of comprehensive studies of ICs of the head and neck on CBCT scans. These studies would need to address the following limitations in studies in the current literature:

- In the recent systematic review by (Dief *et al.*, 2019), only five out of the 10 studies gave a definition of incidental findings. If the reader has a different understanding of an IF to that of the researchers, this may affect the understanding of the entire study.

- Some studies included scans with small, medium, and large FOVs i.e., they did not exclude scans that only included the maxilla or mandible. This would affect the results of the study regarding overall prevalence of IFs.
- As mentioned previously, the database used in some studies only included scans taken for a single specialty and not a generalized population. This inherently skews the results as the study population included a dominant demographic group.
- Not all the studies ensured blinding of the examiners, nor did all assess intra or inter-examiner reliability. There was also a wide variability in the number of examiners chosen; these ranged from 1 to 13 examiners (Dief *et al.*, 2019).
- Not all the studies explicitly explained how they determined their sample sizes, or the statistical methods used.

In addition, only one study was found that investigated the influence that digital brightness and contrast enhancement have on the detection of calcifications (Moreira-Souza *et al.*, 2019). This study reported that calcifications were noted in 44.4% of non-enhanced digital panoramic radiographs and that this percentage increased to 70.8% on enhanced digital images. They stated a moderate agreement of hypothesized calcifications between non-enhanced and enhanced images and acknowledged that although they did not confirm the presence of soft tissue calcifications with the gold standard ultrasound, modification of the contrast and brightness allowed for better visualization of calcifications.

As such, there appears to be scope for studies of ICs of the head and neck on CBCT scans. These need to be comprehensive and should aim at addressing not only the limitations explained above but also explore each calcification mentioned previously, in detail such as specific location, morphology, density, effect on adjacent structures, incidence and any age or sex correlations.

2.6 Conclusion

CBCT imaging is an exciting, fairly new addition to the radiologic armamentarium of dental professionals. It is being used extensively by both general dentists and dental specialists for a range of reasons, pre- and post-treatment. These scan volumes offer a wealth of information for the discerning clinician and need to be examined in its entirety. Structures will be present on the scan volume that are unrelated to the primary indication of exposure, known as incidental findings. The clinical significance of these findings ranges from low to high, and so it becomes apparent that it would be beneficial for clinicians to have an understanding of the frequency and imaging characteristics of IFs.

Of particular interest is the presence of ICs of the head and neck as seen on CBCT scans. This topic has been researched in recent years, especially the incidence of incidental calcification of the carotid arteries, its significance, and the clinical relevance of appropriate referral protocols. However, there seems to be lack of comprehensive studies of all possible calcifications that could be encountered on full FOV CBCT scans (soft tissue, hard tissue, extracranial and intracranial) and ongoing research is required to provide clinicians with a comprehensive bank of literature in order to provide appropriate, holistic, and up-to-date care for their patients.

CHAPTER 3: AIM AND OBJECTIVES

3.1 Aim

To evaluate incidental head and neck calcifications on CBCT records of a Western Cape Province population.

3.2 Objectives

To determine the prevalence of ICs in head and neck CBCT records.

To describe calcifications with regard to location (intracranial vs extra-cranial).

To explore the presentations of calcifications related to specific location, number, and side.

To determine the prevalence of potentially life-altering calcifications that require follow-up or referral to a medical physician.

To document the patient demographics in terms of age and sex of those presenting with head and neck calcifications.

To identify any correlation between patient demographics and presence of calcifications.

CHAPTER 4: MATERIALS AND METHODS

This chapter explains the methodology utilized in this research project. The programme used for CBCT analysis was the OnDemand3D™ Dental software programme.

4.1 Research design

This was a cross-sectional record-based quantitative study.

4.2 Study Population

The target population was manually selected from the record-base of all patients referred for CBCT scans at the Department of Diagnostics and Radiology, Tygerberg Oral Health Centre, Faculty of Dentistry, University of the Western Cape, Cape Town, South Africa.

4.3 Study Size Selection

The entire study population was estimated at 2500; this included all scans taken from the time the CBCT modality was installed in the Radiology Department. We noted that the number of scans taken increased per year as the modality became more popular and acceptable. Over a period of 12-months the number of scans taken was 1247. The primary researcher then filtered these scans according to the inclusion and exclusion criteria set out below, retrospectively, until the sample size of 350 scans was reached.

4.3.1 Inclusion Criteria

Full FOV CBCT scans that included the cranial base to below the inferior mandible were considered.

4.3.2 Exclusion Criteria

Scans of poor diagnostic quality

Scans with moderate motion, technique or metallic artifacts that obscured findings.

Scans for patients where the image request documented was specific for examining a possible calcification.

A total of 1247 full FOV CBCT scans were assessed, until the study size of 350 eligible scans was reached. In order to ensure no repeat inclusions of scans, only a single time point volume was included per patient. Since this was a record-based study, no new CBCT volumes for the intent of this study were acquired and no patient was exposed to radiation for the purpose of reaching the appropriate study size. (Figure 1:)

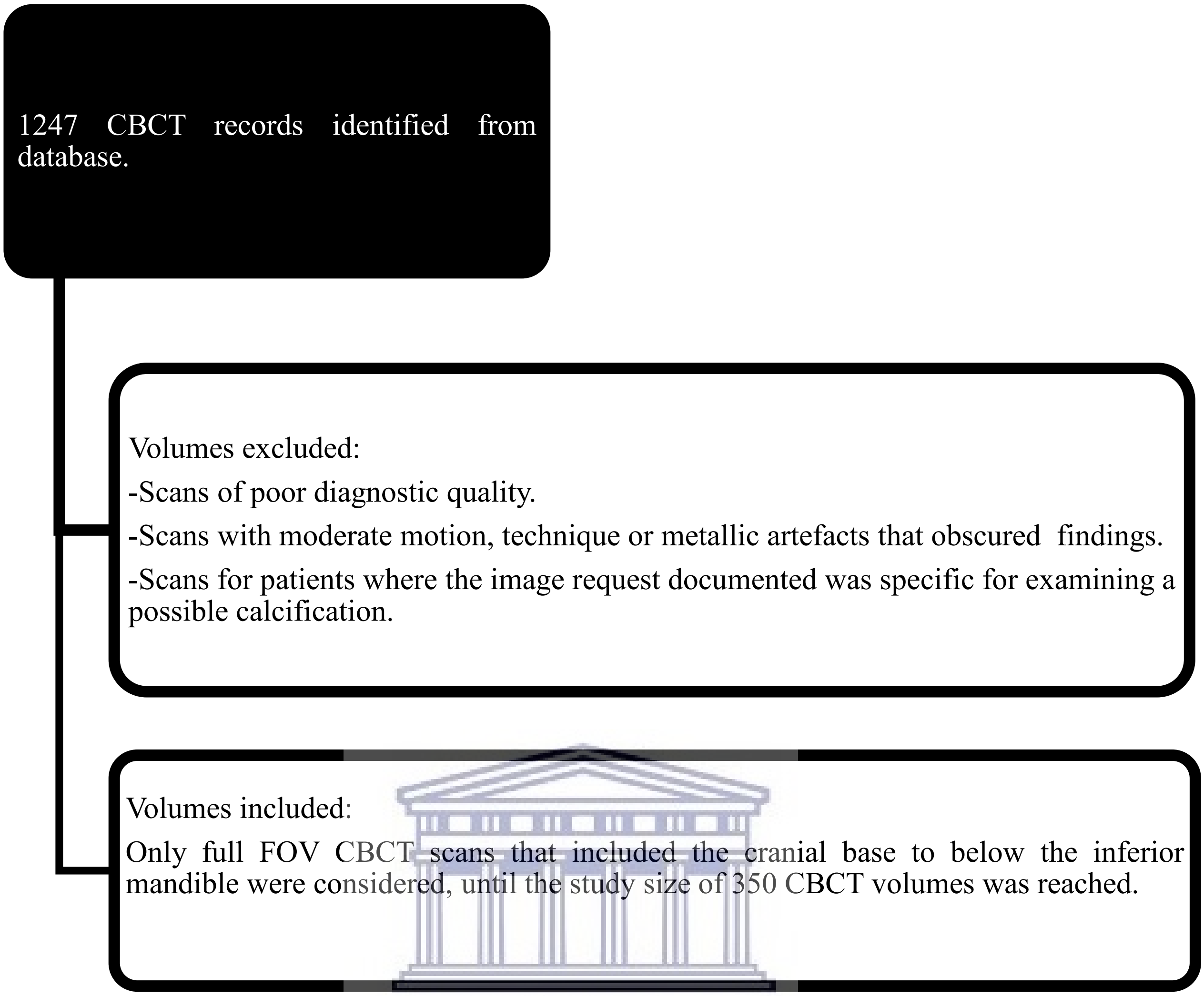

Figure 1: Flow diagram depicting selection sequence of study population.

4.4 Equipment

CBCT volumes were acquired using a NewTom® VGi with NNT® software (version 8). All volumes were taken with the patient in a seated position, either by qualified radiographers or postgraduate students in the field of Oral and Maxillofacial Radiology, in compliance with the manufacturer's instructions. The machine operated at 110 kV, 3-8 mAs with acquisition times between 15 and 21 seconds. Voxel size of 0.30 mm^3 was used to assess reconstructed data.

The CBCT scan evaluation was performed using a Barco® Eonis© 22-inch MDRC-2122 monitor with resolution 1920 x 1080 and a Dell® Inspiron 3580 8^{th} Generation laptop running on Windows® 10 Home, © Microsoft 2019 Corporation. Laptop specifications comprised of an Intel Core i7-8565U CPU @ 1.80 GHhz, x64-based processor, 16 GB RAM, 256GB Ultra-

Fast SSD, 64-bit operating system, 1 TB hard drive and a 15.6” FHD 1920 x 1080 anti-glare display monitor.

The software used to evaluate the CBCT acquisitions was the OnDemand3D™ Dental software programme.

4.6 Methodology

CBCT volumes were exported in the DICOM format and all identifiers except sex and age were removed using DicomCleaner™ PixelMed Publishing™. Scans were then randomly allocated numbers ranging from 1 to 350.

4.6.1 Inter- and intra-examiner reliability

In order to ensure calibration, two examiners (the primary researcher and a dentist with a MSc degree in Oral and Maxillofacial Radiology) revised head and neck anatomy and calcifications together, with no time limit set for the revision session. A spreadsheet containing a list of all possible ICs in the head and neck was created in order to guide the examiners and ensure no calcifications went undetected.

With the final sample size of 350 (N), it was calculated that 10 (n) scans were required for the inter-examiner reliability study. These scans were randomly selected and were included only if they met the inclusion criteria of this study. These 10 scans were individually assessed by each examiner until an appropriate agreement percentage for inter-examiner reliability was reached.

For the intra-examiner reliability study, 10% of the sample size (35 scans) was assessed by the primary researcher, 2 weeks apart. Every 10th scan was included until the sample size of 35 was met.

Gwet’s (Agreement Coefficient) AC was used to test inter- and intra-examiner validity

$$AC = \frac{Po - Pe(\gamma)}{1 - Pe(\gamma)},$$

$$Pe(\gamma) = \text{chance agreement} = 2\ (\frac{(\frac{m1+n1}{N})=}{2})(1 - (\frac{(\frac{m1+n1}{N})=}{2})$$

Gwet’s AC overcomes the well-known paradoxes in Cohen’s Kappa and is not affected by bias (Wongpakaran et al., 2013).

4.6.2 Image assessment

Volumes were assessed by the primary researcher for all ICs in the following manner:

- A minimum slice thickness of 1.0mm was required.
- The volumes needed to be assessed in a minimum of two orthogonal planes (axial &/or sagittal &/or coronal).
- The viewing of the volumes was performed under ambient light.
- Additional forms of image manipulation (magnification, contrast, brightness, or different filters) was allowed.

If any uncertainties were encountered, a second opinion was sought from a chief dentist with a MSc in Oral and Maxillofacial Radiology.

Each scan was assessed for the presence of any of the following incidental calcifications:

- Lingual tonsillolith
- Palatine tonsillolith
- Sialolith
- Antrolith
- Calcified stylohyoid chain
- Calcified triticeous cartilage
- Calcified superior cornu of thyroid cartilage
- Epiglottis calcification
- Lymph node calcification
- Calcinosis cutis
- Pulp stones
- Osteophytes of the TMJ
- Common carotid artery calcification
- External carotid artery calcification
- Extracranial internal carotid artery calcification
- Intracranial internal carotid artery calcification
- Pineal gland calcification
- Choroid plexus calcification
- Habenular calcification

- Dural calcification
- Basal ganglia calcification
- Petroclinoid ligament calcification
- Interclinoid ligament calcification
- Carotico-clinoid ligament calcificati9on
- Phlebolith
- Vertebral canal calcification
- Vertebral ligament calcification
- Unknown/pathological calcification

Each finding was further analysed with regard to position (intra- or extra-cranial), sidedness (central, bilateral, unilateral left or unilateral right), number (single or multiple) and treatment options (no referral or monitoring required, monitoring required, or referral required).

4.6.3 Data collection and management

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of the Western Cape. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing

1) an intuitive interface for validated data capture.

2) audit trails for tracking data manipulation and export procedures.

3) automated export procedures for seamless data downloads to common statistical packages; and

4) procedures for data integration and interoperability with external sources (Harris *et al.*, 2009, 2019). (Appendices A-C)

The data was stored in a password-protected laptop (Dell® Inspiron 3580 8th Generation laptop running on Windows® 10 Home, © Microsoft 2019 Corporation. Laptop specifications comprised of an Intel Core i7-8565U CPU @ 1.80 GHhz, x64-based processor, 16 GB RAM, 256GB Ultra-Fast SSD, 64-bit operating system, 1 TB hard drive and a 15.6" FHD 1920 x 1080 anti-glare display monitor), and periodically backed-up on a portable external hard drive, WD My Passport 2 TB.

Research reporting adhered to the STROBE checklist (Appendix G).

4.7 Statistical analysis

Data analysis was discussed with a statistician and calculations were performed to determine:

- The overall prevalence of ICs of the study sample.
- The rate of ICs per scan.
- The prevalence of each individual calcification found.
- The most commonly occurring calcification.
- The number of intracranial vs extracranial calcifications.
- The number of central vs bilateral vs unilateral left vs unilateral right calcifications.
- The number of single vs multiple calcifications.
- The number of calcifications requiring no follow-up vs requiring monitoring vs requiring referral.
- Any significant correlations between sex or age and the presence of ICs.

Continuous data were tested for normality using a Shapiro-Wilk test. Continuous data were then presented as mean and standard deviation. For categorical data, frequencies and percentages were used. To determine associations between categorical data, a chi-squared test was used. Logistic regression was further performed to detect the strength of the above-mentioned associations. All tests were conducted using StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC. All tests were deemed statistically significant at $p < 0.05$.

4.8 Ethical considerations

This mini-thesis research proposal was presented to the Faculty of Dentistry of the University of the Western Cape Research Committee and was approved by the Biomedical Research Ethics Committee of the University of the Western Cape (approval number: BM21/03/06) (Appendix D).

Permission to access the records required for this study was requested via a letter to the Dean of the Faculty of Dentistry (Appendix E:) and was granted.

This was a record-based study and no CBCT acquisitions were performed for the purpose of the research. All acquisitions were performed by qualified radiographers or postgraduate students in the field of Oral and Maxillofacial Radiology, in compliance with the manufacturer's instructions.

Patient confidentiality was ensured by removing all identifiers (except for sex and age) using a specialty software programme and randomly allocating record numbers (between 1 and 350) to the downloaded volumes. The data will be kept on a password-protected device for a period of five years and deleted thereafter. The results of the study will be used for research and educational purposes only. No conflict of interest is reported.

4.9 Budget

This research project was self-funded.

CHAPTER 5: RESULTS

5.1 Reliability studies

5.1.1 Inter-examiner reliability

To minimize bias and ensure calibration of the primary researcher, inter-examiner reliability was tested. The primary researcher and a qualified Oral Maxillofacial Radiologist (a senior in the department) separately and individually assessed 10 CBCT volumes for any incidental findings. Gwet's (Agreement Coefficient) AC was used to test inter-examiner validity (Table 4).

$$\text{AC} = \frac{Po - Pe(\gamma)}{1 - Pe(\gamma)},$$

$$Pe(\gamma) = \text{chance agreement} = 2\left(\frac{(\frac{m1+n1}{N})=}{2}\right)\left(1 - \left(\frac{(\frac{m1+n1}{N})=}{2}\right)\right)$$

Table 4: Gwet's AC and Confidence Interval for Inter-examiner Reliability Tests

Variable	Gwet's AC	95% Confidence Interval
Cranial Position	1.00	1.00-1.00
First Differential	0.88	0.62-1.00
Second Differential	0.83	0.41-1.00
Third Differential	1.00	1.00-1.00
Fourth Differential	1.00	1.00-1.00
Treatment	0.80	0.35-1.00
Number	0.87	0.54-1.00

All confidence intervals were clipped at the upper limit and the Gwet's AC for all variables ranged between 0.8 and 1 which indicated excellent validity.

5.1.2 Intra-examiner reliability

To ensure the reliability of observations, intra-examiner reliability tests were conducted. The primary researcher selected every 10^{th} scan until 10% of the study population was covered (i.e., 35 scans). These 35 volumes were assessed in their entirety over 2 different time intervals (2-weeks apart). Gwet's (Agreement Coefficient) AC was used to test intra-examiner reliability. (Table 5).

Table 5: Gwet's AC and Confidence Interval for Intra-examiner Reliability Tests

Variable	Gwet's AC	95% Confidence Interval
Side	1.00	0.37-1.00
First Differential	0.96	0.89-1.00
Second Differential	1.00	0.89-1.00
Third Differential	1.00	0.83-1.00
Fourth Differential	1.00	1.00-1.00
Treatment	1.00	1.-1.00
Number	0.95	0.83-1.00

All confidence intervals were clipped at the upper limit and the Gwet's AC for all variables ranged between 0.95 and 1 which indicated excellent reliability.

5.2 Observations

Continuous data were tested for normality using a Shapiro-Wilk test. Continuous data were then presented as mean and standard deviation. For categorical data, frequencies and percentages were used. To determine associations between categorical data, a chi-squared test was used. Logistic regression was further performed to detect the strength of the above-mentioned associations. All tests were conducted using StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC. All tests were deemed statistically significant at $p< 0.05$.

5.2.1 Demographic data

Of the study cohort of 350 (N), n =177 were male (50.58%) and n =173 were female (49.42%). The mean age of patients was 41.53 ± 17.08, with the eldest being 83 years and the youngest being 5 years. The median age was 34 (Table 5). Table 6 outlines the age groups of the study sample. Of the 350 cases, the largest contribution 23.14% (n=81) belonged to the 21-30 age group, second largest belonged to the 31-40 age group (20.57%, n=72), third belonged to 11-20 age group (17.14%, n=60), fourth belonged to the 41-50 age group (13.71%, n=48), fifth belonged to the 51-60 age group (10.29%, n=36), sixth belonged to the 61-70 age group (8.56%, n=30), seventh belonged to the 71-80 age group (3.71%, n=13), eight belonged to the 0-10 age group (2.8%, n=9) and smallest contribution belonged to the 81-90 age group (0.29%, n=1) (Tables 6-7).

Table 6: Study Population Demographics

Sex Ratio (Male: Female)	1 : 0.98
Maximum Age	83
Minimum Age	5
Mean Age	41.53
Median Age	34

*Age in years

Table 7: Study population demographics continued

Age group	No. of Records	Frequency
0-10	9	2.8%
11-20	60	17.14%
21-30	81	23.14%
31-40	72	20.57%
41-50	48	13.71%
51-60	36	10.29%
61-70	30	8.56%
71-80	13	3.71%
81-90	1	0.29%

Logistic Regression

Number of observations = 350
LR chi2 (1) = 84.66
Prob > chi2 = 0.0000
Pseudo R2 = 0.1936

Log likelihood = -176.31351

prev	Odds ratio	Std. err.	Z	P>|z|	{95% conf.	interval}
age	1.081149	.0112333	7.51	0.000	1.059355	1.103392
cons	.1775583	.0576498	-5.32	0.000	.0939663	.3355134

Note: _cons estimates baseline odds

Figure 2: Logistic analysis for age

For a one-unit increase in age, the odds of finding an incidental calcification was 1.08 (95% C.I.: 1.06 to 1.10) (p< 0.001). Prevalence of IFs increases with age (statistically significant)

Logistic Regression

Log likelihood = 218.64349

Number of obs = 350
LR chi2 (1) = 0.00
Prob > chi2 = 0.9754
Pseudo R2 = 0.0000

prev	Odds radio	Std. err.	Z	P>|z|	(95% conf.	interval
sex male	1.007113	.2313686	0.03	0.975	.641989	1.579896
_cons	2.145455	.3502838	4.68	0.000	1.557921	2.954562

Note: _cons estimates baseline odds.

Figure 3: Logistic analysis for sex

The odds of having a calcification if you are male was the same as the odds of having a calcification if you are female, OR=1.00 (95% C.I.: 0.54 to 1.58) (p=0.975).

There was no association between sexes .

5.2.2 Prevalence data

A total of 239 patients out of 350 had ICs (68%). The total number of ICs was 523. This translates to an average of 1.49 incidental calcification per patient. The total number of single calcifications was 163 (31.17%) and multiple calcifications were found to occur 360 times (68.83%). Of the 523 incidental calcifications, 130 were found intracranially (24.86%) and 393 were found extracranially (75.14%). Forty calcifications were located centrally (7.65%), 324 were found bilaterally (61.95%), 80 were found unilaterally on the right (15.30%), and 79 were found unilaterally on the left (15.11%). There were 427 ICs that required no follow-up (81.64%), 18 that required monitoring (3.44%) and 78 that required referral to a medical physician for further follow-up (14.91%). (Table 7).

Table 8: Prevalence Data

	Number	Percentage (%)
Patients with incidental calcifications	239	68
Singular calcifications	163	31.17
Multiple calcifications	360	68.83
Intracranial calcifications	130	24.86
Extracranial calcifications	393	75.14
Central calcifications	40	7.65
Bilateral calcifications	324	61.95

Unilateral right calcifications	80	15.30
Unilateral left calcifications	79	15.11
Calcifications requiring no follow-up	427	81.64
Calcifications requiring monitoring	18	3.44
Calcifications requiring referral	78	14.91

Table 8 continued

Total number of incidental calcifications	523
Average ICs per scan	1.49

Table 9: Ratios

Single: multiple	1: 2.21
Intracranial: extracranial	1: 3.02
Central: bilateral: unilateral left: unilateral right	1: 8.1: 1.98: 2.0
No follow-up: monitoring: referral	1: 0.04: 0.18

Table 10 and Figure 4 (graph) present the percentage (%) and number (n) of each incidental calcification encountered. The most common IC was CSTC (17.02%, n=89), followed by palatine tonsilloliths (11.01%, n=58), petroclinoid ligament calcification (9.75%, n=51), CSC (7.84%, n=41) and calcinosis cutis (7.46%, n=39). There was an equal number of pulp stones and IICAC (6.88%, n=36), followed by CTC (6.31%, n=33), osteophytes of the TMJ (574%, n=30), EICAC (4.6%, n=24) and PGC (3.44%, n=18). EICAC and IICAC were found in 14 (n) cases (2.7%), followed by 11(n) lingual tonsilloliths (2.1%). The next most common IC was ILC (1.91%, n=10), followed by calcified lymph nodes (1.72%, n=9). There were equal numbers of sialoliths and CCAC (0.76%, n=4). ECAC, VLC & other/muscle/pathology occurred an equal number of times (038%, n=2). Finally, there were single cases (019%, n=1) of the following: antrolith, epiglottic calcification, CPC, HCC and VAC.

Table 10: Prevalence of Each Incidental Calcification

Incidental Calcification	Number	Percentage (%)
Lingual tonsillolith	11	2.1
Palatine tonsillolith	58	11.01
Sialolith	4	0.76
Antrolith	1	0.19
Calcified stylohyoid chain (CSC)	41	7.84
Calcified Triticeous cartilage (CTC)	33	6.31
Calcified superior horn of thyroid cartilage (CSTC)	89	17.02
Epiglottis calcification	1	0.19
Calcified lymph nodes	9	1.72
Calcinosis cutis	39	7.46
Pulp stones	36	6.88
Osteophytes of the TMJ	30	5.74
Common carotid artery calcification (CCAC)	4	0.76
Extracranial internal carotid artery calcification (EICAC)	24	4.6
Intracranial carotid artery calcification (IICAC)	36	6.8
EICAC & IICAC	14	2.7
External carotid artery calcification (ECAC)	2	0.38
Pineal gland calcification (PGC)	18	3.44
Choroid plexus calcification (CPC)	1	0.19
Habenular commissure calcification (HCC)	1	0.19
Petroclinoid ligament calcification (PLC)	51	9.75
Interclinoid ligament calcification (ILC)	10	1.91
Vertebral ligament calcification (VLC)	2	0.38
Vertebral artery calcification (VAC)	1	0.19
Other (muscle/pathology)	2	0.38

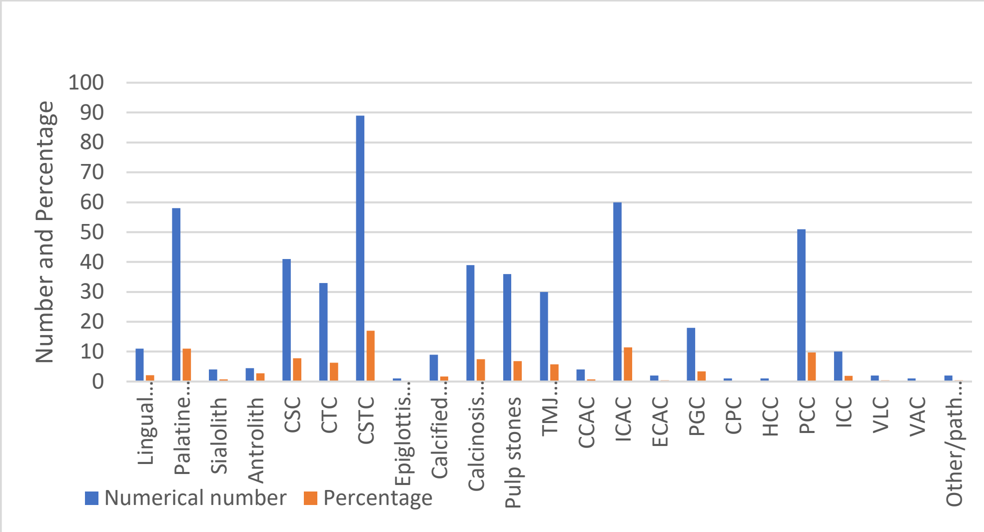

Figure 4: Number and Percentage of each Incidental Calcification

CHAPTER 6: DISCUSSION

The study aimed to investigate ICs of the head and neck on CBCT volumes of a South African population over a 12-month period. An attempt is made to discuss each calcification under the anatomical area of extracranial or intracranial, followed by the clinical significance of the calcifications detected. When detected, the clinician should aim to diagnose the calcification as either pathological or physiological in order to determine the appropriate treatment protocol (MacDonald *et al.*, 2012; Monsarrat *et al.*, 2019)

The study found ICs occur at a rate of 1.49 per CBCT data set. ICs occurred in 68% of the study sample, a figure that corresponds with the current literature (Wells, 2011; Edwards *et al.*, 2014; Missias *et al.*, 2018; Dief *et al.*, 2019; Yalcin and Yalcin., 2020; Bayramov *et al.,* 2022). The above-mentioned articles assessed CBCT volumes with medium to large FOVs and the systematic reviews assessed studies conducted on scans taken over 12-32 months. The detection of ICs has increased following the introduction of the CBCT modality, as the multiplanar, high -resolution functionality allows for superior localisation of structures that may previously have been missed due to superimposition in conventional 2D images (Edwards *et al.*, 2014; Dief *et al.*, 2019). The relatively high detection of ICs in the current study is therefore unsurprising.

Calcifications were found more commonly extracranially than intracranially with the majority occurring bilaterally. This reinforces the view that CBCT volumes need to be assessed systematically, in their entirety (Wells, 2011; Dief *et al.*, 2019; Monsarrat *et al.*, 2019).

Rater agreement is important in clinical research as scientific enquiries need to be based on solid evidence (Gwet, 2014). A Gwet's AC agreement greater than 0.8 and less than or equal to 1 indicates very good agreement for Gwet's AC. The current study therefore met the standard for good to very good inter-rater and intra-rater reliability. A good agreement provides confidence for the diagnoses made through research studies (Wongpakaran *et al.*, 2013).

The results of the current study show that the odds of finding an incidental calcification increases with age. This supports historical literature on physiological and pathological calcifications (discussed under Calcifications), which have been proven to have a higher prevalence in older age groups (Dief *et al.*, 2019; Monsarrat *et al.*, 2019; Uys and Mavuso., 2022). Additionally, the study showed that the odds of having a calcification was the same, regardless of sex. This study was unique in that it assessed for an association between sexes across all noted calcifications; previous studies explored associations between specific calcifications and sex (Uys and Mavuso 2022).

The literature suggests that the majority of incidental findings are non-threatening (Dief *et al.*, 2019). The current study showed similar results as 81.64% of the ICs did not require any follow-up. However, the percentage of findings requiring referral was 14.91%, a figure that is significant and reinforces the need to have CBCT volumes assessed by knowledgeable clinicians who understand the clinical implications of certain calcifications.

There have been relatively few studies that include assessment of full (or large) FOV volumes taken for any clinical indication. Studies have either focused on smaller FOVs (that only include the mandible or only include the maxilla, for example), taken with a specific indication in mind (e.g., pre-implant planning, orthodontic treatment planning etc) (Dief *et al.*, 2019). This study therefore aimed to assess all full FOV CBCT volumes, not limited to a certain indication, and only excluded those based on the exclusion criteria set out previously (Dief *et al.*, 2019; Khalifa and Felemban., 2021).

6.1 Demographic data

One objective of this study was to investigate any correlations between sex and age and the presence of incidental calcifications. The ratio of males to females in this study was 1: 0.98 and it was found that no statistically significant difference exists for the presence of ICs between the sexes. This is in accordance with various other studies that state sex does not play a role in the presence of ICs (Wells, 2011; Monsarrat et al., 2019; Yalcin and Yalcin., 2020; Uys and Mavuso., 2022).

High blood pressure, increased cholesterol, and various other systemic factors (e.g., diabetes mellitus, renal disease) have been shown to contribute to the formation of atherosclerotic plaques, (discussed later) (MacDonald *et al.*, 2012).

Males in early adulthood have been shown to have higher BP (blood pressure) than females of the same age, with this trend reversing in middle to old age (i.e., females have higher blood pressure in middle to old age), across all ethnic groups (Wang *et al.*, 2022) ; in essence there is a balancing of the scales. A recent systematic review and meta-analysis on the prevalence of Type 2 Diabetes in South Africa highlighted the heterogeneity of Type 2 Diabetes across age and gender in South African populations (Pheiffer *et al.*, 2021). The sequelae of arteriosclerosis in diabetic patients is said to be the most common cause of morbidity in these patients (Høilund-Carlsen *et al.*, 2022). The presence of multiple calcifications (such as that seen in Mönkebergs' atherosclerosis or medial artery atherosclerosis, discussed later) therefore needs to alert the clinician to vigorously assess the patient's medical history.

The current study did not access patient information regarding current medical status and cannot therefore comment on association between the presence of incidental vascular calcifications and systemic risk factors. However, there is consensus with current and historical literature stating that there are no associations between sex and the presence of calcifications (Wells, 2011; Uys and Mavuso., 2022). Further studies investigating associations between systemic disease and ICs will be beneficial.

There was a statistically significant correlation between an increase in age and an increase in the number of incidental calcifications. This agrees with a number of previous studies that show an increase in the number of calcifications as a person ages (Wells, 2011; Monsarrat *et al.,* 2019; Yalcin and Yalcin., 2020; Uys and Mavuso., 2022). Part of this may be explained by the mechanism of calcification, in that physiological calcification is an age-related process and its prevalence will therefore be higher in the elderly. Additionally, there is abundant literature proving that pathological calcification increases with age (Wells, 2011; Monsarrat *et al*., 2019; Uys and Mavuso., 2022) and this study agrees with the literature.

6.2 Incidental findings

A definition of incidental findings was given previously.

As seen in the literature, the clinical significance of IFs differs, and as such, the practitioner may be faced with a reporting dilemma (Monsarrat *et al.*, 2019). A recent umbrella review on the prevalence of incidental imaging findings in medical imaging drew attention to the need for more precise guidelines regarding the reporting and management of incidentalomas (O'Sullivan *et al.*, 2018), and Monsarrat *et al*., (2019), agreed that policy makers need to be provided with further robust evidence on incidental findings in order to provide better guidelines to practitioners on their management.

A common theme in the reviews is the need to ensure informed consent of patients. It is suggested therefore, that practitioners advise patients, prior to having imaging, of the potential of detecting IFs. They should also be advised of the possibility that certain IFs warrant further monitoring or referral to medical clinicians (O'Sullivan *et al.*, 2018; Monsarrat *et al.*, 2019). Ultimately, the decision to have imaging rests with the patient and clinicians are required to respect this right to informed consent.

Should the practitioner detect IFs it would be useful to have a framework outlining a possible course of action, such as one presented by Monsarrat *et al*., 2019

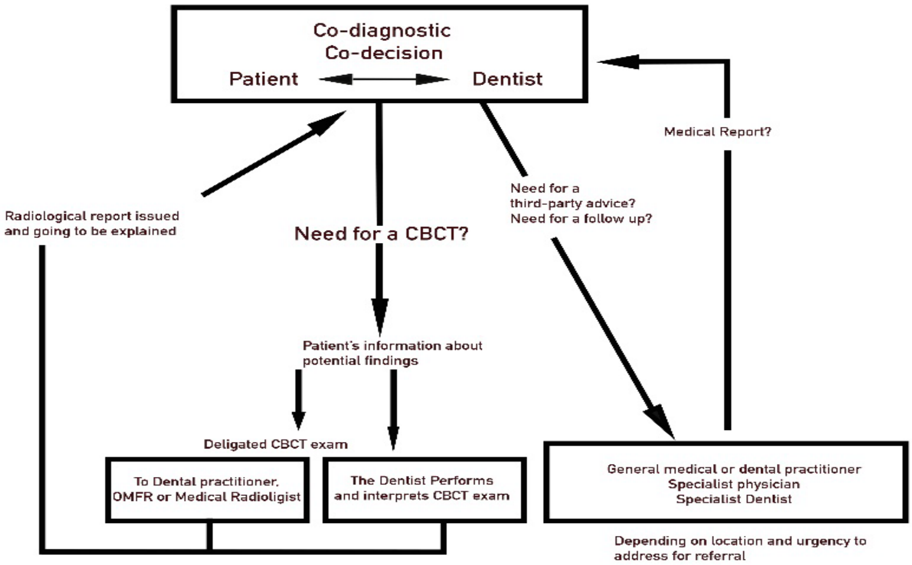

Figure 5: Framework proposed by Monsarrat *et al*., 2019 for CBCT imaging of a dental patient; adapted from Monsarrat *et al*., 2019, according to principles based on patient-care.

To the contrary, reporting of indolent (or clinically insignificant) IFs may result in excessive, unnecessary, or costly interventions, possibly to the psychological detriment of the patient. Further identification of the threshold for clinically significant incidentalomas and a more standardised approach to their treatment/reporting is needed (Khalifa and Felemban., 2021).

The purpose of research such as that compiled in this mini thesis is to add useful data to the literature that could aid policy makers in drawing up guidelines for practitioners to follow should they encounter incidentalomas. Prevalence data is useful in this regard, as well as any associations (or lack thereof) between sexes and/or age and the presence of IFs.

It must be stressed that the current study only assessed for ICs and not the overall prevalence of incidental findings and the results are therefore not generalisable for incidental findings of the head and neck on CBCT.

6.3 Calcification

Functional biominerals such as bone and teeth are formed through normal biomineralization processes. The balance between mineralization at appropriate sites (physiological mineralization) and inhibition of inappropriate mineralisation (e.g., within vascular tissues) is to be found under healthy conditions (Vidavsky *et al*., 2020).

The literature is ambiguous in some regards in distinguishing ossification from calcification, especially pertaining to their presentation on CBCT. The flow-chart below (Figure 6) is adapted from Freire *et al*., 2018, outlining a proposed approach to radiographic evaluation of a focal density on CT.

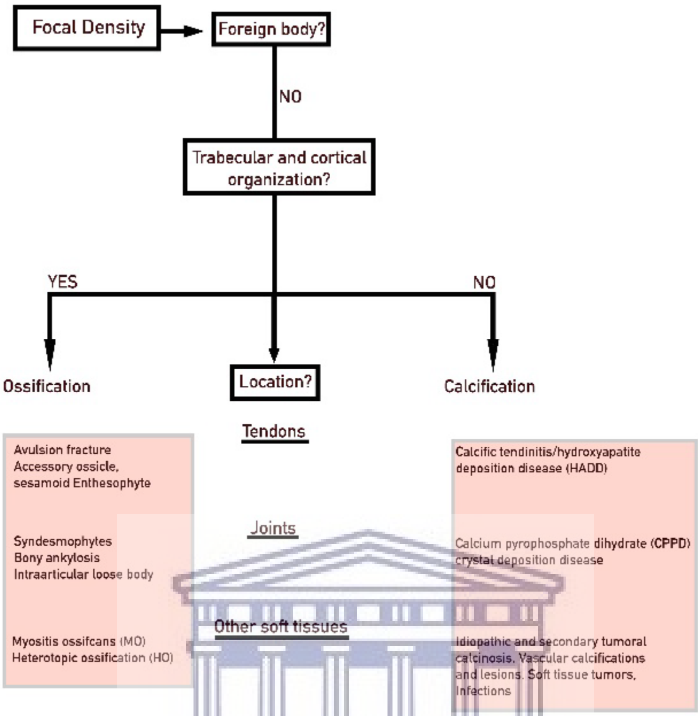

Figure 6: Flow-chart adapted from Freire *et al*., 2018 outlining an approach to radiographic evaluation of a focal density. *CPPD*, calcium pyrophosphate dihydrate, *HADD,* hydroxyapatite deposition disease

As mentioned, there are different categories of calcification that are recognized, viz., dystrophic, idiopathic, or metastatic calcification ((Freire *et al*., 2017). Calcifications occur due to numerous causative factors, have numerous presenting features, and are found in numerous locations (Freire *et al*., 2017).

The next few paragraphs will discuss methods to identify calcifications on CT or MRI, two radiographic modalities that are superior to CBCT when it comes to soft tissue windowing (Dief *et al*., 2019; Monsarrat *et al.*, 2019). With both CT and CBCT, calcifications appear as densities with attenuation coefficients lower than bone but greater than soft tissue (Freire *et al*., 2018). As will be discussed, accurate identification of calcifications versus ossifications involves assessment of the attenuation co-efficient, precise localisation of the density and assessment of the shape and internal patterns of the density.

The Hounsfield unit range for calcifications on CT is between 100 and 400 HU, trabecular bone reaches 700 HU, and cortical bone reaches 1500 HU (Freire *et al*., 2018). Assessing the HU of a density on CT poses one method in attempting to distinguish an ossification from a calcification. However, HU cannot be applied to CBCT due to various reasons and the quantitative use of grey values in CBCT volumes is not advised (Pauwels *et al*., 2015; Candemil *et al*., 2020). For this reason, grey value identification of IFs was not employed in this study and this method could not help distinguish between ossifications or calcifications.

Ossification on radiographs will generally show a distinct bony architecture, with the presence of trabecular and/or cortical patterns. Immature, less organised ossifications will be harder to distinguish. Foreign bodies or image artifacts (such as the ring artifact present on most CBCT scans (Figure 7) appear as geometric structures with generally sharp borders and are relatively easy to identify (Freire *et al*., 2018). Calcifications may appear as round, globular, linear, or rice-grain densities, presentations that aid in drawing a list of differential diagnoses.

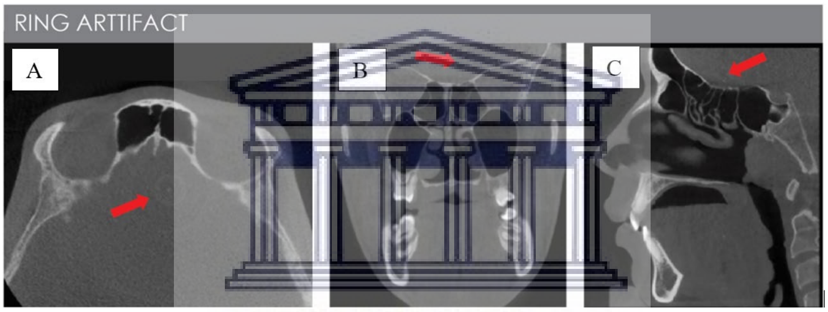

Figure 7: Ring Artifact

A) Axial B) coronal & C) sagittal views localising the ring artifact.

Localisation of the density is also an important factor when assigning it with a differential diagnosis. The table below, adapted from Freire *et al*., 2018, summarises the possible differential diagnosis for ossifications and calcifications based on their location.

Table 11: Summary of possible differential diagnoses for ossifications and calcifications based on their location

Location	**Calcification**	**Ossification**
Tendon	HADD Calcific Tendinitis CPPD deposition disease	Enthesophyte Bone avulsion fracture **Accessory bone/Sesamoid** Tendon Rupture sequela
Articular	**CPPD deposition disease** HADD (crowned dens syndrome) Gout with tophus mineralisation	Ankylosis **Heterotopic ossification**
Other soft tissues	**Secondary calcinosis** Soft tissue tumors **Vascular calcifications**	**Heterotopic ossification**

The most frequent aetiologies are in bold characters. *CPPD*, calcium pyrophosphate dihydrate*, HADD,* hydroxyapatite deposition disease

With the inherent limitations of CBCT discussed above, the differentiation of calcifications and ossifications in this way may not always be possible. This partly explains the inclusion of certain ossifications (e.g., osteophytes of the TMJ) and exclusion of certain ossifications (e.g., idiopathic osteosclerosis) in historical studies of ICs on CBCT volumes. The same applies in the present study.

In the present study, the inclusion of the calcifications was based on the findings from literature reviews on the subject (Dief et al., 2019; Khalifa and Felemban., 2021). However, most previous studies have either encompassed all incidental findings (by dividing the volumes into anatomical boundaries) or have focused on only soft tissue calcifications of the head and neck, with no clarification of ossifications vs calcifications. Certain hyper densities encountered in this study, therefore, were ambiguous on CBCT volumes and required a differential diagnosis (an example being ligament ossifications of the cervical spine vs osteophytes of the cervical spine, discussed later).

In the current study, the number of patients who presented with ICs was 239 (68% of the study population). The rate of ICs was 1.49 per scan. Previous studies have reported a prevalence of 34.75% (Wells., 2011), 33.4% (Yalcin and Yalcin., 2020), and 62.6% (Missias *et al.*, 2018). The results of the current study are higher than the first two but similar to the third. The differences in prevalence could be due to differing study sizes, patient demographics, anatomical regions evaluated, or evaluation methods used. The current study employed a minimum slice thickness of 1.00mm. Not all previous studies noted their minimum slice thickness, and this could explain the relatively smaller number of ICs encountered as the thinner the slice thickness the better the visualisation of small structures becomes.

Multiple calcifications occurred 360 times (68.83%) and singular calcifications occurred 163 times (31.17%). Calcifications may present as either singular or multiple densities within a single tissue, and if they presented as the latter they were recorded as 'multiple'. For instance, bilateral triticeous cartilage calcifications or bilateral petroclinoid ligament calcifications were noted as multiple calcifications. Monitoring of patients with multiple calcifications is recommended (Wells, 2011) as this may be an indicator for undiagnosed systemic disease.

In this study, the percentage of extracranial calcifications was higher than intracranial calcifications (75.18% vs 24.86% respectively). Considering the relative number of anatomical structures that are present extracranially on a CBCT volume compared to intracranially, this result is expected. Not many studies reported on the prevalence of intracranial vs extracranial calcifications on CBCT, but two that did reported a prevalence of 3.95% ((Yalcin and Yalcin., 2020) and 0.42% (Altındağ *et al.*, 2017) respectively, for intracranial calcifications. The large discrepancy between the current study and the two noted can be explained by the fact that the previous studies did not assess for the same intracranial calcifications, and they grouped all intracranial calcifications under one heading, unlike the current study which separated each calcification found.

The majority of calcifications encountered in this study occurred bilaterally (61.95%). 7.65% were found centrally, 15.30% were found unilaterally on the right and 15.11% were found unilaterally on the left. No previous studies assessed for the percentage of central calcifications although the pattern of certain calcifications was explored (e.g., pineal gland calcifications occur centrally within the brain, as discussed later). Additionally, the difference in unilateral sidedness for the overall prevalence of calcifications has not been reported on previously. Other studies reported on the sidedness of each calcification separately (Yalcin and Yalcin., 2020).

MRI and CT remain the superior modalities for anatomical and soft tissue assessment of intracranial calcifications (MacDonald *et al.*, 2012; Bayrak *et al.*, 2019; Saade *et al.*, 2019). The lack of soft tissue windowing on CBCT does not allow for appropriate definition of the intracranial anatomy and minute or early calcifications may therefore be easily missed. Studies assessing the prevalence of ICs on CT will therefore have a higher prevalence of ICs when compared to CBCT studies.

The science of the detection and characterization of calcifications is indeed vast and beyond the scope of this research project. The advent of CBCT allows for better localisation of structures when compared to conventional 2-D imaging, but the lack of soft tissue windowing imposes inherent limitations for complete assessment of soft tissues (Edwards *et al.*, 2014; Dief *et al.*, 2019; Monsarrat *et al.*, 2019). The results of the current study should therefore not be generalised.

6.4 Extracranial calcifications and case examples

All extracranial regions were assessed for the presence of incidental calcifications. In the present study, the most commonly occurring incidental calcification was the superior horn of the thyroid cartilage (17.02% of all calcifications). Within the naso-oropharyngeal region, the next most common calcification were palatine tonsilloliths (11.01%), followed by calcified stylohyoid chain (7.84%), calcified triticeous cartilage (6.31%), lingual tonsillolith (2.1%), and sialolith (0.76%). There was a single case of epiglottis calcification (0.19%) (Table 9).

On 2D imaging, the calcified superior horn of thyroid cartilage (CSTC) or the calcified triticeous cartilage may be easily misinterpreted as carotid artery calcifications (Wells, 2011; Dief *et al.*, 2019; Monsarrat *et al.*, 2019). The volumetric format of CBCT allows for more precise localisation. CSTC may present as linear opacifications that take the shape of the superior horn of the thyroid cartilage, with some cases demonstrating peripheral cortication (Figure 8)

Figure 8 : CSTC

A) sagittal 1.00mm slice thickness, red arrow indicates an interesting pattern of calcification of the superior horn thyroid cartilage that has taken the shape of the cartilage.

This study came across one unusual pattern of CSTC, demonstrating a pseudo-articulation of the cartilage (Figure 9). It is important to differentiate this from an injury to the neck (generally caused by strangulation) (De Bakker *et al.*, 2019).

Figure 9: CSTC pseudo-articulation

A) Sagittal & B) Coronal slices showing a pseudo-articulation within the calcified superior horn of thyroid cartilage.

The prevalence of CSTC has been reported on a continuum between 4.1% and 15% (Wells, 2011; Missias *et al.*, 2018). The current study therefore has a slightly higher detection of CSTC than found previously. This may be attributed to the use of a minimal slice thickness and allowance to use different filters, enabling precise identification of the calcification.

The prevalence of triticeous cartilage calcification has been reported to lie between 11 and 65% (Barghan *et al.*, 2016; Wells., 2011). It appears consistently as a single 'rice-grain' homogenous opacity above the superior horn of the thyroid cartilage on sagittal and coronal views (Figures 10, 11) On axial projections, the calcified triticeous cartilage is generally found postero-medial to the greater cornu of the hyoid bone within the lateral pre-vertebral soft tissue (Wells, 2011). All noted triticeous calcifications in the present study were found using the localisation techniques described in the literature (Wells, 2011; Scarfe *et al*., 2018), with the only ambiguity encountered at times to be the differentiation between the tubercle of the greater horn of the hyoid bone and the triticeous cartilage (Figure 11).

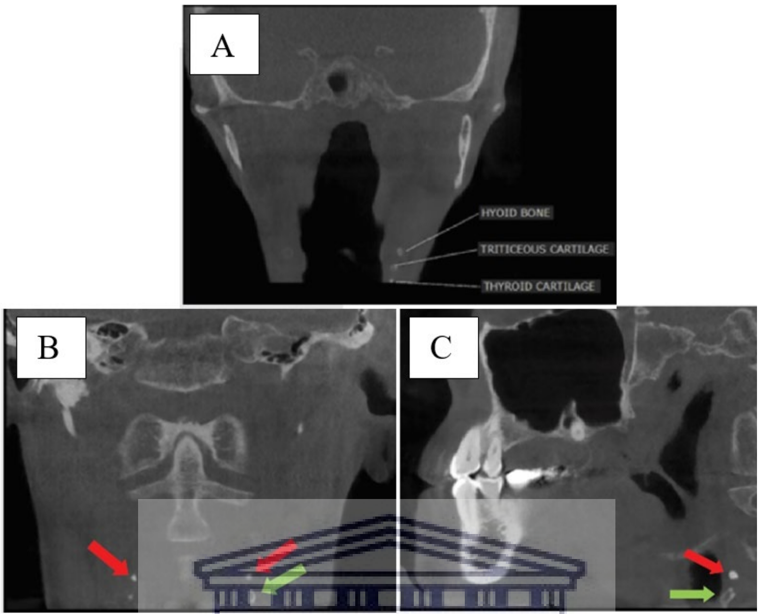

Figure 10: Calcified triticeous cartilage, CSTC

A) Coronal 1.00mm slice demonstrating the relative positions of the hyoid bone, calcified triticeous cartilage and calcified superior horn of thyroid cartilage to one another. B) Coronal & C) Sagittal slices of a 50-year-old female patient, red arrows indicate bilateral calcified triticeous cartilage and green arrows indicate unilateral calcification of the superior horn of thyroid cartilage.

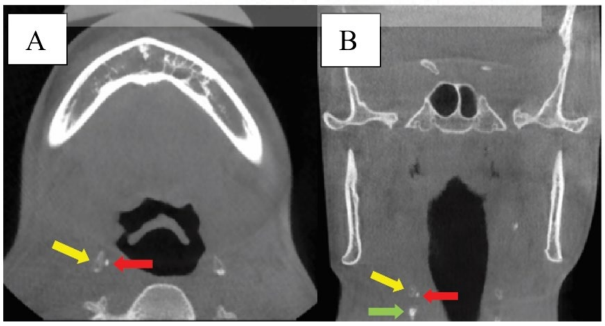

Figure 11: Calcified triticeous cartilage

A) Sagittal & B) Coronal slices of a 78-year-old male demonstrating an unusual position of the calcified triticeous cartilage (red arrow). Yellow arrow- hyoid bone, green arrow- calcified superior horn of thyroid cartilage.

Calcification of the stylohyoid chain has been reported in 19 studies (Monsarrat *et al*., 2019), with a prevalence of 5.06% (Avsever *et al*., 2018) and 3.7% (Yalcin and Yalcin., 2020). The results of the current study are slightly higher, again, possibly due to enhanced image manipulation. One study assessed calcified stylohyoid ligament (18.3%) separately from an elongated styloid process (45.1%) in FOVs encompassing both the maxilla and the mandible (Missias *et al.*, 2018). This was the only study noted to have done this, but in order to try and avoid ambiguity the researcher of the present study decided to assess the stylohyoid chain for any deviation from normal (Figures 12). The stylohyoid chain includes the lesser cornu of the hyoid bone, the styloid process and the stylohyoid ligament (Jadav *et al.*, 2022). A styloid process longer than 3.5mm was considered elongated (Wells, 2011) and any opacification along the length of the stylohyoid ligaments was noted as calcified stylohyoid chain.

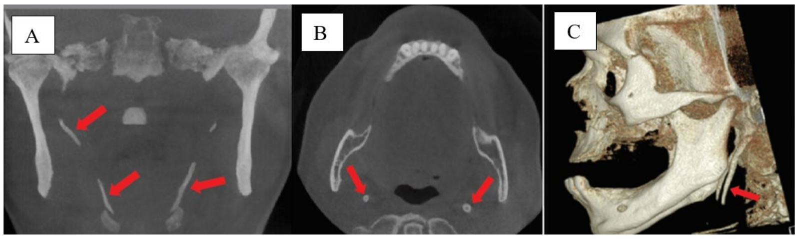

Figure 12: Calcified stylohyoid chain

A) Coronal 5mm MIP slice demonstrating calcification along the stylohyoid chain (stylohyoid ligament) of a 36-year-old female patient. Note insertion of the ligament along the superior border of the hyoid bone. B) 1.00mm slice thickness axial view of calcification along the stylohyoid chain in a 42-year-old male patient. The red arrows demonstrate two circular hyper-densities with a hypo-dense central region. C) 3D reconstruction in bone overlay of the same patient in B) demonstrating the length of the calcified stylohyoid ligament that projects beyond the angle of the mandible.

As mentioned, the presence of calcifications along the stylohyoid chain is noteworthy if there are accompanying symptoms. Literature exists where cause of death of individuals (fall from height, choking and sudden death) was attributed to Eagle syndrome (Jadav *et al.*, 2022). Although not requiring immediate referral or intervention, calcifications along the stylohyoid chain in symptomatic individuals warrants monitoring. Unfortunately, the current study did not have access to patients medical or symptomatic history and correlations between the presence of symptoms and calcifications could not be made.

Previous studies found a prevalence of tonsilloliths between 1.3-14.3% in studies conducted on scans taken over 12-32 months (Dief *et al.*, 2019), but did not differentiate between lingual, palatine or adenoidal tonsilloliths. Waldeyer's ring, circumferential lymphoid tissue of the pharynx, is formed by lingual, palatine and pharyngeal (adenoidal) tonsils (Challita *et al.*, 2020). Tonsilloliths present pathognomonically (Wells, 2011) as singular or multiple (more often) homogenous dense opacifications within Waldeyer's ring (Figures 13, 14). Pharyngeal (or adenoid) tonsilloliths are commonly found as single central homogenous opacifications in the superior pharyngeal region (Figure 15).

The presence of tonsilloliths in the elderly, very young, or immunosuppressed are noteworthy due to the risk of developing aspiration pneumonia (Mutalik *et al.*, 2018).

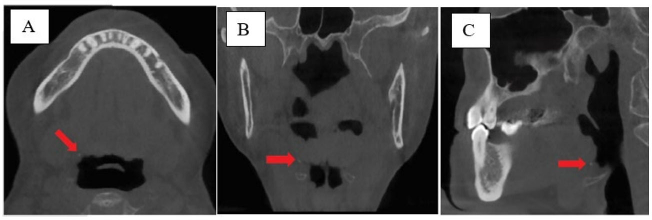

Figure 13: Lingual tonsillolith

58-year-old male patient. Red arrows indicate a single high-density on the RHS. Slice thickness 1.00mm. A) Axial slice; demonstrates position of lingual tonsillolith anterolateral to the oropharynx. B) Coronal slice & C) sagittal slice; demonstrates position of lingual tonsillolith at the inferior posterior border of the tongue.

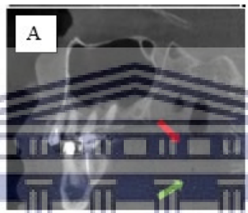

Figure 14: Lingual and palatine tonsillolith

83-year-old female patient. A) sagittal 1.00mm slice demonstrating the relative position of a single palatine tonsillolith (red arrow) to a single lingual tonsillolith (green arrow).

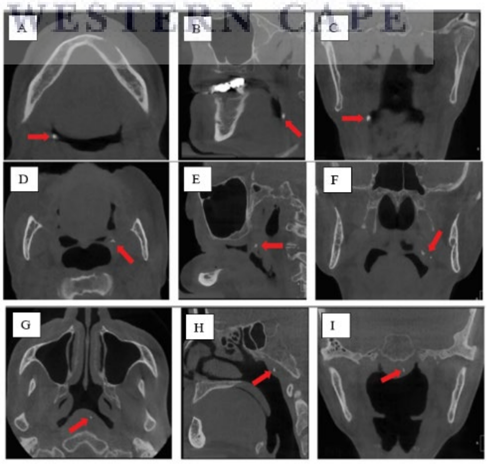

Figure 15: Palatine tonsilloliths

Red arrows indicate the different locations of palatine tonsilloliths in axial, sagittal and coronal views at 1.00mm slice thicknesses. Note all are located above the inferior border of the tongue; A)- F) demonstrates hyper-densities within the tonsillar pillars; G)- I) demonstrate a single hyper-density within the adenoidal tonsils.

The systematic review by Dief *et al.*, 2019 reported the prevalence of sialoliths between 0.3 and 1%. The review assessed studies conducted on scans taken over 12-32 months. The result of the current study falls within this range. The formation of calculus within the ducts or parenchyma of salivary is a common cause of sialolithiasis (Romano *et al.*, 2017). These patients therefore require monitoring or further imaging and definitive treatment. The submandibular gland is most commonly affected (due to the tortuous nature of the duct and saliva consistency) (80-90%), with the sublingual and minor salivary glands affected in about 5% of cases (Romano *et al.*, 2017). Both cases of sialoliths in the current study involved the submandibular gland (Figure 16). On CBCT, sialoliths present as fairly homogenous opacities that may be round to oval.

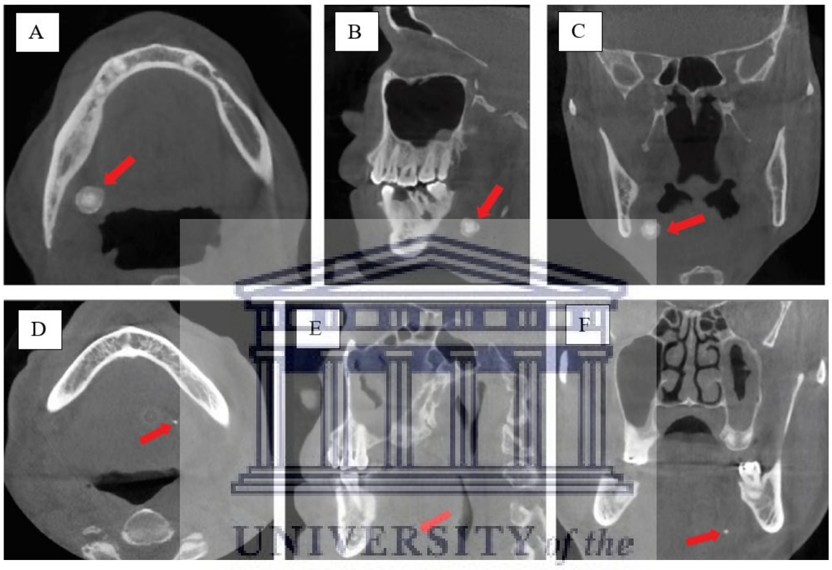

Figure 16: Sialolith

Red arrows indicate submandibular sialoliths in axial, sagittal and coronal views at 1.00mm slice thicknesses. A)- C) a large single hyper-density in a 40-year-old male, central region is more dense than outer layers. D)- F) a smaller hyperdense structure in a 70-year-old male.

Notably, vascular lesions such as haemangiomas with calcium deposits may appear similar to sialoliths and it is therefore important to differentiate the two in order to ensure appropriate therapy. Doppler sonography is an appropriate diagnostic tool for this endeavour (Wells, 2011).

There was a single case of a maxillary sinus antrolith in the current study (0.19%). A study by Chen *et al.*, 2021 reported the prevalence of antroliths to be between 0 and 3.2%. Antroliths range in size and may be seen in association with chronic sinus inflammatory processes (Singer *et al.*, 2021), presenting as single or multiple homogenous high densities of varying shapes

(Figure 17). In the case of missing maxillary posterior teeth, the differential for an antrolith should include a displaced tooth or root (Figure 17).

Figure 17: Antrolith

Red arrows indicate a potential antrolith within the RHS maxillary sinus of a 40-year-old male patient, presenting as a hyper-dense structure surrounded by an iso-intense soft tissue structure, at 1.0mm slice thickness. A) axial B) sagittal and C) coronal. The missing posterior molars indicate the structure may be a displaced root remnant.

Calcification of the epiglottis has been rarely documented and is poorly understood (Jeph *et al.*, 2017), although it is thought to be a normal physiological degenerative process (Ampanozi *et al.*, 2021). The case presented here, from the current study, demonstrated a linear opacity directly inferior to the epiglottis, posterior to the hyoid bone (Figure 18).

Figure 18: Epiglottic calcification

Red arrows indicate epiglottic calcification in a 70-year-old male, presenting as linear hyper-densities anterior to the airway space and behind the hyoid bone.

Calcification of the epiglottis may alter its morphology and function (elasticity), leading to symptoms such as dysphagia and/or dysphonia (Jeph *et al.*, 2017). Extra-osseous calcification is seen in patients with secondary hyperparathyroidism (Jeph *et al.*, 2017). Thus, a patient such as the above may benefit from close monitoring or haematological tests to rule out systemic disease.

The prevalence of pulp stones in the current study was 6.88%, and they presented as round to oval homogenous high densities within the pulp chamber of affected teeth. Pulp stones were noted in all teeth (incisors, premolars, and molars). A recent systematic review on the prevalence of pulp stones gave an overall global estimate figure of 36.5%,with the prevalence in the studies examined ranging from 2.1- 27.8% (Jannati *et al.*, 2019). The result of the present study therefore agrees with the literature.

The association between pulp stones and systemic disease has been researched. A 2022 systematic review and meta-analysis on the association between pulp stones and cardiovascular disease found a positive association (Almadhoon *et al.*, 2022). Careful screening of the medical histories of patients presenting with multiple pulp stones has been suggested (Almadhoon *et al.*, 2022).

As discussed, the inclusion of osteophytes of the TMJ is based on previous studies. The prevalence of TMJ osteophytes in the present study was 5.74%. Dief *et al*., (2019), in their systematic review, noted the prevalence of osteophytes of the TMJ to be between 3.4% and 10.7%. The result of the present study falls within this range. A recent systematic review and meta-analysis on the prevalence of TMJ disorders reported the prevalence to be approximately 31% for adults and 11% for children/adolescents (Valesan *et al.*, 2021), and the results of the current study may be explained by these figures.

Osteophytes of the TMJ present as 'bird-beak like' surface outgrowths of the TMJ or as small hyper dense structures apparently 'floating' within the articular disc space (Singer *et al.*, 2021) (Figure 19).

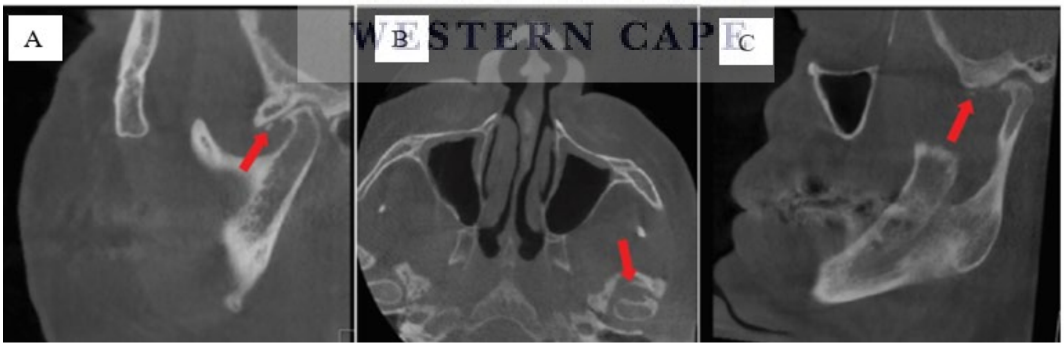

Figure 19: Osteophytes of the TMJ

A) Sagittal view of a 65-year-old female showing a free-floating hyper-density anterior to the TMJ as well as a 'bird-beak' outgrowth of the anterior TMJ condylar surface. B) same patient as A) C) Sagittal view of a 55-year-old male showing a free-floating hyper-density anterior to the TMJ.

Calcinosis cutis had a prevalence of 7.46% in the present study. It presented as single or multiple high-density structures only within the dermis of the skin (Figure 20). Previous studies have reported a prevalence of 3.2% and 2.27% (Gunduz *et al.*, 2018; Safi *et al.*, 2016) respectively. Calcinosis cutis is distinguished from osteoma cutis by the deposition of calcium salts within the dermis, the latter characterised by deposition of organized bone material (Kim *et al.*, 2017). Kim *et al.*, 2017 reported a prevalence of 42.1% of hypodermal calcifications on CT. There is therfore heterogenicity in the litertaure regarding this incidental calcification. CT displays superior soft tissue imaging compared to CBCT and detetction of smaller, immature calcifications is easier. This explains the higher prevalence of hypodermal calcifications in CT. The use of filters and thin slice thicknesses in the current study may have contributed to the higher prevalence noted. Additionally, it is not apparent if the previous studies differentiated between osteoma cutis and calcinosis cutis. This differentiation may be possible on CT imaging by employing and comparing Hounsfield unit values.

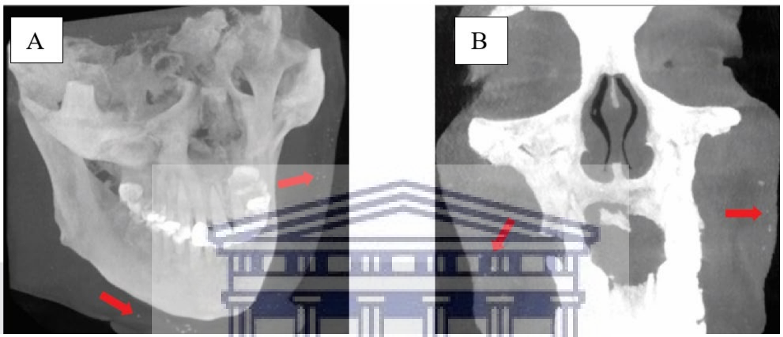

Figure 20: Calcinosis Cutis

A) calcinosis cutis in a 60-year-old male patient, 3D volumetric image with MIP overlay. B) calcinosis cutis in a 63-year-old male patient, 10mm MIP coronal view.

Calcinosis cutis is easily distinguished from other structures that may present as multiple high densities, namely implanted material such as Sasuk or calcium hydroxyapatite fillers (Singer *et al.*, 2021). Sasuk are implanted metal needles used as talismans, often seen in women of Southeast Asia. Sasuk present as linear hyper densities throughout the dermal layers, fillers often present in the malar region as linear hyper densities (Singer *et al.*, 2021). Dental practitioners should be aware of the imaging characteristics of calcinosis cutis and implanted materials on CBCT.

There was a single case of calcified lymph nodes in the present study (0.19%). Diniz *et al.*, 2020, reported a prevalence of 6.67%. Missias *et al.*, 2017 reported a prevalence of 0.2%. The results of the current study agree with the literature. However, due to the high numbers of TB and lymphoma in South Africa one would expect calcified lymph nodes to be more prevalent in this population (Ayles, Mureithi and Simwinga, 2022).

On CBCT, calcified lymph nodes appear as irregularly-shaped hyper densities of varying sizes, that may be singular or multiple, following the path of a nodal chain (Singer *et al.*, 2021). Furthermore, they are generally found posterior to sialoliths, a useful characteristic when localising.

Two cases of incidental calcification within the external auditory meatus were encountered in the current study (Figure 21), a single case of a globular extremely dense incidental calcification within the sternocleidomastoid muscle was encountered (Figure 22) and a single case of large heterogenous incidental maxillary sinus calcification was encountered (Figure 23). These calcifications were designated as 'unknown/other/pathology' as further studies are required along with clinical assessment and history taking.

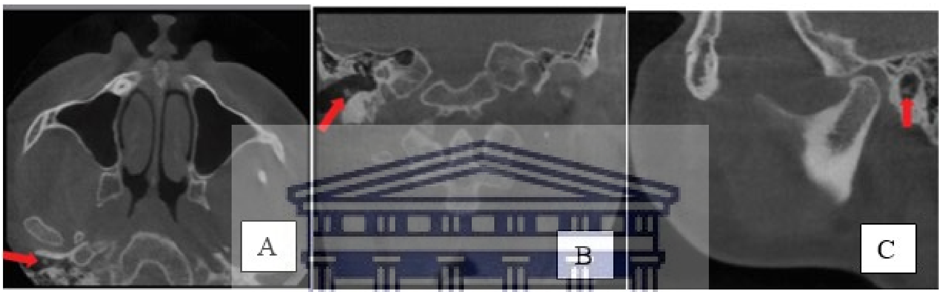

Figure 21: External Auditory Meatus Calcification

A) axial B) coronal & C) sagittal views of a hyperdense structure within the RHS external auditory meatus

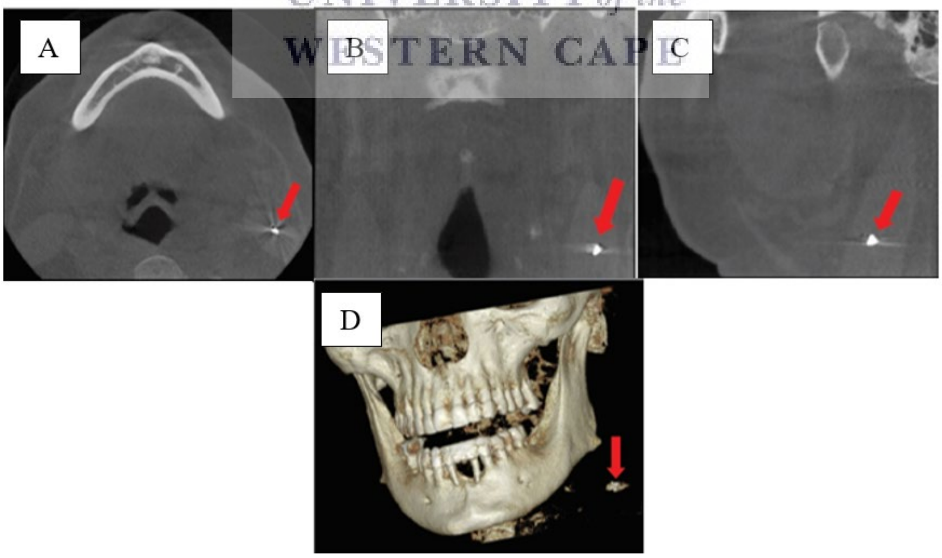

Figure 22: Unknown calcification. Extremely dense structure noted within the sternocleidomastoid muscle of a 75-year-old male. A) axial B) coronal C) sagittal & D) 3D volumetric format

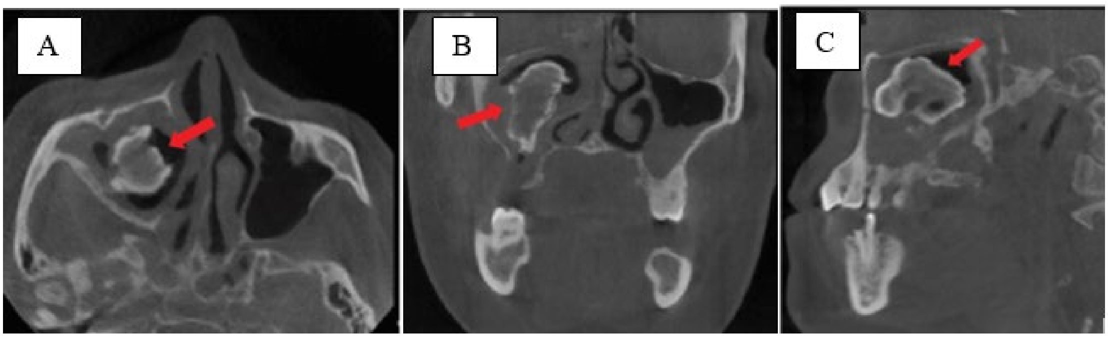

Figure 23: Antral calcification

In the present study, the vertebral column was assessed for any incidental calcifications. There were two cases of incidental ligamentous calcification noted (0.38%) and one case of vertebral artery calcification (0.19%). In a 2019 systematic review, the prevalence of vertebral findings was between 0.5% and 45.6% (Dief *et al*., 2019). However, these were only noted as a total finding under 'degenerative changes'. A systematic review of incidental findings of the clivus and cervical spine reported a prevalence of posterior longitudinal ligament ossification to be 0.8% and disc calcification to be 0.1% (Alsufyani, 2017). Monsarrat *et al*., (2019), noted 19 articles (27% of their study sample) investigated the cervical vertebra region.

It was noted in the current study that osteophytes of the cervical region presented as small singular round to oval hyper-dense structures adjacent to the cervical vertebrae. This is somewhat in contrast to the presentation of ligamentous calcification, a single case of which presented as more linear hyper-densities (Figure 24). In certain cases, the differentiation was challenging and a differential diagnosis of either vertebral osteophytes or vertebral ligament calcification was reached.

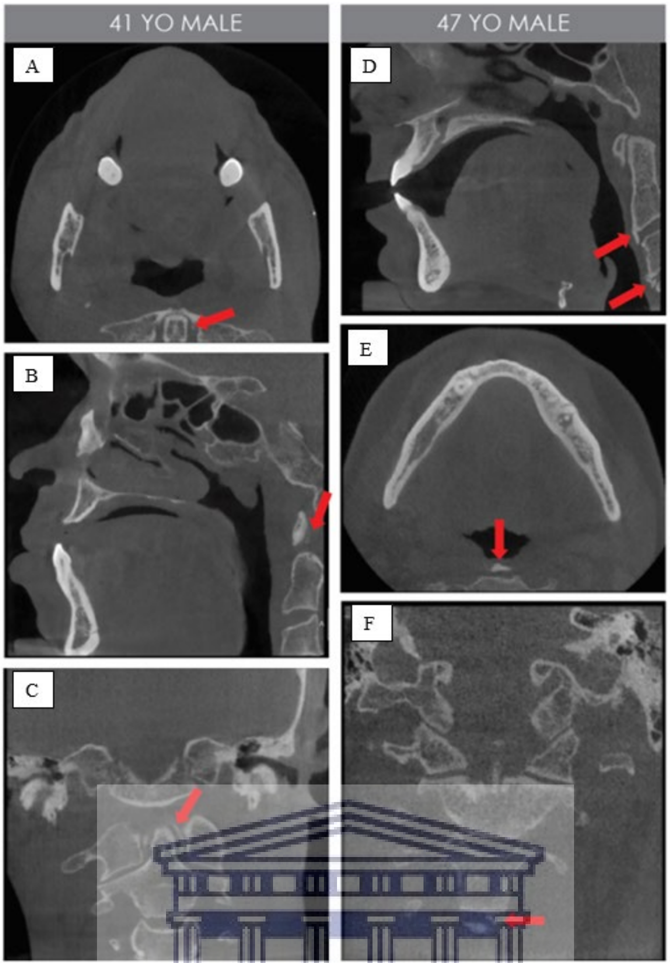

Figure 24: Vertebral Ligament Calcifications

A)-C) linear hyper density of the cervical spine. D)-F) note thicker, denser structure than A)-C).

Osteophytes of the spine serve as a principal radiographic finding of osteoarthritis (Scarfe *et al.*, 2018). These osteophytes will therefore be seen in conjunction with the other signs of degenerative disease. Calcification of the spinal ligaments may affect the anterior and posterior ligaments, inter-spinous ligament, alar ligaments or transverse ligaments (Scarfe *et al.*, 2018). These ligamentous calcifications may appear nodular, similar to osteophytes, but may also present as more linear hyper-densities, either vertically or horizontally (Scarfe *et al.*, 2018).

In advanced cases, osteophytes or intra-articular loose bodies may cause localised narrowing of the pharynx (Alsufyani, 2017). Therefore, it is important to assess the cervical spine for any incidental findings.

The final extracranial incidental calcification encountered in the present study was a single case of vertebral artery calcification (Figure 25). The discussion will now turn to vascular arterial calcification of the head and neck, a condition that occurs both extracranially and intracranially.

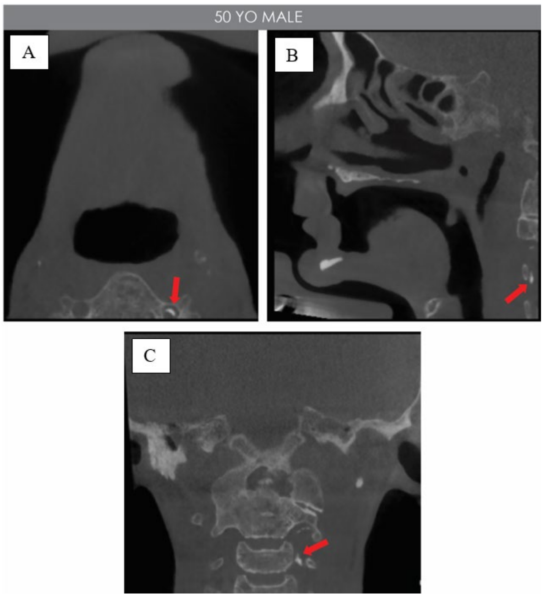

Figure 25: Vertebral Artery Calcification

A) Axial, B) sagittal & C) coronal slices demonstrating a single semi-circular hyper-density along the LHS vertebral artery.

6.5 Vascular arterial calcification

Atheromatous plaques are depositions of fatty substances and cholesterol either within the tunica intima of elastic arteries such as the carotid artery (known as calcified carotid artery atheroma or CCAA) or within the tunica media of smaller muscular arteries (known as medial artery arteriosclerosis or MAA) (MacDonald *et al*., 2012). The plaques within the tunica intima may cause narrowing of the blood vessel (stenosis) which leads to restricted blood flow through the vessel (MacDonald *et al*., 2012). Carotid artery atheroma calcification occurs due to maturation of the atheromatous plaque. Additionally, these plaques may develop into emboli which may ultimately occlude a cerebral end artery (MacDonald *et al.*, 2012). The risk of a cerebrovascular accident (CVA) (stroke) has been shown to increase with the presence of arterial calcifications (MacDonald *et al.*, 2012; Scarfe *et al.*, 2018; Uys and Mavuso., 2022). MAA does not cause narrowing of the lumen of the affected blood vessel (MacDonald *et al.*, 2012; Tahmasbi-arashlow *et al.*, 2020)

MAA tends to be a more generalised form of arteriosclerosis than CCAA and radiographically appears as multiple, circumferential 'pipe stem' high densities along the arterial wall (MacDonald *et al.*, 2012). The prevalence of MAA (concerning the entire body) has been reported to be 6.9% for females and 13.3% for males (Tahmasbi-arashlow *et al.*, 2020), and literature states it is an age-related condition (MacDonald *et al.*, 2012; Tahmasbi-arashlow *et al.*, 2020).

Although the exact pathogenesis is not well understood, it has been suggested that necrosis of medial smooth muscles due to degenerative processes is a possible mechanism (Tahmasbi-arashlow *et al.*, 2020).

In the present study, there were two cases of MAA of the facial artery (a branch of the external carotid artery) which had an incidental calcification prevalence of 0.38% (Figures 26, 27).

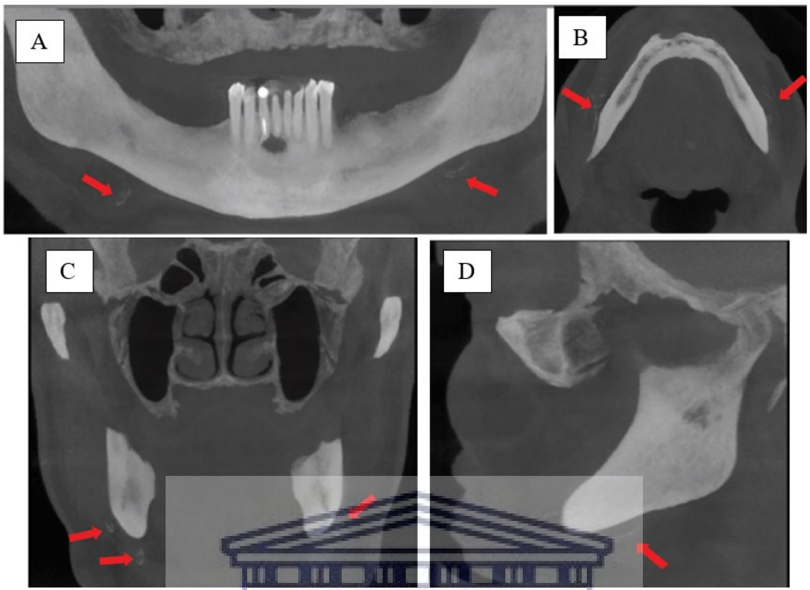

Figure 26: MAA

A) Reformatted panoramic radiograph, B) axial, C) coronal & D) sagittal 10mm MIP slices of MAA in a 70-year-old male patient. Calcification has occurred in the facial artery.

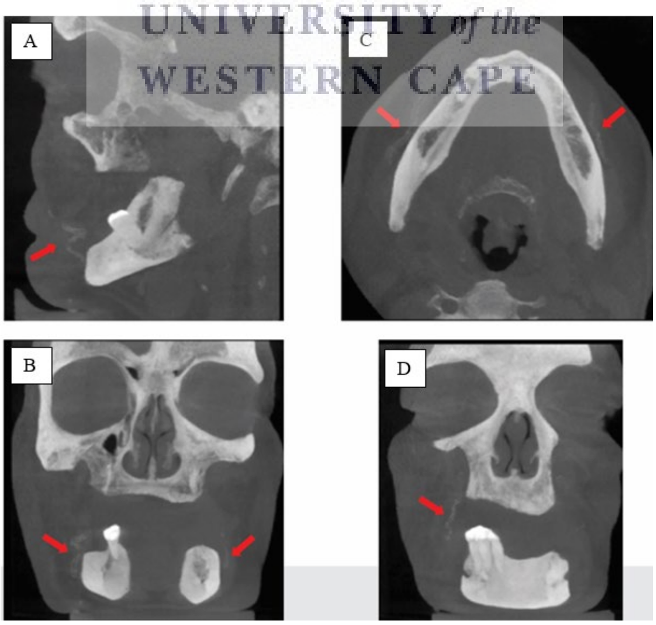

Figure 27: MAA

A)- C) 10mm MIP slices demonstrating calcifications along the facial artery in a 77-year-old male patient.

Identification of this calcification should lead the clinician to assess the patient's medical history closely for diabetes or renal disease as the association of these diseases with MAA has been documented (MacDonald *et al.*, 2012; Tahmasbi-arashlow *et al.*, 2020). As mentioned, the researchers of the current study did not have access to patient's medical records and associations between calcifications and systemic disease for this study population could not be drawn.

Calcification of atherosclerotic plaques in the carotid arteries is documented to have a prevalence between 2.0% and11.6% (Dief *et al.*, 2019). In the present study, common carotid artery calcification (CCC) was noted in four cases (0.76%) (Figure 28), external carotid artery calcification (ECAC) presented in 0.38% of cases and extracranial internal carotid artery (EICAC) presented in 4.6% of cases. The results of the current study therefore agree with the literature.

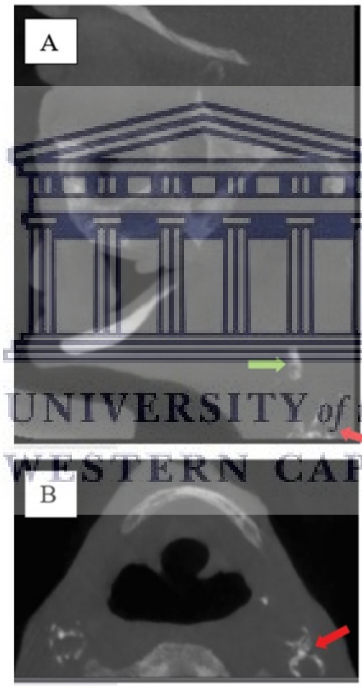

Figure 28: Common carotid artery calcification

A) sagittal 10mm MIP slice & B) axial 10mm MIP slice of common carotid artery calcifications at the level of the carotid bifurcation in a 75-year-old female (red arrows). Calcifications present as semi-circular to concentric hyper-densities. Green arrow indicates a linear-globular hyper-density (calcification) within the external carotid artery.

Extracranial carotid artery calcifications in this study presented commonly as multiple linear, curvilinear or 'rice-grain' hyperdense structures within the postero-lateral soft tissues of the cervical neck region. On axial views, these structures were noted postero-laterally to the greater cornu of the hyoid bone. On sagittal views the structures often presented in the C3-C4/5 cervical vertebrae region, always anteriorly to the vertebrae. Careful tracing of the soft tissue shadow of the arteries in the sagittal view allowed the primary researcher to differentiate the internal carotid artery from the external carotid artery and the location was then confirmed in the other orthogonal views. On sagittal views, the external carotid artery courses more anteriorly to the internal carotid artery (Scarfe *et al.*, 2018). The presentation and location of the extracranial carotid artery calcifications is in accordance with that described in the literature (Wells, 2011; MacDonald *et al.*, 2012) (Figure 29).

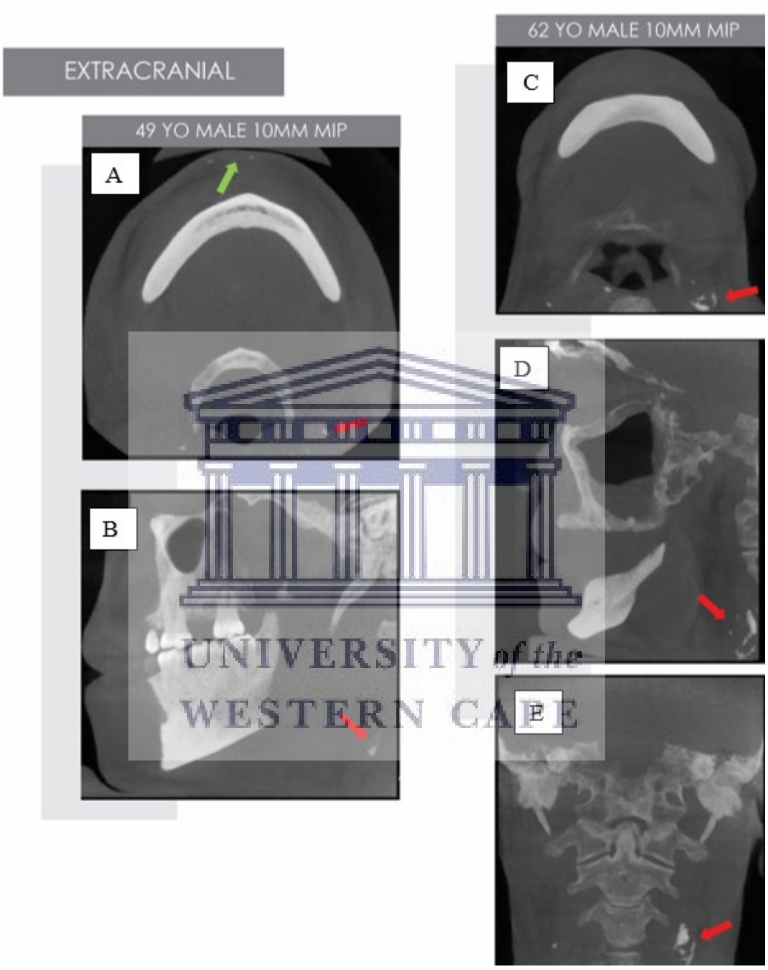

Figure 29: EICAC

A) – E) red arrows demonstrate linear-to-semicircular hyper-densities within the EICAC of two patients (cervical segment of internal carotid artery). Green arrow- calcinosis cutis.

The localisation of arterial calcifications is important as the decision to refer a patient for further medical assessment may prove financially and emotionally costly for the patient (Monsarrat *et al.*, 2019). If the primary clinician is unsure of the radiological diagnosis a consultation with an experienced maxillofacial radiologist is advised.

MacDonald *et al.,* 2012, stated that 80-86% of patients who present with CCAA on panoramic imaging demonstrate only low-grade stenosis, a stenosis which is not haemodynamically significant. With this in mind, they suggest that only patients who present with no previous medical history of cardiovascular disease or those with high risk factors (hypertension, high cholesterol, diabetes, smokers) should be referred for an in-depth medical assessment.

The most common medical imaging modality used to assess degree of stenosis of the cervical carotid arteries is carotid artery duplex ultrasound imaging (MacDonald *et al.*, 2012). Further advanced imaging (computed tomography angiography, magnetic resonance angiography and digital subtraction angiography) are reserved for situations where surgery is required (MacDonald *et al.*, 2012).

6.6 Intracranial calcifications and case examples

In the present study there were less intracranial ICs than extracranial ones. Due to the limitations of the CBCT image when assessing soft tissue structures of the brain, this result is not surprising. The prevalence of intracranial calcifications in the current study was 24.86%. The reported prevalence of intracranial calcifications varies widely: 3.9% by Yalcin *et al*., 2021; 0.42% by Altındağ *et al*., 2017 , 27.11% by Barghan et al., 2016, 33.1% by Bayrak *et al*., 2018, 35.2% by Sedghizadeh *et al.,* 2012, and 49.4% by Tepe *et al.,* 2022. The discrepancy in the figures may be explained by the fact that the current study assessed for numerous intracranial calcifications, compared to other studies that only assessed for one or two calcifications (viz., intracranial carotid artery and pineal gland calcifications). Additionally, the manipulation of images (slice thickness, filters) in the current study may have allowed for better visualisation of smaller or less mature calcifications than in previous studies.

There is limited literature comparing the prevalence of all possible intracranial and extracranial calcifications. A comparison for each intracranial calcification may be drawn, however the relatively high prevalence of intracranial calcifications in the present study reinforces the view that the entire CBCT volume needs to be thoroughly assessed by a competent clinician (Dief *et al.*, 2019; Monsarrat *et al.*, 2019; Uys and Mavuso, 2022).

The presence of intracranial internal carotid artery was 6.8% in the current study. In the recent study by Uys *et al*., 2022, the presence of ICAC was reported to be 34.88% and a 2019 article by Mutalik *et al,* reported a prevalence of 43.8% of ICAC. Overall, ICAC presented second most commonly in the present study. There were 14 patients (out of 350) who presented with both IICAC and EICAC, a rate almost double to that reported by Uys and Mavuso., 2022. The difference in results can only be speculated to be due to differences in study populations and patient ages. Calcifications of the intracranial carotid artery were discovered in segments described by Uys and Mavuso., (2022) (Figure 30). Careful tracing of the course of the artery in all orthogonal planes along with appropriate knowledge of its anatomy was required to detect these calcifications.

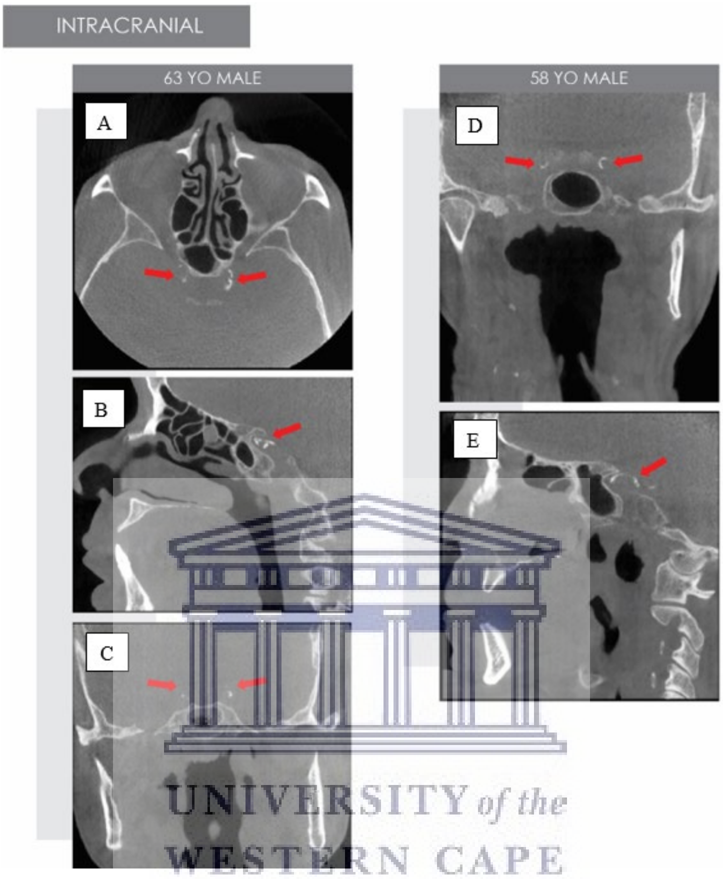

Figure 30: IICAC

Calcifications within the cavernous segment of the internal carotid artery presenting as linear to semi-circular hyper-densities.

The detection of such calcifications is extremely important as the association between atherosclerotic plaques and stroke is well documented (Wells, 2011; MacDonald *et al.*, 2012; Monsarrat *et al.*, 2019; Uys *et al.*, 2022). As with extracranial carotid artery calcifications, high-risk patients should be referred for further medical assessment and management (Uys *et al.*, 2022).

Pineal gland calcification presented in 3.44% of the current study sample. The systematic review by Dief *et al.*, 2019 reported that pineal gland calcification is the second most commonly occurring soft tissue calcification of the head and neck, with a prevalence between

0.5% and 19.2%. The results of the present study agree with the literature. Pineal gland calcification presented as punctate to round hyper-dense structures in the midline of the posterior cranium (Figure 31), posterior to the region of the habenular commissure. As mentioned, pineal gland calcification is an age-related phenomenon and although it has been noted in young patients (Singer *et al.*, 2021; Tepe *et al.*, 2022), its presence in children younger than 9 years of age may warrant further investigation. Mutalik *et al.,* 2017 reported the prevalence of pineal gland calcification on CBCT in patients referred for implant therapy to be 58.8%. There is a proposed link between pineal gland calcification and neuro-degenerative disorders, and the authors of the afore-mentioned study advised that a thorough medical history be taken in patients who present with pineal gland calcification and assessment should be made for any signs or symptoms of a neuro-degenerative disease (Mutalik *et al.*, 2017).

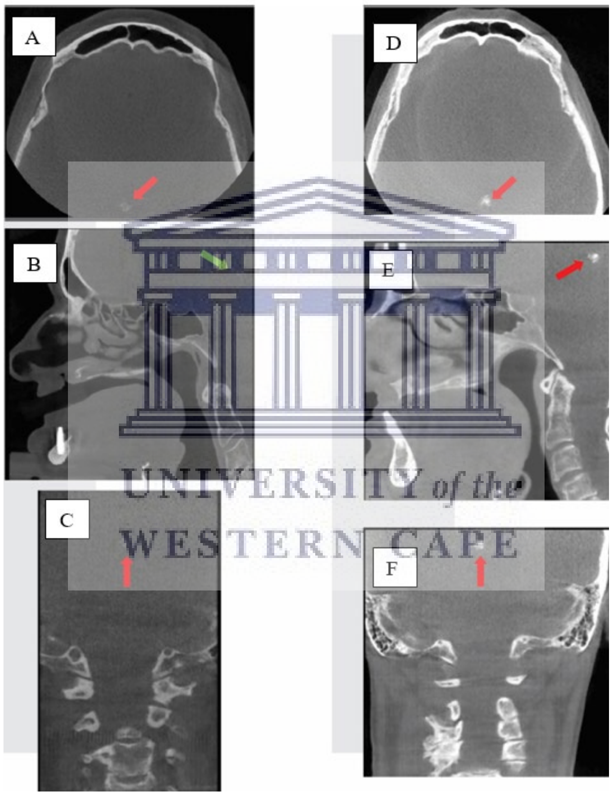

Figure 31: Pineal Gland Calcification

A)-C) pineal gland calcification in a 60-year-old female, D)-F) pineal gland calcification in an 80-year-old female patient (red arrows). Calcifications appear as circular hyper-densities along the midline of the posterior cranium.

There was a single case where the presence of pineal gland calcification was distinguishable from the habenular commissure calcifications (Figure 32). This 60-year-old female patient presented with a distinct separation between a singular anterior hyper-density (habenular commissure) and a circular, more posterior hyper-density (choroid plexus). The differentiation on CBCT between pineal gland and habenular commissure calcifications is sometimes challenging due to the lack of brain tissue anatomy and their close proximity (Sedghizadeh *et al.,* 2012).

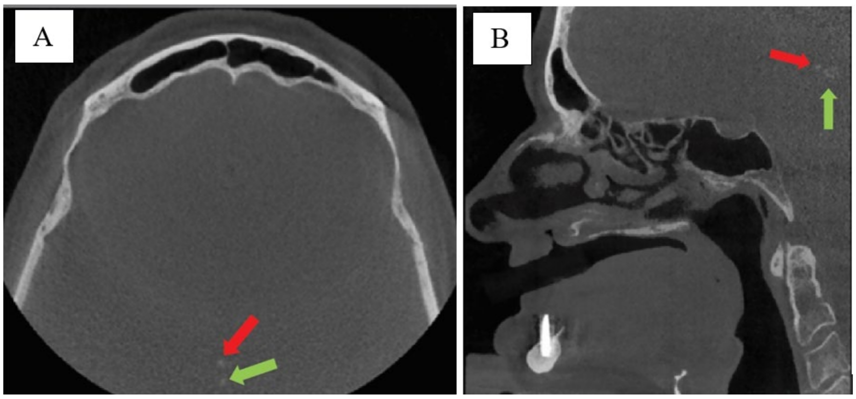

Figure 32: Habenular Commissure Calcification

A) Axial & B) sagittal slices of a 77-year-old female patient demonstrating habenular commissure calcification (red arrow) situated anterior to pineal gland calcification (green arrow).

There was a single case of choroid plexus calcification in the present study (0.19%). Bayrak *et al.,* 2019 reported a prevalence of 2.4% in their study of physiological intracranial calcifications on CBCT. They also reported an increase in age is associated with an increase in the presence of choroid plexus calcification. The patient in the current study was a 40-year-old male who also presented with an assumed calcification of the falx cerebri (noted under 'other/unknown'). The choroid plexus calcifications presented as two distinct circular hyper-densities laterally on either side of the midline, a presentation that is in agreement with the bilaterality of this structure (Sedghizadeh *et al.*, 2012; Bayrak *et al.*, 2019). When compared to the calcifications seen in the pineal gland, the choroid plexus calcifications presented as fainter hyper-densities, a presentation described by Sedghizadeh *et al.*, 2012. The differential of a falx cerebri calcification was reached based on the anterior and central location of the second calcification. Tepe *et al.*, (2022), reported a prevalence of 6.3% for falx cerebri calcification. Calcification of the falx cerebri is seen in Gorlin-Goltz syndrome and its presence should therefore warrant appropriate assessment for other radiological signs of the disease (Tepe *et al.*, 2022).

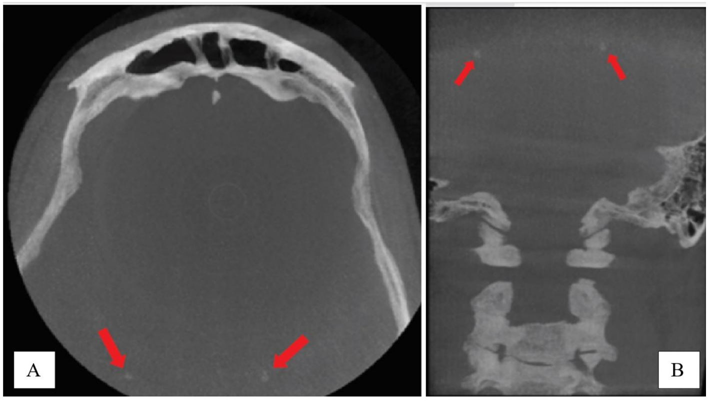

Figure 33: Choroid Plexus Calcification

A) Axial 10mm MIP & B) sagittal 10mm MIP views of bilateral choroid plexus calcifications that present as faint bilateral circular hyper-densities.

There were at least six cases of dural calcification in the present study (1.15%), listed under ‘other/unknown’ (Figure 34). Tepe *et al.,* 2022 reported a prevalence of 3.6% in their study of intracranial calcifications on CBCT. In the present study, these calcifications were detected in a multitude of areas within the cranium, as hyper-densities solely presenting along the inner periphery. Dural calcifications are not considered pathological findings (Tepe *et al.*, 2022), but as evidenced, may be detected on CBCT volumes encompassing the cranium.

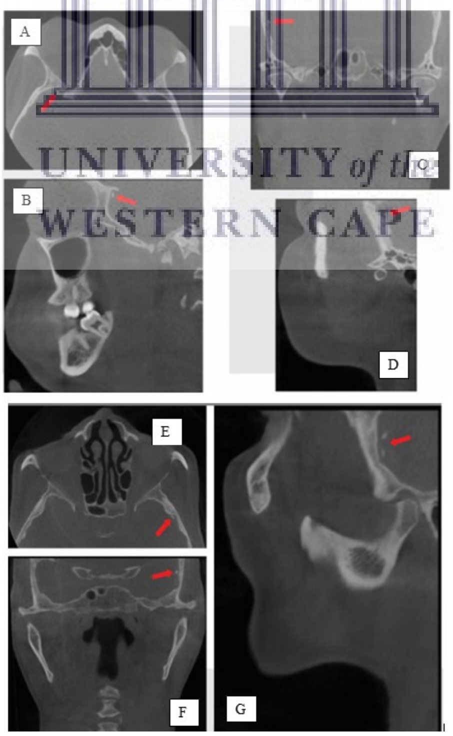

Figure 34: Dural calcifications

A) & B) 17-year-old female patient. C) & D) 40-year-old female patient. E)-G) 32-year-old male patient. Red arrows indicate the various positions of dural calcifications. Note all are situated along the inner periphery of the cranium.

Calcification of intracranial ligaments may cause compression of adjacent structures or cause complications during surgery (Bayrak *et al.*, 2019). Petroclinoid ligament calcification (PLC) presented in 9.75% of the present study sample. Previous studies have reported a prevalence of 8% (Sedghizadeh *et al*., 2012) , 2.7% (Bayrak *et al.*, 2019) and 22.1 % (Tepe *et al.*, 2022). The slightly higher results of the present study may be attributed to patient demographics (older age) or superior image manipulation that allowed for better identification of these ligaments. Figure 35 demonstrates the presentation of petroclinoid ligament calcification. In the current study, they were found either bilaterally or unilaterally as linear hyper-densities on axial views. Localisation was best achieved in the sagittal view by tracing the ligament posteriorly from the tip of the posterior clinoid process.

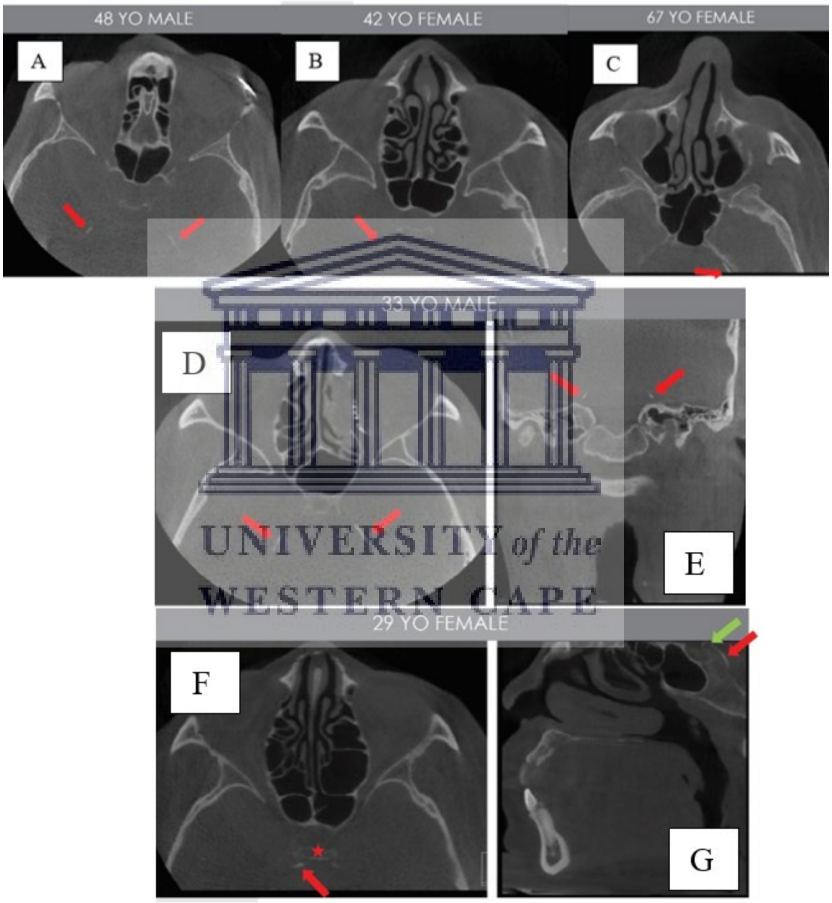

Figure 35: Petroclinoid Ligament Calcification

A)-D) axial slices demonstrating different presentations of calcified petroclinoid ligaments (red arrows). E) coronal slice demonstrating location and presentation of petroclinoid ligament calcification. Note they are less circular than internal carotid artery calcifications. F) horizontal hyper-densities (red arrow) indicates calcification directly posterior to posterior clinoid process (star). G) sagittal slice demonstrating the relationship of the calcified petroclinoid ligament (red arrow) to the posterior clinoid process (green arrow).

Interclinoid ligament calcification (ILC) presented in 1.91% of the study sample; Bayrak *et al*., (2019) reported a prevalence of 4.88% and Tepe *et al*., (2022) reported a prevalence of 1.2%. The current study therefore agrees with the literature. ILC was found to present as either bilateral or unilateral, partial or complete, between the anterior and posterior clinoid processes (Figure 36). The anatomy of the interclinoid ligament region is especially important when surgery involving the intracranial internal carotid artery is planned (Bayrak *et al.*, 2019).

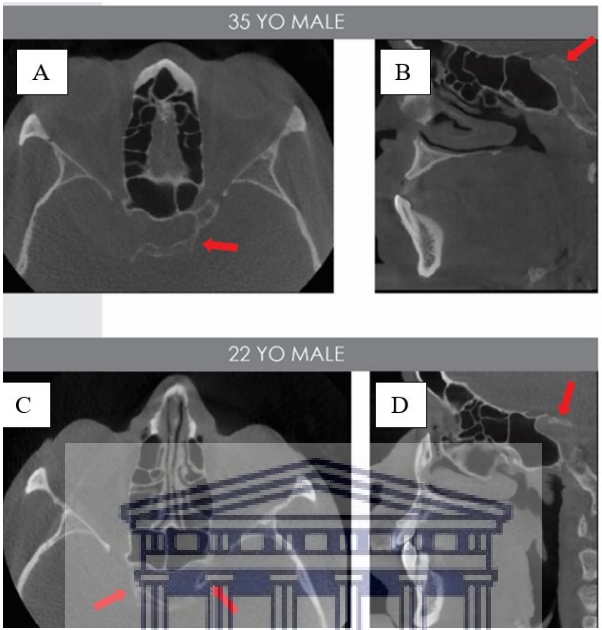

Figure 36: Interclinoid Ligament Calcification

A) Axial & B) corresponding sagittal slices of a unilateral complete calcification of the interclinoid ligament. B) shows the connection between the anterior and posterior clinoid processes. C) & D) axial and corresponding sagittal slices of bilateral complete interclinoid ligament calcifications.

A final and interesting calcification detected in the current study was a single case of apparent olfactory bulb calcification (Figure 37). This is a rare finding whose association to hyposmia requires further research (Ishman *et al*., 2003).

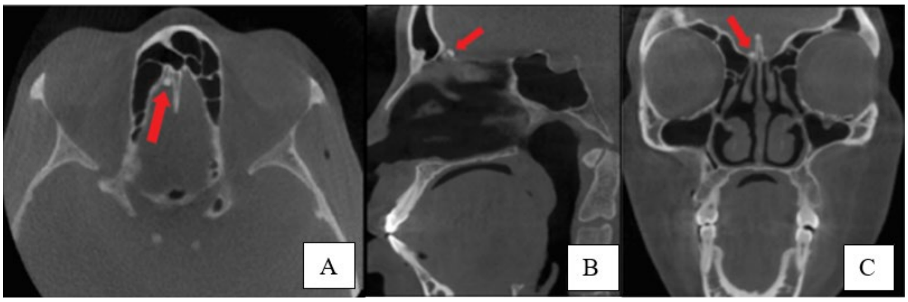

Figure 37: Olfactory Bulb Calcification

A) Axial B) sagittal & C) coronal views of olfactory bulb calcification in a 45-year-old female.

6.7 Clinical significance of ICs on CBCT

Clinicians need to be aware of the clinical significance of ICs as this will dictate the treatment protocol for their patients. Failure to detect clinically significant findings may have medico-legal consequences. As demonstrated by this study, most ICs are of low risk and require no follow-up (81.64%), a result that is in keeping with the literature (Dief *et al.*, 2019). Khalifa and Felemban., (2021), reported the percentages of low-significant IFS to range between 43.46% and 71.1%. Clinicians are advised to familiarise themselves with physiological calcifications so that inappropriate referral or additional imaging is avoided.

However, the presence of multiple calcifications in one patient may prompt the clinician to vigorously assess the patient's history for systemic disease; indeed, careful screening of the medical histories of patients presenting with multiple pulp stones is suggested (Almadhoon *et al.*, 2022). 3.44% of calcifications in the current study required monitoring. These included pineal gland calcification in children, despite ambiguity in the literature regarding this (Wells, 2011; Tepe *et al.*, 2022). Osteophytes of the TMJ or cervical vertebrae, due to their association with degenerative joint disease, may warrant monitoring of the patient in follow-up appointments.

The prevalence of ICs requiring referral was 14.91%. Khalifa *et al.,* reported a prevalence of highly significant IFS to be between 0.3% and 31.39%. In the current study, all patients with carotid artery calcifications were designated as requiring referral. As mentioned, MacDonald et al., (2012) suggests that only high-risk patients who demonstrate calcification of the carotid arteries be referred.

6.8 Cone-beam Computed Tomography

Khojastepour *et al*., (2017) reported that up to 4% of pantomographs have calcifications present. Mischkowski *et al*., (2008) concluded that CBCT images proved statistically comparable to CT in the detection of soft tissue calcifications. It would stand to reason that the prevalence of soft tissue calcifications on CBCT would be higher than that on 2D images, due to the multiplanar nature of CBCT (Wells., 2011). As mentioned, CBCT allows for detailed 3D interpretation of anatomical structures, providing images of high resolution and definition (Dief *et al.*, 2019). This is an obvious advantage over conventional 2D imaging, wherein the inherent limitations of superimposition, magnification and/or distortion lie (Scarfe et al.,2008). CBCT does, however, have its own disadvantages.

The cone-shaped beam of the CBCT allows for a more rapid acquisition of the data set than the fan-shaped beam of CT machines (Scarfe et al., 2008), which translates to less radiation exposure for the patient. However, the detection of large amounts of scattered radiation decreases image quality due to noise and poorer contrast resolution than conventional CT. The effective dose of a CBCT with a large FOV ranges between 70 and 1073 μSv, compared to that of a conventional pantomograph that ranges between 2.7 and 23 μSv (Dief *et al.*, 2019). CBCT imaging should therefore only be chosen in case-specific instances, as a diagnostic tool, and adherence to the principle of As Low as Reasonably Achievable (ALARA), radiation protection protocols and SEDENTEXCT principles is of utmost importance (Horner *et al.*, 2009; Dief *et al.*, 2019). In an attempt to reduce the radiation exposure to a patient, clinicians may opt to utilize limited FOVs (Scarfe *et al.,* 2008). However, this does not negate the possibility of encountering incidental findings.

Any research involving CBCT needs to include a basic understanding of the technical aspects of a maxillofacial CBCT, notwithstanding the particular parameters of the specific research (e.g., in the current study sound anatomical knowledge of the head and neck was a pre-requisite). In this regard, a knowledge of CBCT image characteristics was required, specifically in distinguishing image artifacts from incidental calcifications. Scarfe *et al*., (2008), defined artifacts as '…any distortion or error in the image that is unrelated to the subject being studied.' Ring artifacts are scanner-related artifacts and appear as concentric hyperdense rings, centred around the axis of rotation (Scarfe *et al*., 2008; Schulze *et al*., 2011), and result from poor scanner calibration or other imperfections within the scanner detection. By localising the artifact in more than one orthogonal plane, one should be able to differentiate the ring artifact from a possible incidental calcification.

The various applications of CBCT in dentistry have been discussed in the literature review. A recent review article on two decades of research in CBCT imaging concluded that there have been various publications and systematic reviews related to CBCT applications in all fields of dentistry. The authors stressed that not all CBCT models marketed have been scientifically validated and care should be taken not to indiscriminately extrapolate *in vitro* results to clinical settings, and that results should not be generalized (Gaêta-Araujo *et al.*, 2021).

However, the ever-increasing use of the CBCT imaging modality mandates ongoing and thorough research, in order to arm practitioners with as much knowledge as possible regarding the modality. This, in turn, aims to ensure adequate informed consent and autonomy for patients, from practitioners who have adequate knowledge based on a sound bank of literature.

CHAPTER 7: CONCLUDING REMARKS

7.1 Limitations

- Sample size in the current study was 350 scans. There were a total of 897 scans that did not meet the inclusion criteria for the current study. Although adequate, a study with a greater sample size would have provided a larger data base for analysis, as the current study sample may not be truly representative of the entire study population.
- Due to there only being one observer, operator fatigue could have played a role in the capturing of data. This was addressed by applying time constraints to data collection periods. However, this was not always possible.
- The researchers did not have access to patients' medical or treatment histories, therefore associations between presence of calcifications and systemic disease could not be drawn.
- The current study assessed for the prevalence of ICs of the head and neck only and the results are therefore not generalisable for the overall prevalence of incidental findings.
- Only full FOV volumes were assessed, and the results are therefore not generalizable for small or medium FOV volumes.
- Grey value identification of IFs was not employed in this study and this method could not help distinguish between certain ossifications or calcifications. Results of the current study may therefore be skewed.

7.2 Recommendations

Further studies aimed at a larger South African population (including populations from other tertiary institutions and private practises) that investigate the prevalence of IFs and ICs as well as any associations between ICs and systemic disease will be beneficial. This will potentially aid policymakers in drawing up a standardised image assessment and referral protocol for incidental calcifications. Additionally, further studies investigating grey-level values of calcifications and ossifications on CBCT could potentially provide evidence to help clinicians distinguish between these entities and limit future ambiguity.

7.3 Conclusion

The current study aimed to assess ICs in head and neck full FOV CBCT scans of a South African population in the Western Cape Province. 68% of the studied sample had incidental calcifications, and there is a positive association between an increase in age and the possibility of having an incidental calcification. The majority of findings require no treatment (81.64%), 3.44% require monitoring and 14.91% require follow-up or referral due to clinical significance. It is the prerogative of the requesting clinician to advise patients of the possibility of encountering incidental calcifications, and their clinical significance, before image-taking so as to ensure adherence to the principle of informed consent and patient autonomy

CHAPTER 8: BIBLIOGRAPHY

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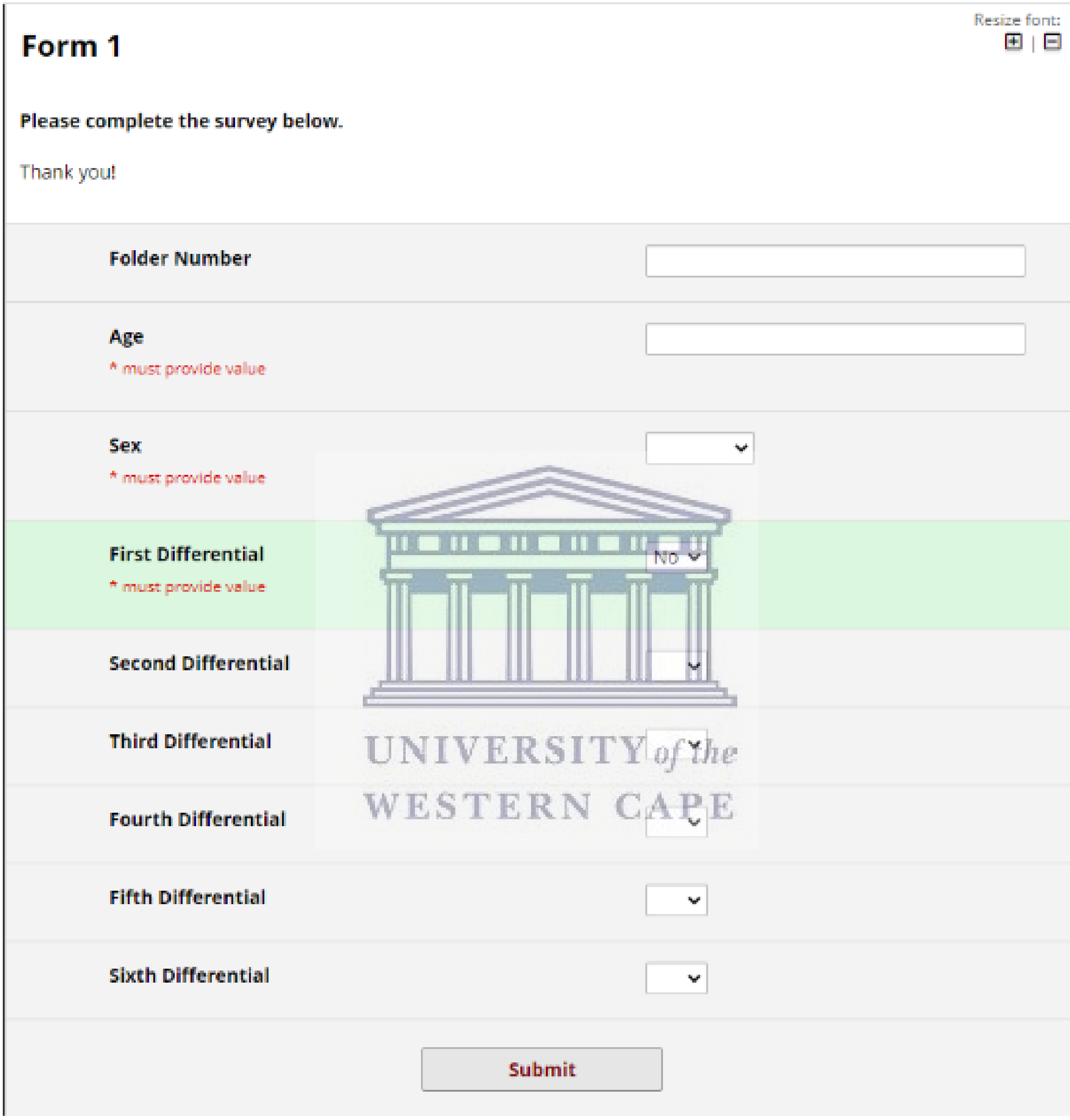
APPENDICES

Appendix A: REDCap survey form



Form 1

Resize font:

Please complete the survey below.

Thank you!

Folder Number

Age
* must provide value

Sex
* must provide value

First Differential
* must provide value

No

Second Differential

Third Differential

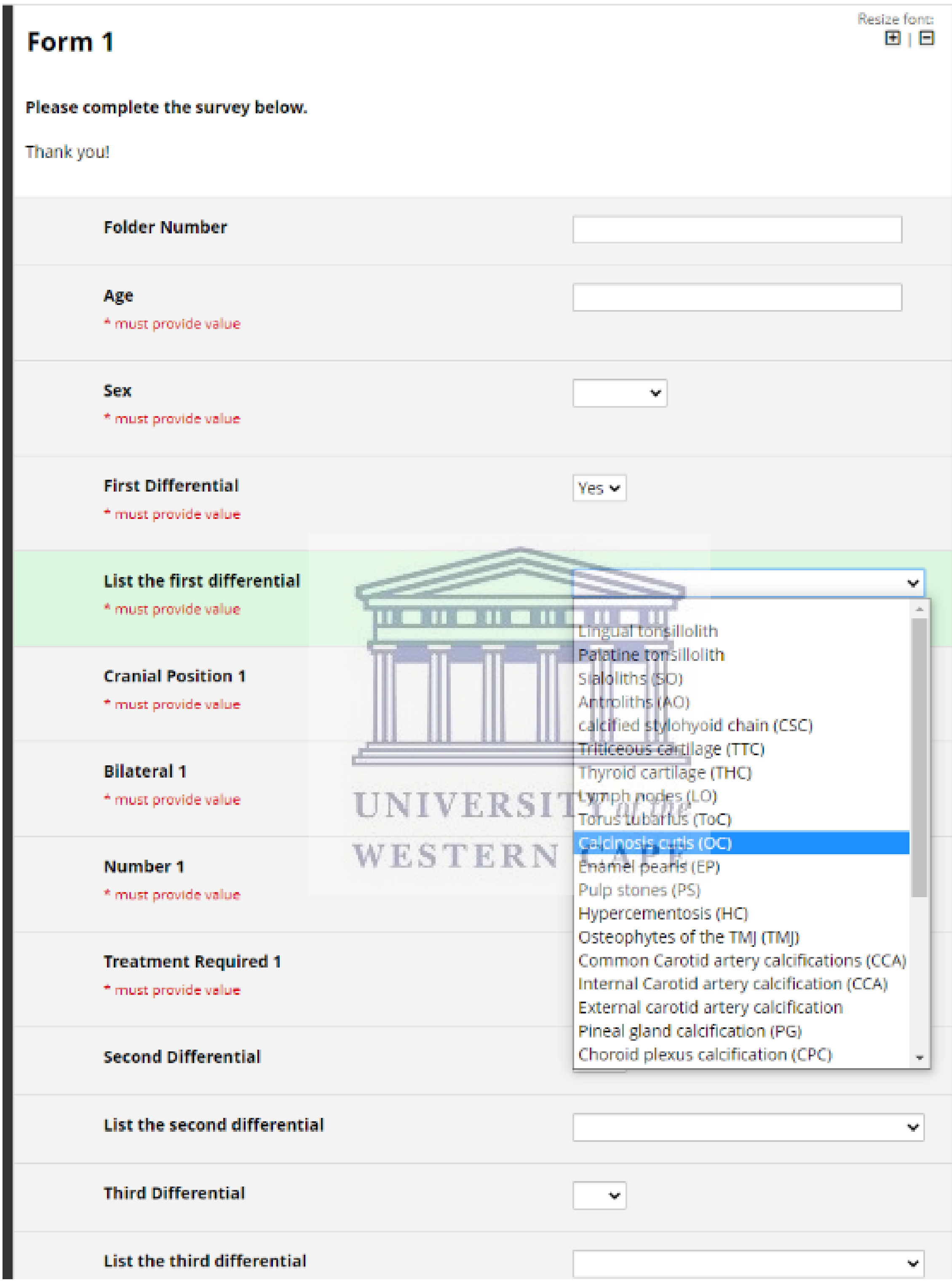
Fourth Differential

Fifth Differential

Sixth Differential

Submit

Appendix B: REDCap survey form with drop-down list of incidental calcifications



Resize font:

Form 1

Please complete the survey below.

Thank you!

Folder Number

Age
* must provide value

Sex
* must provide value

First Differential
* must provide value
Yes

List the first differential
* must provide value

Lingual tonsillolith
Palatine tonsillolith
Sialoliths (SO)
Antroliths (AO)
calcified stylohyoid chain (CSC)
Triticeous cartilage (TTC)
Thyroid cartilage (THC)
Lymph nodes (LO)
Torus tubarius (ToC)
Calcinosis cutis (OC)
Enamel pearls (EP)
Pulp stones (PS)
Hypercementosis (HC)
Osteophytes of the TMJ (TMJ)
Common Carotid artery calcifications (CCA)
Internal Carotid artery calcification (CCA)
External carotid artery calcification
Pineal gland calcification (PG)
Choroid plexus calcification (CPC)

Cranial Position 1
* must provide value

Bilateral 1
* must provide value

Number 1
* must provide value

Treatment Required 1
* must provide value

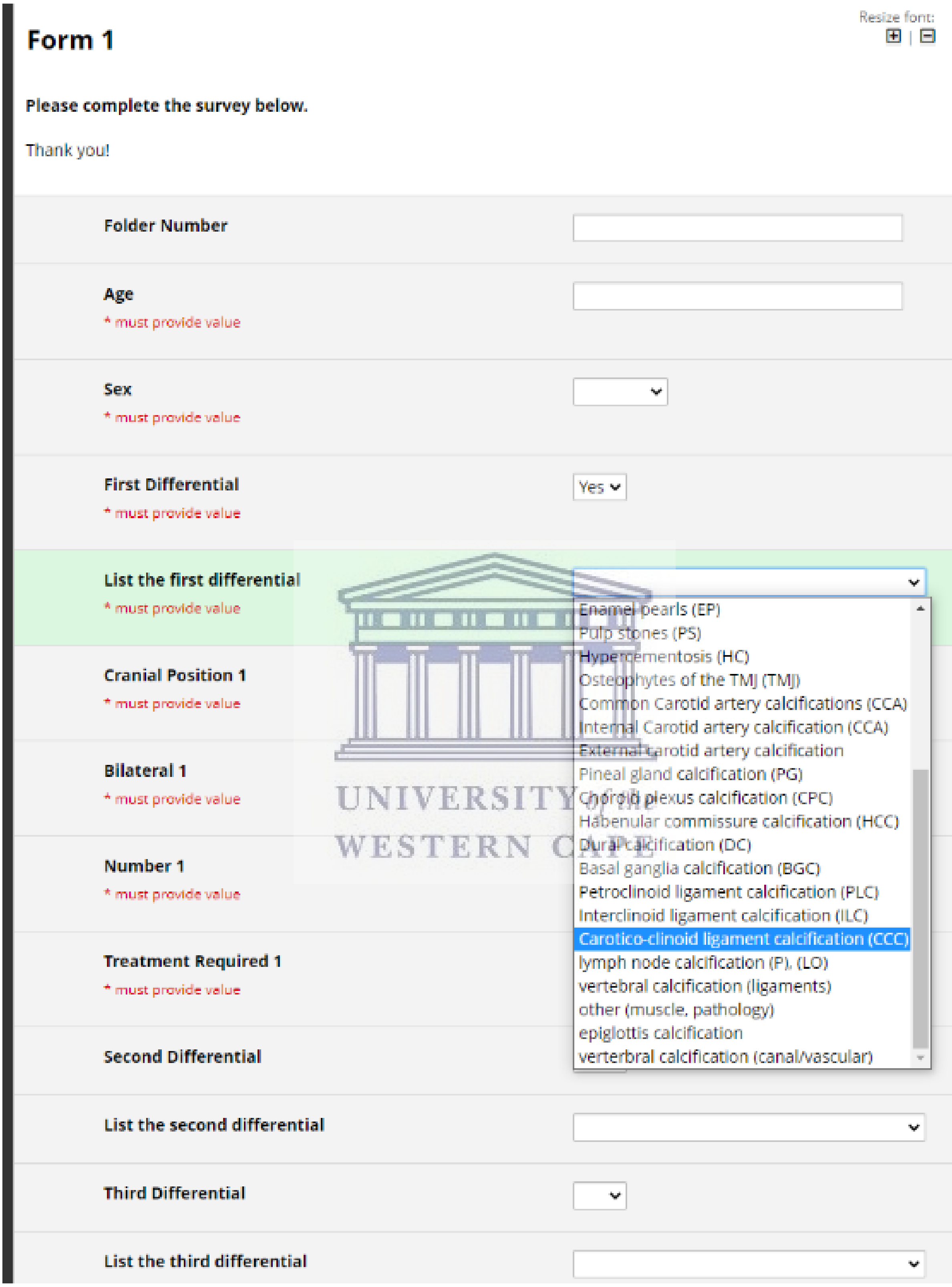
Second Differential

List the second differential

Third Differential

List the third differential

Appendix C: continued REDCap survey form with drop-down list of incidental calcifications



Form 1

Resize font:

Please complete the survey below.

Thank you!

Folder Number	
Age * must provide value	
Sex * must provide value	
First Differential * must provide value	Yes
List the first differential * must provide value	
Cranial Position 1 * must provide value	
Bilateral 1 * must provide value	
Number 1 * must provide value	
Treatment Required 1 * must provide value	
Second Differential	
List the second differential	
Third Differential	
List the third differential	

Enamel pearls (EP)
Pulp stones (PS)
Hypercementosis (HC)
Osteophytes of the TMJ (TMJ)
Common Carotid artery calcifications (CCA)
Internal Carotid artery calcification (CCA)
External carotid artery calcification
Pineal gland calcification (PG)
Choroid plexus calcification (CPC)
Habenular commissure calcification (HCC)
Dural calcification (DC)
Basal ganglia calcification (BGC)
Petroclinoid ligament calcification (PLC)
Interclinoid ligament calcification (ILC)
Carotico-clinoid ligament calcification (CCC)
lymph node calcification (P), (LO)
vertebral calcification (ligaments)
other (muscle, pathology)
epiglottis calcification
verterbral calcification (canal/vascular)

Appendix D: Ethics approval and research project registration letter

UNIVERSITY *of the* WESTERN CAPE

60 YEARS *of hope, action & knowledge*

11 May 2021

Dr L Ebrahim
Diagnostics and Radiology
Faculty of Dentistry

Ethics Reference Number: BM21/03/06

Project Title: Incidental Calcifications of the Head and Neck on CBCT scans

Approval Period: 07 May 2021 – 07 May 2024

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report annually by 30 November for the duration of the project.

Permission to conduct the study must be submitted to BMREC for record-keeping.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

Director: Research Development
University of the Western Cape
Private Bag X 17
Bellville 7535
Republic of South Africa
Tel: +27 21 959 4111
Email: research-ethics@uwc.ac.za

NHREC Registration Number: BMREC-130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE.

Appendix E: Letter requesting permission to access CBCT records

UNIVERSITY of the WESTERN CAPE

FACULTY OF DENTISTRY
Private Bag X 1, Tygerberg, 7505
Cape Town, South Africa
T: +27 937 3110 F: +27 931 2287
E-mail: ebrahimleila@gmail.com

Dear Dr T Van Zyl

RE: Request for permission to access the UWC Tygerberg Oral Health Centre's Department of Radiology's CBCT database.

I am writing this to request permission of the Dean's office to access and analyze the CBCT records of scans that meet the inclusion criteria of my study as set out in the research proposal. The purpose is to complete my mini-thesis that is in partial fulfilment of the requirements for the degree of a Masters in Oral and Maxillofacial Radiology.

All ethical considerations will be adhered to as set out in my research proposal and protocol presentation (18/09/2020).

Thank you kindly for your consideration
Regards

Dr Leila Ebrahim
1st year MSc Student
Department of Oral and Maxillofacial Radiology
University of the Western Cape

FROM HOPE TO ACTION THROUGH KNOWLEDGE.

Appendix F: Authorization letter to access CBCT volumes

FACULTY of DENTISTRY
UNIVERSITY of the WESTERN CAPE

FACULTY OF DENTISTRY
Department of Diagnostics and Radiology
Private Bag X1, Tygerberg, 7507
Cape Town, South Africa
T:+ 27 21 937 3110
HOD: Dr T van Zyl
E-mail: tvanzyl@uwc.ac.za

April 2022

To whom it may concern:

RE: Permission to use the record of the Department of Diagnostics and Radiology

I hereby grant permission to Dr L Ebrahim to use the records of the CBCT volumes from the Department of Diagnostics and Radiology.

The purpose is to complete her research that is in partial fulfilment of her MSc (Maxillofacial Radiology) degree.

All ethical considerations will be adhered to as set out in her protocol presentation and BMREC application.

Hope this meets your consideration.

Kindest regards
Dr Tineke van Zyl
Dip.OH, BChD, PDD(OMFR), MSc(OMFR)
Acting HOD Department of Oral and Maxillofacial Radiology
Oral MaxilloFacial Radiologist/Stomatologist/Senior Lecturer/Supervisor
BDS III Year coordinator
Teaching champion
Department of Oral and Maxillofacial Radiology
University of the Western Cape Dental Faculty
Cape Town
South Africa
Email: tvanzyl@uwc.ac.za
Tel: +27 21 937 3110/370 4419
https://orcid.org/0000-0002-5186-9262

"If you want to go fast.....go alone; but if you want to go far....go together..."

Appendix G: STROBE Guidelines for cross-sectional studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	ii
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			1
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	1
Methods			21
Study design	4	Present key elements of study design early in the paper	21
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	21
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	21
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	23
Bias	9	Describe any efforts to address potential sources of bias *User fatigue, machine,*	23
Study size	10	Explain how the study size was arrived at	21
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	23
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	23
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	22
		(b) Give reasons for non-participation at each stage	22
		(c) **Consider use of a flow diagram**	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	29
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	31
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	31
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	35
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	68
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	61
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27