COMPARING PANORAMIC RADIOGRAPHS AND CBCT: IMPACT ON RADIOGRAPHIC FEATURES AND DIFFERENTIAL DIAGNOSES

Li Zhen Lim

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Approved by:

Donald Tyndall

Glenn Reside

Ricardo Padilla

ABSTRACT

Li Zhen Lim: Comparing Panoramic Radiographs and CBCT: Impact on Radiographic Features and Differential Diagnoses
(Under the direction of Donald Tyndall)

Cone beam computed tomography (CBCT) is known to have many advantages over panoramic radiography (PAN). However, few studies quantitatively demonstrate the benefits of CBCT for imaging intraosseous pathology. The aims of this study were to determine whether lesion features appear differently on PAN and CBCT, and the clinical impact of CBCT vs PAN. Three oral radiologists reviewed 33 sets of PANs and CBCTs of biopsy-proven lesions, described lesion features and provided up to three ranked differential diagnoses and their confidence levels associated with each diagnosis. Confidence levels were weighted by the rank at which the correct diagnosis was provided. Differences were present between PAN and CBCT with respect to lesion border definition, continuity of corticated borders, effect on neurovascular canals, expansion, cortical thinning and destruction. There was no association between the two modalities and the rank at which the correct differential diagnoses was made, or with the observers' weighted confidence levels.

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LIST OF ABBREVIATIONS

AAE	American Association of Endodontists
AAOMR	American Academy of Oral and Maxillofacial Radiology
AOT	adenomatoid odontogenic tumor
ALARA	As Low As Reasonably Achievable
A_z	Area under the ROC curve
BRONJ	bisphosphonate-related osteonecrosis of the jaw bone
CBCT(s)	cone beam computed tomography (scans)
CCOT	calcifying cystic odontogenic tumor
CDT	Current Dental Terminology
CI	confident intervals
CPT	Current Procedural Terminology
DICOM	Digital Imaging and Communications in Medicine
FOV	field of view
HIPAA	Health Insurance Portability and Accountability Act of 1996
IAC	inferior alveolar canal
ICRP	International Commission on Radiological Protection
IRB	institutional review board
KCOT	keratocystic odontogenic tumor
LNT	linear-non-threshold
MDCT/CT	multiple detector computed tomography/computed tomography
MF	multifocal
MPR	multiplanar reformatted
μSv	micro-Sieverts
MRI	magnetic resonance imaging
OCIS	UNC School of Dentistry's Office of Computing and Information Systems

OR	odds ratio
PAN(s)	panoramic radiograph(s)
ROC	receiver operating characteristic (curve)
SBC	simple bone cyst
SEDENTEXCT	Safety and Efficacy of a New and Emerging Dental X-ray Modality
TIFF	Tag Image File Format
TMJ	temporomandibular joint
UNC	University of North Carolina at Chapel Hill
VRF	vertical root fracture

REVIEW OF THE LITERATURE

Introduction

Imaging plays a crucial role in the diagnosis and treatment-planning of pathology in the oral and maxillofacial region. The radiographic features of an intraosseous lesion can provide insight about the lesion's characteristics and behavior. By correlating all the available information, including imaging studies, the clinician can classify the lesion in the best-fitting category and decide on the appropriate management plan.

The most commonly employed imaging modalities for dental and maxillofacial pathology include 2-dimensional intra-oral periapical radiographs, extra-oral panoramic radiographs, or 3-dimensional cone beam computed tomography (CBCT). In situations where the pathology is anticipated to be more extensive, advanced imaging such as multiple detector computed tomography (MDCT) or magnetic resonance imaging (MRI) might be indicated. In this manuscript, the focus will be on the comparison of panoramic radiographs and CBCTs for imaging intraosseous pathology. Since CBCTs result in higher radiation doses than panoramic radiographs for the same field of view (FOV)[1], it is important to know which imaging modality maximizes the diagnostic information at the lowest possible dose.

The first objective of the study is to determine whether the radiographic signs of a lesion differ between the two imaging modalities. The second objective is to determine whether these differences have any clinical impact. For example, does using CBCT result in a more accurate differential diagnosis, or increase the confidence levels of oral and maxillofacial radiologists? Unlike other fields in dentistry such as orthodontics[2], endodontics[3] and implantology[4] where recommendations for the use of CBCT have been published, there are currently no guidelines for the usage of CBCTs for evaluating pathology. The answers to the questions posed above could help to provide a starting point for developing evidence-based selection criteria.

Radiographic Signs

When a patient with a lesion is imaged, it is assumed by many that the radiographic presentation of the lesion will most likely remain the same whether in 2-dimensions or 3-dimensions. Some of these features include the location, shape, periphery, internal contents and effects on surrounding structures. This information, also known as radiographic signs, usually correlate with the behavior of a lesion and enables classification under one or more of the following categories: inflammatory, fibro-osseous lesions and diseases of bone, cysts and cyst-like lesions, benign tumors and malignant tumors. The following section outlines the principles of radiographic interpretation and the significance of each radiographic sign as described in a commonly referenced textbook by White and Pharoah.[5]

Location: The location and epicenter of the lesion can indicate the tissue of origin. For example, lesions that are located above the inferior alveolar canal (IAC) often consists of odontogenic tissue, while the opposite is true for lesions inferior to the IAC. If the lesion is found within the canal, it is likely neural or vascular in origin. Lesions may also have predilections for specific sites. For example, adenomatoid odontogenic tumors (AOT) are often found around the crowns of impacted maxillary canines.[6] Some conditions may have a more generalized appearance in the jaw, and this may indicate a systemic metabolic or endocrine disease, such as hyperparathyroidism or Paget's disease. Only a few conditions have a multifocal presentation, and this can help a clinician to narrow down their differential diagnosis. Nevoid basal cell carcinoma syndrome or periapical cemental dysplasia are examples of these conditions.[5]

Shape: The shape of a lesion can be described as round/circular, scalloped, or irregular. Cysts usually present as circular lesions because of their hydraulic nature of expansion. A scalloped shape can reflect the way in which a lesion grows within the jaw with minimal expansion and up in between the roots of teeth. This is typical of keratocystic odontogenic tumors (KCOTs) and simple bone cysts (SBCs).[5]

Periphery: Borders can be described as well-defined or ill-defined. Well-defined borders are easily traceable, while ill-defined borders tend to blend into the surrounding trabecular bone with a wide zone of transition. Well-defined borders usually indicate slow growth benign behavior. Well-defined borders that are corticated can further be described in terms of the thickness and continuity of the cortication.

Such borders are often seen in cysts and benign tumors. In contrast, ill-defined borders often indicate aggressive behavior and are associated with malignancies or, in some cases, inflammation.[5]

Internal structures: The internal architecture of a lesion can be described by its radiodensity and the presence of internal septae. Radiodensity depends on the lesion's internal contents which can range from air, fluid and soft tissue, which would appear more radiolucent, to cortical bone or enamel, which would appear radiopaque. When a lesion contains internal structures with varying calcifications, it is described as mixed. The type of calcified structures within mixed lesions may include bone, teeth, amorphous or dystrophic calcifications, and can provide an indication of tissue origin. When a lesion consists of only one chamber, it is unilocular. When it is divided by septae into two or more chambers, it is considered multilocular. The pattern of internal septae can also aid in diagnosis as different multilocular lesions have characteristic appearances. For example, the septae in ameloblastomas tend to be curved and thick, while those in central giant cell granulomas appear more fine and wispy.[5]

Effects on surrounding structures: The behavior of a lesion can manifest in how it affects the normal structures around it. These structures include the surrounding anatomic boundaries, the adjacent alveolar and cortical bone, mandibular or incisive canals, and nearby teeth. Benign, space occupying lesions tend to cause expansion and thinning of cortical bone, as well as displacement of teeth and the mandibular canal. In contrast, aggressive lesions are more likely to cause cortical destruction of the alveolus and the mandibular canal.[5] Resorption of teeth occurs more commonly in benign or long-standing conditions, and is characteristic of certain lesions such as ameloblastomas.[6]

The accurate identification of radiographic signs and ability to characterize the lesion is important to the process of developing a reasonable differential diagnosis, and the ability to do this may be influenced by the imaging modality employed. The following section describes the physical principles of panoramic radiography and cone beam computed tomography, as well as the capabilities and limitations of each modality.

Imaging Modalities: Panoramic Radiography and Cone Beam Computed Tomography (CBCT)

Panoramic imaging involves a thin x-ray beam that passes through the patient's head and is captured by a detector behind a slit-shaped shield, both of which are rotating around the patient at the same speed as the x-ray source.[7] Only the jaws, which fall within a horseshoe-shaped image layer, are minimally distorted while all other objects outside the image layer appear blurred.[8] This mode of acquisition means that all anatomic structures that are in the path of the x-ray beam are represented on the final image. Panoramic radiographs are advantageous for providing an overview of the maxilla and mandible in a single image.[7,8] The effective radiation dose from a panoramic radiograph is also generally lower than that of a CBCT, and significantly less than an intraoral full mouth series.[1]

The limitations of panoramic radiographs are largely related to how the panoramic image is acquired. As mentioned previously, the passage of the x-ray beam through the patient's head results in the superimposition of all structures that the beam encounters.[8,9] This compression of complex 3-dimensional anatomy onto a flat, 2-dimensional image often makes interpretation challenging, especially in the maxilla because of its approximation to the surrounding facial bones. The presence of air shadows and ghost images can further complicate image interpretation. Panoramic radiographs are also sensitive to patient positioning errors, which can worsen the distortion that is already inherent in this technology. The unequal magnification in the horizontal and vertical dimensions also makes measurements on these images unreliable.[8,9]

Despite these limitations, the accessibility and availability of panoramic units means that it is the often the first-line imaging modality for visualizing pathology, especially when the region of interest is larger than what can be seen on a periapical or bitewing radiograph. However, with the increasing availability of CBCT, clinicians now have an additional tool in their imaging armamentarium for their diagnostic needs.

CBCT units also involve an x-ray source and a detector that revolve around the patient's head simultaneously. However, instead of a narrow rotating beam that forms one seamless 2D image, a cone-shaped x-ray beam rotates 180 – 360º around the region of interest and acquires 100 to more than 600 basis projection images.[10,11] These images are reconstructed using a filtered back projection algorithm to

form a 3D volume, which can be navigated in various orientations slice by slice.[10,11] This system provides unobstructed views of anatomic structures in their precise location in any plane, and offers perspective on spatial relationships. These views include the orthogonal axial, sagittal and coronal planes as well as the non-orthogonal multiplanar reformatted (MPR) views.[8–10,12] The ability to view structures simultaneously in different planes provides CBCTs with a large advantage over panoramic radiographs.[10] Other advantages include the lack of magnification and distortion, as well as the ability to make accurate measurements because of the isotropic voxels that form the basic unit of each CBCT scan.[9–11]

Although CBCT has many advantages over panoramic radiographs, it does have its own set of limitations. One major limitation of CBCT over panoramic radiography is the increased radiation dose to the patient.[13] Data from the atomic bomb survivors demonstrate a relationship between radiation exposure and cancer-induction.[14] Although radiation doses encountered in dental imaging are exponentially smaller than atomic bomb doses, the currently held linear-non-threshold (LNT) theory assumes that the risk of stochastic effects is present even at low levels of radiation, with risk increasing proportionally to dose.[14] In a 2012 review by Lorenzoni *et al*, using 2005/2007 International Commission on Radiological Protection (ICRP) weighting factors, the effective dose of a digital panoramic radiograph ranged from 2.7 to 24.3 μSv.[1] The dose range of a 10 to 15cm medium FOV CBCT volume which would encompass the same structures as a panoramic radiograph was 48 to 680 μSv.[1] These numbers must be interpreted with caution as the actual effective dose could vary based on the actual volume of radiation-sensitive tissues scanned as well as the imaging parameters used.[1] In a 2014 meta-analysis, Ludlow *et al* reported effective dose of a medium FOV CBCT to be 9 to 560 μSv in adult phantoms.[15] However, these values included low-dose scan protocols. When only standard protocols were considered, the range was 47 to 560 μSv with average being 177 μSv.[15]

CBCTs are also susceptible to various artefacts, which can impair visualization of the structures of interest. The sources of these artefacts include metallic restorations, patient motion, inadequate scanner calibration, volume averaging and undersampling.[8,10,16] CBCTs also have poor soft tissue contrast as a result of Compton scattering, which occurs because the divergent cone-shaped beam is attenuated by

peripheral structures, instead of only the structures of interest in the direct path of the beam.[10,16] This restricts the usefulness of CBCT to the evaluation of osseous structures.[10]

With the introduction of any new imaging modality, the modality must be evaluated to determine whether it is at least as efficacious as the existing diagnostic tools in terms of image quality factors and its benefit to clinicians, patients and society. Fryback and Thornbury developed a hierarchical model consisting of six levels, which provides a framework for the various aspects above to be analyzed.[17] The levels of their hierarchy are briefly described using CBCT as the imaging modality in question:

- Level 1, Technical efficacy: Image quality parameters of the CBCT are assessed. Examples include brightness, contrast, resolution and sharpness.
- Level 2, Diagnostic accuracy efficacy: The ability of an observer to make an accurate diagnosis from a CBCT is assessed through measures of diagnostic performance such as sensitivity, specificity, positive and negative predictive values and receiver operating characteristic (ROC) curves.
- Level 3, Diagnostic thinking efficacy: This level assesses whether a CBCT is helpful in changing the clinician's opinion of their diagnosis, for example, whether the differential diagnoses remains the same or whether their confidence level about their diagnosis changes.
- Level 4, Therapeutic efficacy: The focus shifts from a diagnostic standpoint to treatment planning. This asks whether CBCT changes the way that the clinician chooses to manage the patient and whether CBCT was helpful in treatment planning.
- Level 5, Patient outcome efficacy: This level evaluates whether patient outcomes have been improved with the use of CBCT. Here, the costs and benefits using CBCT are weighed against each other. Parameters may include patient morbidity, life expectancy, quality of life, pain, monetary costs and radiation dose.
- Level 6, Societal efficacy: The final level weighs the overall cost and benefit of CBCTs to society, and can have an impact on how healthcare resources are allocated.

The diagnostic benefit of CBCTs in various dental specialties has been widely investigated, but the number of publications that evaluate the efficacy of CBCT for oral and maxillofacial pathology are limited. A review of the available literature appears below.

Efficacy of CBCT in Dentistry

The use of CBCT for dentoalveolar pathology such as caries, periodontitis and endodontic conditions was reviewed by Tyndall & Rathore in 2008.[18] They reported that the diagnostic yield of CBCTs for proximal caries had equivocal reports, while studies examining the use of CBCTs for occlusal caries were limited. A more recent review article by Park *et al* in 2011 drew similar conclusions in that the diagnostic efficacy of CBCT for proximal and occlusal caries detection was inconclusive, with a trend towards an increase in sensitivity, but also accompanied with a concurrent decrease in specificity.[19] In another review, Wenzel concluded that CBCT could not be recommended as the main imaging modality for detecting proximal cavitations due to the drawbacks of radiographic artefacts, cost and radiation dose.[20] The published guidelines from the Safety and Efficacy of a New and Emerging Dental X-ray Modality (SEDENTEXCT) project also stated that caries diagnosis was not an indication for CBCT usage.[13]

In periodontology, Walter *et al* published a systematic review in 2016, with a focus on the benefit of CBCT for diagnosis and treatment planning furcation-involved teeth and vertical bone defects.[21] From the five studies that were included, the reviewers concluded that CBCT has high diagnostic accuracy for both situations in molar teeth. CBCT was shown to provide financial cost benefits and time-savings for furcation-involved maxillary molars, especially for more complex treatments involving maxillary second molars.[21,22] There was no cost-benefit data available for the use of CBCT for vertical bone defects, and no evidence supporting its routine use.[21] Later that year, Nikolic-Jakoba *et al* also published a review of the diagnostic efficacy of CBCT for intrabony defects and furcations, with an overlap of some of the studies included in Walter *et al*'s review.[23] The authors included 16 studies and found that most of them were assigned to level 2 (diagnostic accuracy efficacy) on the Fryback and Thornbury hierarchical model. While the literature showed that CBCT provided higher diagnostic accuracy of the above defects compared to conventional 2D modalities, the authors pointed out that the applicability to actual clinical situations may

be limited as the ex-vivo studies utilized artificially induced periodontal defects, and the CBCT scans used were not subject to motion artefacts. The authors also highlighted the other drawbacks of CBCT which include artifacts and increased radiation doses compared to panoramic radiographs, and the fact that were currently no guidelines for the use of CBCT for periodontology.[23] The authors of both systematic reviews recommended that clinicians should apply the ALARA (as low as reasonably achievable) principle in each clinical situation encountered.[21,23]

In endodontic applications, CBCT has been used for diagnosis of periapical lesions, evaluation of both root and canal morphology, identification of internal and external root resorption, and assessment of iatrogenic complications.[18,24] A systematic review by Rosen *et al* evaluated the diagnostic efficacy in CBCT in endodontics based on Fryback and Thornbury's efficacy model.[25] They found that most studies were assigned to level 2 and there were limited publications at higher levels, indicating that current scientific evidence supporting the use of CBCT in endodontics is still not robust. A similar review by Kruse *et al* evaluated the specific application of CBCT for diagnosis of periapical lesions.[26] They also found that all but one study in their review was at level 2. They concluded that CBCT showed an increased detection and accuracy of periapical lesions in ex-vivo studies. However, they also noted that these results may not be applicable to actual clinical scenarios since the periapical defects were artificially simulated, and there was a lack of clinical studies that used a histological gold standard.[26] With the current available evidence substantiating the use of CBCT in endodontics, the most recent position statement released by the American Association of Endodontics(AAE)/American Academy of Oral and Maxillofacial Radiology (AAOMR) provides conservative guidelines and recommendations for the use of CBCT where the diagnostic yield is predicted to outweigh the risks of radiation.[3]

Although Tyndall & Rathore also mentioned the use of CBCT for detection of root fractures, this has since proven to be controversial.[18] In 2016, Talwar *et al* published a meta-analysis evaluating the use of CBCT for diagnosing vertical root fractures (VRFs).[27] In the same year, a systematic review by Chang *et al* also assessed the use of CBCTs for diagnosing VRFs in root canal treated teeth.[28] Talwar *et al* found that CBCTs demonstrated higher sensitivity than periapical radiographs in detecting VRFs in both filled teeth which contain root-fills or metallic posts, and unfilled teeth, and higher specificity in unfilled teeth.

CBCTs had lower specificity for VRF detection in filled teeth, which they attributed to the presence of artefacts that resemble fracture lines. Overall, the diagnostic odds ratio of CBCT was higher than periapical radiographs for unfilled teeth, while there was no significant difference between both modalities in filled teeth, although periapical radiographs performed slightly better.[27] Chang *et al* reported in their systematic review that there was limited evidence that CBCTs were efficacious for accurately diagnosing VRFs, and that a detailed clinical examination prior to acquiring a CBCT was necessary to improve the chances of fracture detection.[28]

In the field of orthodontics, the area in which CBCT has been shown to provide the greatest enhancement to diagnosis and treatment planning is in the localization of impacted canines.[29–32] A study by Hodges *et al* also evaluated the impact of CBCT in orthodontics.[33] They found that the participants tended to change their diagnosis and treatment plans more often when patients appeared to have unerupted teeth, root resorption or severe skeletal deviations. These findings were in agreement with the recommendations published by the AAOMR for the use of CBCT in orthodontics.[2] The conditions for which a pre-treatment CBCT is likely to be indicated are for dental anomalies, which include impacted teeth and supernumeraries, ectopic teeth, variations in tooth number or morphology, and internal and external root resorption.[2]

In the same position statement, CBCTs were only recommended as "possibly indicated" in the setting of moderate to severe temporomandibular joint (TMJ) signs and/or symptoms.[2] A review article published by Larheim *et al* on the diagnostic value of CBCT in TMJ evaluation found that the available evidence mostly belonged to levels 1 and 2 on the Fryback and Thornbury hierarchical model.[34] The diagnostic information gained from the use of CBCT in these studies was also found to be limited to the description of morphological and osseous changes.[34] There was only one study that evaluated the impact of CBCT on diagnosis and management of TMJ disorders.[35] The authors reported that clinically relevant changes were made to the differential diagnosis in 28% of the patient sample, and to the actual management in 15% after viewing the CBCT images.[35]

In oral surgery, the application of CBCT includes evaluation of impacted and supernumerary teeth, trauma, implant planning, pre-orthognathic surgical planning, cleft management, TMJs and

pathology.[36] A review of the efficacy of CBCT for evaluating impacted mandibular third molars concluded that CBCT was helpful in judging the spatial relationship of the third molars to the mandibular canal, a level 2 application on the Fryback and Thornbury model.[37] The authors stated that there was otherwise very limited evidence at higher levels, and conventional radiographs would suffice in most situations.[37] A more recent study by Wolff *et al* which evaluated the clinical impact of CBCT found that CBCT provided more surgically relevant information than panoramic radiographs for implant treatment, maxillary sinus conditions and trauma, but not for removal of third molars, bony pathosis, TMJ disorders or pain diagnoses.[38] In addition, CBCT did not demonstrate any significant impact on the surgical treatment plan in any of the above categories.[38] In contrast, Kaeppler *et al* reported that the use of CBCT led to treatment plan changes in 9.52% of their study sample of mandibular fractures.[39]

Efficacy of CBCT for Evaluating Intraosseous Maxillofacial Pathology

There are a limited number of studies comparing the diagnostic efficacy of panoramic radiographs (PAN) and CBCT for intraosseous pathology in the oral and maxillofacial region. Two studies involve comparing mandibular invasion of squamous cell carcinoma based on PAN and CBCT[40,41], while another study compared radiographic signs of bisphosphonate-related osteonecrosis of the jaw bone (BRONJ).[42]

In the study by Momin *et al*, the extent of alveolar bone and mandibular canal involvement by gingival carcinoma was evaluated in 50 patients who had panoramic radiographs and CBCT volumes.[40] The gold standard used was histopathologic examination of the mandible post-mandibulectomy. The authors found that the Az values of receiver operating characteristic (ROC) analysis for CBCT was significantly higher than for panoramic radiographs, indicating that CBCT was superior for detecting mandibular invasion. The sensitivity of CBCT for evaluating both alveolar bone and mandibular canal involvement was found to be significantly superior to panoramic radiographs. Specificity was inferior but not statistically significant. The authors cautioned that the sensitivity of CBCT for detecting alveolar bone involvement was considered to be low (89%), and was more prominent in the cases with shallow alveolar

invasion that was obscured by metal artefacts and noise. The authors highlighted this as the limitations of the imaging modality.[40]

Hendrikx *et al* also compared mandibular invasion of oral squamous cell carcinoma on panoramic radiographs, CBCT, and MRI in 23 patients, confirmed by histopathological examination of resection specimens.[41] The results showed that CBCT outperformed panoramic radiographs in sensitivity, specificity, positive and negative predictive values, and overall test efficiency. However, statistical significance could not be achieved due to the small sample size.[41]

Kämmerer *et al* compared the radiographic findings of 14 BRONJ patients on PAN and CBCT, and found statistically significant differences in the visibility of periosteal changes, osteosclerosis, bone remodeling, integrity of cortical bone and bony sequestra.[42] The effects of imaging on treatment-planning decisions were also investigated. In their survey of eight oral surgeons who were initially only presented with clinical photos, half of them changed their treatment approach with radiographic imaging, and reported CBCT as being responsible for the change.[42]

Multiple articles described the usefulness of CBCT in the diagnostic process and management of specific pathology, but did not provide a quantitative comparative assessment of radiologic signs on CBCT and panoramic radiographs, nor its clinical impact. These reports are briefly presented below. They are preceded by a broadly-scoped article by Ahmad & Freymiller[43], and are subsequently organized by benign lesions, malignancies and inflammatory conditions.

Ahmad & Freymiller presented a broad overview of the utility of CBCTs in various disease categories, including benign cysts and tumors, malignancies and inflammatory conditions.[43] In benign lesions, MPR views can demonstrate expansion, internal contents, reaction of surrounding trabecular bone, extent of osteolytic changes and cortical involvement, while 3D volume renders can provide information about morphology and spatial relationships.[43] CBCTs could also be useful for detecting small intraosseous malignancies, which may otherwise be obscured on 2D radiographs.[43] Finally, inflammatory changes such as periosteal proliferations and bone sequestrum may be more detectable on CBCT due to the ability to navigate through thin image slices and to adjust brightness and contrast.[43]

The authors of a case series of four keratocystic odontogenic tumors (KCOTs) evaluated the usefulness of CBCT compared to panoramic radiographs.[44] They described the ability of CBCTs to reveal expansion of a KCOT into the nasal cavity in one case, and multilocularity in another case, all of which were not obvious on the initial panoramic radiographs. The authors concluded that CBCT was useful for providing information about the lesions' borders as well as anatomic relationships. However, these features were not formally compared between the imaging modalities.[44]

In another case series involving seven desmoplastic ameloblastomas, radiologic findings on panoramic radiographs and CBCTs were collected.[45] Although statistical analysis was not performed, the data showed a lack of complete agreement between the two modalities in terms of lesions' locularity, border definition and internal contents. The authors also used CBCTs to describe lesion expansion, cortical erosion and involvement of the mandibular canal and maxillary sinus. In their conclusion, CBCT was valuable for describing lesion borders, internal contents, expansion and involvement of surrounding structures.[45]

In a case report of an odontogenic myxoma, CBCT was deemed crucial in developing the differential diagnosis as it revealed a pattern of internal septae which are characteristic of myxomas and helped to differentiate it from other similar-appearing lesions including ameloblastomas and KCOTs.[46] This finding was not found to be obvious on the other radiographs that were acquired, which consisted of panoramic, periapical and conventional CT. Thinning of the lingual and buccal cortical plates was also highlighted on the CBCT[46]. The same author published another study evaluating the characteristics of enostosis based on panoramic radiographs and CBCT.[47] Although the study aimed to compare radiographic features between the two modalities, no comparisons were made. Information about the sites, density, margins, relationship to teeth was gathered from the panoramic radiographs, while the relationship to cortices and shape was determined based on CBCT.[47]

CBCT was shown to be helpful in a case report of a calcifying cystic odontogenic tumor (CCOT) associated with an odontoma.[48] The authors stated that appropriate treatment planning could only be carried out after the CBCT scan demonstrated the presence of an expansile, cyst-like lesion and its relationship with an odontoma, since the margins were not well-visualized on intraoral radiographs. In a

separate report of a CCOT, the detailed internal pattern of calcifications which could not be seen on the panoramic image was visible on CBCT, and its peripheral pattern helped the clinicians to distinguish this CCOT from an adenomatoid odontogenic tumor (AOT).[49] The authors emphasized the importance of CBCT in providing information about the internal content, extent and anatomic relationships of lesions, which is often obscured on conventional 2D radiographs.[49]

In a case series of three mandibular cancers, patients had multiple clinical and radiographic investigations including panoramic radiographs, MRI and CBCTs.[50] In two of the cases, the CBCT demonstrated greater involvement than was initially obvious on the panoramic radiographs or the MRI and this led to a change in the cancer staging and diagnosis of these patients, which also affected survival prognosis. In one patient, the surgical treatment plan was also altered. In both of these cases, the cancers were located in the anterior mandible, and the limitation of panoramic radiography in imaging this region was highlighted. CBCT was helpful in overcoming these deficiencies and was able to provide information about the size and extent of invasion of the cancers.[50]

The usefulness of CBCT in detecting subtle changes was also demonstrated in a study of patients with BRONJ.[51] The observers were asked to evaluate CBCT and panoramic images for lytic or sclerotic changes, bony sequestra, periosteal reactions, effect on the cortex, mandibular canal, maxillary sinus and soft tissue. Although the authors did not report on the agreement/discordance between two modalities, they described the ability of each modality to detect those radiographic signs at the various stages of disease severity. For example, in the early stages, they found that CBCT was able to detect osteosclerosis and cortical thickening, while panoramic radiographs could not. In the more extensive stages of the disease, both modalities were able to demonstrate osteosclerosis. However, discrete details were more visible on CBCT, and the full extent of the lesion could be visualized in 3 dimensions.[51]

In another descriptive study of seven BRONJ cases, PANs and CBCTs were compared for assessment of bony cortices, sequestra, osteolysis, osteosclerosis, bone mottling and extraction-related sequelae.[52] The authors reported that both modalities had good agreement, but CBCT was better able to demonstrate the detail and extent of disease. In two cases, extraction-related findings such as oro-antral communication and persistent socket which were not seen on PANs could be detected on CBCTs. In spite

of these findings, the authors cautioned that additional research proving the diagnostic benefit of CBCT is necessary before imaging guidelines can be developed.[52]

Guidelines for Imaging Intraosseous Maxillofacial Pathology with CBCT

In the 2008 executive opinion statement issued by the AAOMR on the use of CBCT, it was recommended that among other responsibilities, clinicians should have knowledge of the indications of CBCTs.[53] However, unlike other clinical specialties in which position statements have been issued, there are currently no specific parameters from the AAOMR for imaging intraosseous maxillofacial pathology. In the SEDENTEXCT project, the Panel offers two basic guidelines for imaging bony pathology.[13] Firstly, conventional CT or MRI is recommended over CBCT if the soft tissues need to be evaluated. Secondly, if the diagnosis of bony involvement from oral carcinoma affects the treatment plan yet cannot be adequately assessed on conventional CT or MRI, a limited FOV, high resolution CBCT can be used.[13]

Without additional guidelines which are applicable to a wider range of pathology, clinicians are left with relying on basic principles. While these may be rationally sound, they are inadequate in providing clinicians direction with regards to which situations CBCTs would provide maximum benefits. The European and American councils and academies are in consensus regarding these general principles, which are listed below:

- CBCT examinations should be based on patient history and a detailed clinical examination. [8,13,54–56]
- CBCTs should only be indicated if lower-dose imaging such as panoramic radiographs cannot provide the diagnostic information that is necessary, and it is anticipated that CBCT can provide the additional information.[8,13,55]
- Justification: There must be evidence that the CBCT will provide benefit to the patient, which outbalances the risk of radiation.[14,54–56]
- Optimization: The amount of radiation involved in the radiographic examination should be As Low As Reasonably Achievable (ALARA).[8,53,56,57] This could be achieved by using the smallest necessary FOV or the most appropriate resolution at the lowest dose for the diagnostic task.[55]

Rosen *et al* proposed a case selection algorithm for the indication of CBCTs based on a risk-benefit analysis.[57] Their suggested decision-making process follows this sequence of assessments: "Need, Benefit, Benefit vs Risk". Firstly, if the information gathered from the patient's history, clinical examination and lower-dose conventional radiographs is sufficient for the diagnostic task, then CBCT is not needed. However, if the above information is insufficient, the decision-making proceeds to the next level in their algorithm. At this level, the authors submit that CBCT must have been proven to be diagnostically efficacious for the clinical task. If there is no scientific evidence of diagnostic benefit, then the CBCT is not indicated. At the final level of their algorithm, they state that the potential benefits must exceed the potential risks of the CBCT examination with regards to the possible long-term health effects.[57]

The benefits of CBCTs for imaging maxillofacial pathology are indisputable. However, it is important to know specifically what these benefits are and when they will be maximized. The critical questions that need to be asked are: What information does a CBCT volume provide that a panoramic radiograph does not? Which radiographic signs change when a CBCT is used? Does this increase the accuracy of differential diagnosis made by an oral radiologist, or their confidence levels? These are the questions that we aim to address in this manuscript. When these questions are answered, an attempt can be made to identify specific radiographic signs or disease characteristics on panoramic radiographs that may be predictive of when a CBCT is likely to provide maximum diagnostic benefit. This evidence can then be used as the foundation for developing selection criteria.

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MANUSCRIPT

Introduction

Radiographic imaging plays a crucial role in the diagnosis and treatment planning of intra-osseous pathology in the oral and maxillofacial region. The radiographic features of a lesion can provide insight about its characteristics and behavior. Some of these features include the location, shape, periphery, internal contents and the lesion's effects on surrounding structures. These enable a lesion to be classified under one or more of the following categories: inflammatory, fibro-osseous lesions and diseases of bone, cysts and cyst-like lesions, and benign or malignant tumors. Following this, the clinician can use the information to aid in designing the appropriate management plan.

The ability to identify radiographic signs accurately may be influenced by the imaging modality employed. Common imaging modalities for dental and maxillofacial pathology include two-dimensional panoramic radiographs, or three-dimensional cone beam computed tomography (CBCT). Panoramic images are formed by a rotating x-ray beam that passes through the patient's head to a detector on the opposite side.[7] Panoramic radiographs are advantageous for providing an overview of the maxilla and mandible in a single image.[7,8] However, there are also many limitations associated with this modality, including superimposition of structures, air shadows, ghost images, sensitivity to patient positioning errors and distortion resulting from unequal magnification in the horizontal and vertical dimensions.[8,9]

In contrast, CBCT scans are composed of 100 to more than 600 basis projection images which are reconstructed to form a 3D volume.[10,11] This can be navigated slice by slice in various planes, which includes orthogonal axial, sagittal, coronal as well as non-orthogonal multiplanar reformatted (MPR) views.[8,10–12] This provides unobstructed views of anatomic structures in their precise location in any plane, which can offer perspective on spatial relationships. This is a large advantage of CBCT over panoramic radiographs.[10] Other advantages include the lack of magnification and distortion, as well as

the ability to make accurate measurements because of the isotropic voxels that form the basic unit of each CBCT scan.[9–11]

CBCTs have their own drawbacks, which include susceptibility to various artefacts as a result of metallic restorations, patient motion, inadequate scanner calibration, volume averaging and undersampling.[8,10,16] CBCTs also have poor soft tissue contrast which limits the usefulness of CBCT to the evaluation of osseous structures.[10] The increased radiation dose compared to panoramic radiographs is the most significant concern. The effective dose of a digital panoramic radiograph ranges from 2.7 to 24.3 μSv[1]. The effective dose of a medium field of view (FOV) CBCT volume has been reported to range from 48 to 680 μSv[1], although low-dose protocols can reduce the radiation exposure to as low as 9 μSv[15]. Since CBCTs result in higher radiation doses than panoramic radiographs for the same field of view, it is important to know which imaging modality maximizes diagnostic information at the lowest possible radiation dose.

While there appear to be significant benefits of CBCTs for imaging maxillofacial pathology, it is important to know specifically what these benefits are and when they will be maximized. In the 2008 Executive Opinion Statement issued by the American Academy of Oral and Maxillofacial Radiology (AAOMR) on the use of CBCT, it was recommended that among other responsibilities, clinicians should be familiar with the indications for CBCTs.[53] However, unlike other clinical specialties in which position statements have been issued, there are currently no specific parameters from the AAOMR for imaging intraosseous maxillofacial pathology.

The first objective of this study is to determine whether the radiographic features of intraosseous lesions differ between the two imaging modalities. The second objective is to determine whether the imaging modalities have any clinical impact in terms of providing accurate differential diagnoses or changing the confidence levels of oral and maxillofacial radiologists in their evaluation of gnathic lesions.

Materials and Methods

This study was approved by the University of North Carolina at Chapel Hill (UNC) Institutional Review Board (IRB) (Study #15-1328). Waivers of informed consent for research and Health Insurance

Portability and Accountability Act of 1996 (HIPAA) authorization were provided. An electronic search of patient records at the UNC School of Dentistry was conducted by the School of Dentistry's Office of Computing and Information Systems (OCIS). Cases were also requested from UNC oral and maxillofacial surgeons and from the School of Dentistry CBCT log. The search strategies are detailed in Appendix 1. A total of 498 cases were retrieved and reviewed, and case selection was performed based on the following criteria:

Inclusion criteria:

- Subjects must have had biopsy-proven intraosseous pathology located within the maxilla or the mandible
- Subjects must have had a digital panoramic radiograph (PAN) and CBCT taken within 3 months of each other
- Pathology is demonstrated on the PAN and/or CBCT
- If pathology is recurrent, the recurrences must also be biopsy-confirmed
- If the lesions were multifocal, the lesion which was biopsied was selected. If there were multiple sites were biopsied, then the largest lesion was selected.

Exclusion criteria:

- Soft tissue pathology
- Incomplete records- PAN, CBCT or biopsy results could not be retrieved
- Inconclusive biopsy results
- PAN or CBCTs that are of poor diagnostic quality i.e. blurring due to patient motion
- PAN or CBCTs that do not include entire region of interest or the contralateral side of the jaw
- Biopsy or surgery must not have been performed in between when PAN and CBCT was taken
- Surgical defects which mask the appearance of a lesion
- Lesion was removed prior to acquisition of PAN or CBCT

The final sample consisted of 33 subjects. PANs were exported as Tag Image File Format (TIFF) images while CBCTs were exported as Digital Imaging and Communications in Medicine (DICOM) files. All

PANs and CBCTs were de-identified and randomized on www.random.org. In order to prevent memory bias, PANs and CBCTs belonging to the same subject were not placed in consecutive viewing order.

Each PAN and CBCT was labeled with a new assigned ID and a description of the lesion's location. For each PAN, the label was embedded within the image using GIMP (GNU Image Manipulation Program) 2.8.16 (https://www.gimp.org). For each CBCT, the label was used as both the file name and the "Patient Name". For cases that had multifocal lesions, observers were made aware of its multifocal nature in the lesion description, which was preceded with "(MF)". The lesion that they were asked to describe was the one for which the location was provided. Figure 1 shows an example of a PAN and a screen-capture of a CBCT that observers reviewed.

The images and volumes were provided to the observers for viewing in the sequence of 5 PANs, 5 CBCTs, 5 PANs, 5 CBCTs etc. The PANs were viewed on MiPACS Dental Enterprise Viewer 3.1.1404 (Medicor Imaging, 1927 South Tryon Street, Suite 200, Charlotte, NC 28203) while the CBCTs were viewed using InVivo 5.4.5 by Anatomage (Anatomage, 303 Almaden Blvd, Suite 700 San Jose, CA 95110).

The expert observers consisted of three Board-certified oral and maxillofacial radiologists with 34, 25 and 5 years of experience as specialists. All observers first underwent a calibration session for standardization. During the observation sessions, the observers reviewed the PANs and CBCT volumes in a dimly-lit room, using a monitor with a resolution of at least 1680 x 1050. No clinical information was provided. Observers were allowed to navigate and manipulate the images to adjust magnification, brightness and contrast, and also to create volume renders and custom-sections on the CBCTs. After reviewing each PAN or CBCT, the observers were asked to complete a case report form on Qualtrics (https://software.unc.edu/qualtrics/) to answer questions about lesion features, to provide up to three differential diagnosis and state their level of confidence for each differential diagnosis. No time restrictions were imposed.

On the case report form, Questions 1 to 12 pertained to lesion features and Question 13 asked for differential diagnoses and confidence levels. For the cases with multifocal lesions, observers were asked to answer Questions 1 to 12 only based on the lesion indicated in the location description.

However, they were allowed to consider the appearance and presence of the other lesions when answering Question 13. To test for intra-observer agreement for lesion features (Questions 1 to 12), observers were asked to review 10 randomly selected PANs and 10 CBCTs again after a "wash-out" period of at least four weeks. The questions and possible answers options on the case report form were as follows:

Q1. What is the lesion's shape?

a. Round/ovoid

b. Scalloped

c. Irregular (not round, ovoid or scalloped)

d. Cannot tell

Q2. Are its borders well-defined?

a. Yes

b. No

c. Cannot tell

Q3. Are its borders well-corticated in terms of thickness?

a. Yes

b. No

c. Cannot tell

Q4. Are its borders continuously corticated?

a. Yes

b. No

c. Cannot tell

Q5. The lesion's internal contents are mostly:

a. Radiolucent on panoramic image/ Equal to soft-tissue density or lower on CBCT

b. Mixed

c. Radiopaque on panoramic image/ Equal to bone density or higher on CBCT

d. Cannot tell

Q6. Is the lesion multilocular?

a. Yes

b. No

c. Cannot tell

Q7. Does the lesion appear to be affecting the incisive canal or the inferior alveolar canal? (This can include expansion, displacement or destruction)

a. Yes

b. No

c. Cannot tell

Q8. Does the lesion appear to expand the normal surrounding anatomic boundaries?

a. Yes

b. No

c. Cannot tell

Q9. Does the lesion appear to be causing cortical thinning?

a. Yes

b. No

c. Cannot tell

Q10. Does the lesion appear to be causing cortical destruction?

a. Yes

b. No

c. Cannot tell

Q11. Does the lesion appear to be causing tooth displacement?

a. Yes

b. No

c. Cannot tell

Q12. Does the lesion appear to be causing root resorption?

a. Yes

b. No

c. Cannot tell

Q13. i. List up to three differential diagnoses in order of rank.

ii. State your confidence level for each differential from 1 to 5

(5 = Very confident 4 = Confident 3 = Somewhat confident 2 = Slightly confident 1 = Not confident at all)

Differential diagnosis #1: _____ Confidence level: ____

Differential diagnosis #2: _____ Confidence level: ____

Differential diagnosis #3: _____ Confidence level: ____

Statistical analysis:

For objective 1, there was an insufficient number of "Cannot tell" responses for Questions 1 to 12 to create a category of its own for statistical analysis. Thus, "Cannot tell" responses were excluded from analysis. After exclusion, Question 1 (lesion shape) and Question 5 (internal contents) were ternary with 3 remaining possible response options. All other lesion features were binary, with only Yes/No response options.

Simple kappa statistics were computed for each observer to assess the concordance between the responses given by that observer for the pairs of PANs and CBCTs. PROC FREQ (SAS v. 9.4) (SAS Institute Inc, 100 SAS Campus Drive Cary, NC 27513) was used for all assessments of concordance and discordance.

Conditional logistic regression was used to account for the correlated data structure and assess whether there were differences in the odds of a "Yes" response between PAN and CBCT, controlling for observer effect. PROC LOGISTIC (SAS v. 9.4) was used for analyzing all binary lesion features. Conditional logistic regression could not be performed on Question 1 (lesion shape) and Q5 (internal

contents). Cochran-Mantel-Haenszel test with general association statistics was used to assess for associations between modality with lesion shape and internal contents.

Intra-observer and intra-observer agreement was reported as percent agreement. "Cannot tell" responses were retained in these calculations for in order to assess raw agreement.

For objective 2, PROC FREQ (SAS v. 9.4) was used to perform four Cochran-Mantel-Haenszel tests with row mean scores differ statistics. This test was used to account for the ordinality of the response variables and the correlated data structure. The tests were used to assess whether there was a difference in: the distribution of when correct diagnosis was obtained between the two modalities and the distribution of weighted confidence scores when correct diagnosis was obtained between the two modalities. The weights assigned for confidence levels were: 3 points if the observer stated the correct diagnosis on their first differential diagnosis; 2 points on the second differential diagnosis; 1 point on the third differential diagnosis; and 0 points if the correct diagnosis was not given. Level of significance was set at 0.05 for all analyses.

Results

All 3 observers evaluated all 33 cases, consisting of a total of 66 PANs and CBCTs. Cases 13 and 31 were excluded from analysis as one observer had provided the CBCT report for Case 31 within the past 6 months as part of patient's clinical care, and another observer reported recollection of Case 13. Statistical analysis was performed on the remaining 31 cases.

Table 1 shows the histopathological diagnosis, time-span between the acquisition of the PAN and CBCT and location details of the 33 lesions that were included in this study. Table 2 contains the summary of these lesions organized by category. The 33 cases reviewed included 10 benign tumors, 8 cysts, 5 lesions of bone, 3 fibro-osseous lesions, and 4 lesions belonging to miscellaneous categories.

Table 3 shows the overall agreement between PAN and CBCT with respect to lesion features. Kappa values ranged from 0.10 to 0.80. Strongest agreements between PAN and CBCT were seen with respect to lesions' internal contents (κ=0.74), effect on the incisive canal or inferior alveolar canal (IAC)

(κ=0.80) and tooth displacement (κ=0.73). Weakest agreements between PAN and CBCT were seen with respect to border definition (κ=0.28), expansion of surrounding anatomic boundaries (κ=0.19), cortical thinning (κ=0.10) and cortical destruction (κ=0.23).

Table 4 reports the odds ratio (OR) of a "Yes" response on CBCT compared to a "Yes" response on PAN for all lesion features except for shape and internal contents. There were statistically significant differences between PAN and CBCT with respect to border definition (OR=5.45, p=0.004), continuity of border cortication (OR=0.34, p=0.035), effect on the incisive canal or IAC (OR=6.38, p=0.043), expansion of surrounding anatomic boundaries (OR=18.56, p<0.001), cortical thinning (OR=30.22, p<0.001) and cortical destruction (OR=9.80, p<0.001). Examples of cases demonstrating these differences are shown in Figures 2 to 7. The odds ratios for the remaining lesion features were not statistically significant. Analysis with the Cochran-Mantel-Haenszel tests found no association between modality and lesion shape (p=0.28) or internal contents (p=0.43).

Table 5 summarizes the intraobserver agreement between the individual observers' original responses and their responses on the 10 repeated PANs and CBCTs. There was a high proportion of intraobserver agreements (61 out of 72 assessments) in the range of 80% to 100%. Lower intraobserver agreement was seen with Observer 1 with respect to cortical destruction and root resorption on CBCT (both 60%) and Observer 3 with respect to cortical destruction on CBCT (50%). Observers 1 and 3 appeared to be more consistent with themselves on PAN while Observer 2 displayed slightly higher intra-observer consistency on CBCT compared to PAN.

Table 6 reports interobserver agreement. Percent agreement is reported in a paired manner between observers for each modality. Interobserver agreement was varied and ranged from 51.61% to 100%. Lower interobserver agreement was seen between Observers 1 & 2 with respect to lesion shape on PAN (64.52%); between Observers 1 & 3 and Observers 2 & 3 with respect to continuity of border cortication on PAN (51.61%); between Observers 2 & 3 with respect to expansion on CBCT (64.52%); and between Observers 2 & 3 with respect to cortical thinning on PAN (61.29%).

Table 7 to Table 18 displays the pooled frequency tables of observer responses for each lesion feature, excluding the "Cannot tell" responses.

Table 19 contains the frequency table of whether observers provided the correct diagnosis in any of their differential diagnoses on PAN vs CBCT. In 24.73% of cases, observers did not provide the correct diagnosis on either PAN or CBCT. In 53.76% of cases, the observers provided the correct diagnosis on both the PAN and CBCT. In 11.83% of cases, the observers provided the correct diagnosis on CBCT, but not on PAN. The reverse is true in 9.68% of cases.

When only the first differential diagnosis was considered, the overall accuracy rate of correct diagnosis decreased on both PAN and CBCT. Table 20 contains the frequency table of whether observers provided the correct diagnosis in their first differential diagnoses on PAN vs CBCT. In 39.78% of cases, observers did not provide the correct diagnosis on either PAN or CBCT. In another 39.78% of cases, the observers provided the correct diagnosis on both the PAN and CBCT. In 9.68% of cases, the observers provided the correct diagnosis on CBCT, but not on PAN. The reverse is true in 10.75% of cases.

Analysis with the Cochran-Mantel-Haenszel tests showed that there was no association between the two modalities and the point at which the correct differential diagnosis was made, when controlling for multiple observers and case IDs (p=approx. 1)

Table 21 reports the average confidence levels of observers at the first differential diagnosis on PAN and CBCT, regardless of whether their diagnosis was correct. Observers 1 and 2 showed a slight increase in confidence levels on CBCT compared to PAN (3.94 vs 3.61 and 3.65 vs 3.55 respectively). Observer 3 had the same confidence levels on both PAN and CBCT.

Table 22 provides the frequency of confidence level changes for each observer from on PANs versus CBCT at the first differential diagnosis, regardless of whether their diagnosis was correct. Among all observers, there was no change in confidence levels with CBCT in one-half to two-thirds of the cases. Observer 1 had twice the number of cases (10) where CBCT led to an increase in confidence levels as opposed to a decrease (4). Observer 2 and 3 both had an approximately equal number of cases where CBCT led to an increase as well as a decrease in confidence levels.

In order to take the accuracy of differential diagnoses into consideration in the analysis of observer confidence levels, relative weights were provided according to the rank at which the correct differential diagnoses was provided. These weighted confidence levels on PAN and CBCT were then used

in the statistical analysis. Analysis with the Cochran-Mantel-Haenszel tests shows that there was no association between the two modalities and the weighted confidence levels at the point when correct differential diagnosis was made, when controlling for multiple observers and case IDs (p=0.45).

Discussion

With the introduction of any new imaging modality, the modality must be evaluated to determine whether it is at least as efficacious as existing diagnostic tools in terms of image quality factors and the risks and benefit to clinicians, patients and society. Fryback and Thornbury developed a hierarchical model consisting of six levels, which provides a framework for the various aspects above to be analyzed.[17] In this study, the use of CBCT for evaluating intraosseous pathology in the oral and maxillofacial region was evaluated at level 2 (diagnostic accuracy efficacy) and at level 3 (diagnostic thinking efficacy).

The various advantages of using CBCT for imaging pathology has been published previously, although only a few studies reported their findings in a quantitative manner.[40–42] The first objective of this study was to report the differences in radiographic signs of lesions on PAN and CBCT. Statistically significant differences were found with respect to border definition, continuity of border cortication, effect on the incisive canal or the IAC, expansion of surrounding anatomic boundaries, cortical thinning and cortical destruction. These radiographic signs will be discussed first, followed by the radiographic signs in which significant differences between PAN and CBCT were not found.

The most significant differences that presented between PAN and CBCT were in the expansion of anatomic boundaries (OR=18.56, p<0.001), cortical thinning (OR=30.22, p<0.001) and cortical destruction (OR=9.80, p<0.001). These are the areas in which CBCTs appear to provide the greatest benefit in terms of diagnostic information. Ahmad & Freymiller wrote that 2D images only are limited to providing mesiodistal and superio-inferior information, and the ability to view different planes on a 3D CBCT volume can provide buccolingual information that is missing from a panoramic image.[43] The limited size of a panoramic image also means that the full extent of a lesion may not be captured if significant expansion has occurred. This was demonstrated in a case report of an expansile giant cell lesion.[58] While

jaw enlargement was visible on the PAN, the entire mandible could not be captured on the radiograph and a CBCT was necessary to visualize the entire extent of expansion.[58] CBCTs can also reveal the buccal or lingual direction in which expansion is occurring.[45] This information may be valuable for surgical treatment planning, especially in the earlier stages of expansion where the direction of growth may not be discerned by clinical examination alone.

When lesion expansion reaches the cortical plates or the inferior cortex of the mandible, cortical thinning or destruction may manifest. Therefore it is not surprising that these three radiographic signs are in accord with each other. Cortical destruction occurs when the integrity of the cortical bone is disrupted, while cortical bone is considered to be thinned if it is still intact. These findings could be considered to lie on a spectrum of severity. Thinning of cortical bone is usually considered to be as a result of benign, space occupying lesions.[5] In contrast, aggressive lesions are more likely to cause cortical destruction of the alveolus.[5] However, these findings are not mutually exclusive and they are not limited to any particular category of disease. The ability of CBCT to demonstrate cortical thinning and/or destruction has been presented in multiple publications in a wide range of disease categories.[8,40–46,48–50,52,58–60] Demonstration of this radiographic sign and understanding the aggressiveness of a lesion's behavior can help a radiologist in developing their differential diagnoses. In their article, Ahmad & Freymiller also stated that knowledge cortical integrity is not only important for surgical treatment planning, but can also inform lesion recurrence.[43]

In this study, oral radiologists found that lesions appeared to be better defined on CBCT compared to PAN (OR=5.45, p=0.004). The ability of CBCT to provide better border definition is in agreement with previous studies and case reports.[44,45,48,52,61] The ability to define lesion extent, which is slightly different from, but related to, the concept of border definition has also been reported as an advantage of CBCT.[21,40,41,43,49,51,52] Knowing the extent of a lesion is important for determining surgical margins as well as avoiding iatrogenic damage to surrounding vital structures. The advantage of CBCT over PAN is likely due to the superimposition of anatomic structures on 2D imaging. This is especially problematic in the mid-facial and sinus regions[8,62] as well in the anterior parts of the jaw due to the superimposition of the cervical vertebrae.[8]

In a case series of three mandibular cancers in 2007, Closmann *et al* highlighted the limitations of panoramic radiography in imaging the anterior mandible. CBCT played a pivotal role in changing the staging of two cancers located in that region by revealing their true extent.[50] In a case series of two calcifying cystic odontogenic tumors (CCOTs) located within the posterior maxilla, the authors demonstrated the usefulness of CBCT in providing information about the lesions' extents within the maxillary sinus.[49] A future direction of our study is to determine if differences in border definition on PANs and CBCTs is related to lesion location. If CBCT is proven to demonstrate better border definition when lesions are located in specific areas of the maxilla or mandible, it could provide evidence-based justification for the use of CBCT in those situations.

In terms of evaluating the continuity of corticated lesion borders, the kappa statistic demonstrated moderate agreement between the two modalities ($\kappa = 0.42$), as well as statistically significant differences in the odds of "Yes" response on CBCT compared to PAN (OR=0.34, p=0.035). The interpretation of this is as follows- if a lesion appeared to be continuously corticated on PANs, it may not appear continuously corticated on CBCT. This finding may be related to the differences in image acquisition between the two modalities. In panoramic tomography, structures are projected on top of one another. Lesion borders that may not be continuous in different planes may then appear continuous on the final image because of superimposition. Conversely, when CBCTs are viewed slice by slice, the "overlap" effect disappears and the detailed structure of the borders can be seen.

The evaluation of effects on the incisive canal and the IAC on PAN and CBCT was interesting in that it was the only radiographic sign that showed both substantial agreement and significant differences on the two modalities ($\kappa=0.80$; OR=6.38, p=0.043). In this study, effects on canals included expansion, displacement and destruction. Observers found agreement between PAN and CBCT in 78 out of 85 paired assessments. However, in this study, we did not account for cases where lesions were not in close enough proximity to the incisive canal or IAC to cause any effects. In such cases, observers are likely to have responded "No" for both PAN and CBCT and this may have led to an inflation in agreement.

There were 6 cases where observers identified canal effects on CBCT but not on PAN, and only 1 case where an observer saw an effect on PAN but not on CBCT. The ability of CBCT to detect changes to

the inferior alveolar canal is in agreement with previous studies.[40,41,45,51,62] In a quantitative study, Momin *et al* reported that CBCT had higher Az values and sensitivity for detecting IAC invasion by squamous cell carcinoma compared to panoramic radiographs.[40] Our findings support that while 2D and 3D findings are mostly equivalent with respect to canal effects, CBCT is still able to afford more information compared to PAN.

The following section discusses the lesion features in which significant differences were not seen between PAN and CBCT. In this study, there was substantial agreement between both modalities with respect to lesion shape (κ=0.65), although agreement was not perfect. Approximately half the observations described the lesion as being round/ovoid on both PAN and CBCT. An additional 12% of observations also reported lesions as being round/ovoid on PAN, but irregular or scalloped on CBCT. Being able to detect variations in shape on CBCT may be related to the ability to scroll through different planes through the various depths of the lesion. The fact that border definition is improved on CBCT may also aid in visualization of lesion shape. However, there was no association noted between modality and lesion shape in this study.

In evaluating whether the lesion borders were well-corticated in terms of thickness, there was moderate agreement between the two modalities (κ=0.60), and no significant difference in the odds ratio of a "Yes" response on CBCT compared to PAN (OR=0.77, p=0.59). Observers appeared to be almost as likely to say that a lesion was well-corticated on a CBCT but not on a PAN as they would the reverse. This may reflect a lack of calibration among the observers on the definition of "thickness". Another possible explanation is that the perception of thickness could depend on the CBCT slice thickness setting. A larger slice thickness may lead to the perception of thick and well-corticated borders. As the slice thickness setting on CBCT was not a controlled factor, it may have introduced variability among the observers.

In terms of evaluating the lesions' locularity, there was only moderate agreement between PAN and CBCT (κ=0.56), and the odds ratios of a "Yes" response were not significantly different (OR=0.50, p=0.57). Our sample size was not adequate for evaluating this radiographic sign as more than 90% of the cases did not appear to be multilocular. A larger sample that includes more multilocular lesions would be necessary to detect differences on the two modalities, or to confirm that there was no difference. In

the literature, CBCT has been reported to provide detailed information about a lesion's internal septations.[44–46] In a case report of an odontogenic myxoma, CBCT was deemed crucial in developing the differential diagnosis as it revealed a pattern of straight internal septae which are characteristic of myxomas. This finding was not obvious on the other radiographs that were acquired, which consisted of panoramic, periapical and conventional CT. This helped to the authors to differentiate it from other similar-appearing lesions such as ameloblastomas and KCOTs.[46]

There was substantial agreement between both modalities and lesions' internal contents (κ=0.65). The interpretation of this is that if a lesion appeared to be radiolucent, mixed or radiopaque, the observers were likely to describe it similarly on both PAN and CBCT. Our sample of lesions were largely radiolucent, and this may have prevent us from detecting differences between the two modalities if they did exist. A larger sample size with a more equal distribution of radiodensities may help to detect differences between PAN and CBCT. Mixed density lesions would be of particular interest due to the variability in distribution of internal calcifications. Previous articles have reported that CBCT was useful in demonstrating the internal contents of mixed lesions.[45,48,49] In one case report of a CCOT, the detailed internal pattern of calcifications which could not be seen on the panoramic image was visible on CBCT, and its peripheral pattern helped the clinicians to distinguish this CCOT from an adenomatoid odontogenic tumor (AOT).[49]

In evaluating the effects of lesions on the surrounding teeth, there was substantial agreement between PAN and CBCT with respect to tooth displacement (κ=0.73), and the odds ratio was not statistically significant (OR=1.39, p=0.61). This is consistent with the expected results as tooth displacement tends to be obvious radiographically when it does occur. Differences are not likely to be seen between the two modalities unless the degree of tooth displacement is very subtle. In terms of root resorption, there was only moderate agreement between PAN and CBCT (κ=0.48), and the odds ratios were not statistically significant (OR=0.83, p=0.70). Fewer than 20% of the total observations reported root resorption in either PAN or CBCT. As with the other radiographic signs that were not well-represented in this sample, additional cases of lesions causing root resorption are necessary to test for differences on PAN and CBCT.

In evaluating the diagnostic impact of the imaging modalities, there was no association between either modality with the rank at which the correct differential diagnosis was made. It should be pointed out that the observations were carried out by experienced oral and maxillofacial radiologists. Therefore, these results may not be generalizable to general dentists or specialists in other fields. It is also important to highlight that the authors of this study are not advocating for imaging to be a replacement for histopathological diagnoses. However, having an accurate differential diagnosis based on imaging can help to direct the appropriate management recommendations and to convey the urgency of the required treatment. These recommendations can range from no treatment to clinical and/or radiographic monitoring, or biopsy. Therefore, knowing the diagnostic efficacy of CBCT for imaging intraosseous maxillofacial pathology is important.

When the accuracy of the observers' diagnosis were not taken into consideration, the confidence levels of the observers were similar and ranged from 3.55 to 3.90 on PAN and 3.65 to 3.94 on CBCT at their first differential diagnosis, regardless of whether their diagnosis was correct. We also found that the use of CBCT does not always result in an increase in confidence. While the observers had 10, 6 and 5 cases respectively where their confidence increased with CBCT at their first differential diagnosis, they also had 4, 5 and 5 cases respectively out of 31 cases in which their confidence levels decreased.

We were also interested in evaluating the confidence levels of the observers when the correct diagnosis was provided. Therefore, weighting was applied to the observers' confidence levels, with higher weights assigned when the correct diagnosis was provided at a higher rank. Analysis was then performed on these new weighted confidence levels. There was no association found between the modalities and the weighted confidence levels of the observers at the point at which the correct differential diagnosis was made.

The implication of these findings is that CBCT has not been proven to be efficacious for imaging intraosseous oral and maxillofacial pathology at levels 2 and 3 of the hierarchical model developed by Fryback and Thornbury.[17] With the use of CBCT, there was no change in the accuracy of observers' differential diagnoses, nor their weighted confidence levels when the accuracy of their differential diagnoses were taken into account.

Observers generally had high intraobserver agreement when comparing original responses to the responses provided for the 10 repeated PANs and CBCTs. 61 out of 72 assessments were in the range of 80% to 100%. When the findings across all lesion features were averaged, the intraobserver agreements for Observers 1, 2 and 3 were 95%, 85% and 91.67% respectively on PAN and 88.33%, 85.83% and 85.83% respectively on CBCT. Observers 1 and 3 appeared to be more consistent with themselves on PAN while Observer 2 was only slightly more consistent with CBCT. Lower agreement was seen with Observers 1 and 3 with respect to cortical destruction on CBCT (60% and 50% agreement respectively). This can partly be attributed to the increased number of "Cannot tell" responses on the repeat cases. The problems associated with the option "Cannot tell" will be reviewed later on in the discussion. Lower self-agreement was also seen with Observer 1 with respect to root resorption on CBCT, with inconsistencies seen in reporting whether root resorption was present or not (60%).

Interobserver reliability was assessed by comparing raw agreement between Observers 1 & 2, 1 & 3 and 2 & 3. Interobserver agreement ranged from 51.61% to 100%. When the findings across all lesion features were averaged, the interobserver agreement between Observers 1 & 2, 1 & 3 and 2 & 3 were 79.57%, 81.45% and 75.54% respectively on PAN and 83.07%, 84.68% and 82.53% respectively on CBCT. Observers 1 & 3 appeared to have higher agreement with each other than with Observer 2. Observers also had higher agreement on CBCT than on PAN. Examples of lower interobserver agreement occurred with respect to lesion shape, continuity of border cortication, and cortical thinning on PAN and expansion on CBCT. Some of the disagreements can be attributed to the differing uses of "Cannot tell" responses, while other disagreements resulted from Yes/No discordances in observers' perceptions of whether a radiographic sign was present. Due to the subjective nature of this research, it is not surprising that some variabilities between observers were seen. The use of the conditional logistic regression statistical model also accounted for these observer effects when assessing for differences between PAN and CBCT.

A major limitation in our study was allowing observers to answer "Cannot tell". The observers appeared to have different thresholds at which they were willing to commit to a Yes or No response, as opposed answering "Cannot tell". During calibration, observers were asked to answer "No" if they could

not see evidence of an effect, even if they knew that a particular sign may not be visible on a panoramic radiograph, for example bucco-lingual thinning or expansion. They were asked to answer "Cannot tell" in situations where the lesion's effects were unable to be assessed for reasons apart from the limitations of the modality, for example, if they were unsure about where the lesion was. However, given the varying prevalence of "Cannot tell" responses, it is clear that the definition and calibration among observers in using this answer option was inadequate. This may be related to their knowledge of the limitations of panoramic radiographs.

There was also an insufficient number of "Cannot tell" responses for Questions 1 to 12 to have a category of its own for statistical analysis and these responses had to be excluded from analysis. Out of a total of 2232 responses, there were 53 instances where observers responded "Cannot tell". Out of these, 48 responses were seen on PAN observations and only 5 were from CBCT observations. Out of the 48 "Cannot tell" responses on PAN, only 1 of the corresponding CBCT responses was also "Cannot tell". The remaining 47 observations had Yes or No Reponses on the corresponding CBCT. The implication of this excluding "Cannot tell" responses from our analysis is that the agreement between PAN and CBCT may have been over-estimated in our study. Furthermore, in these situations, information is gained from the CBCT where it would have otherwise not been available from the PAN.

Due to the strict inclusion and exclusion criteria, the final sample size was limited to 31 cases. Furthermore, not all radiographic signs manifested in the cases that were included in this study. For example, out of 31 cases, there was only 1 case in which all observers reported as being multilocular on both PAN and CBCT. The lack of differences detected on PAN and CBCT with respect to the locularity of lesions could be attributed to the sample of cases that were available. A larger sample would improve the statistical power and the robustness of the findings that achieved statistical significance in this study. It may also enable detection of differences between PAN and CBCT with respect to the remaining radiographic signs.

Due to the retrospective study design, there was no control over the units or parameters that were used to acquire PANs and CBCTs. These variations may have introduced confounders into the study

if there were differences in image qualities. On the other hand, the fact that images and volumes are obtained from different acquisition units is representative of clinical reality.

The time-lag seen between PANs and CBCTs in this study is a variable that could be better controlled with a prospective study design. Ideally, the two imaging modalities should be acquired successively with minimal time-lag between the two procedures. The longer this is, the higher the chances of differences in radiographic signs being related to disease progression, rather than to the imaging modality. To control for this, we restricted the time-frame to 3 months, where each image/volume had to be acquired in the 3 months prior or 3 months after the other was taken.

Since one of the objectives of the study was to test whether diagnostic accuracy changed with CBCTs compared to PANs, the selected cases had to be biopsy-confirmed. Because of this requirement, this sample was not appropriate for evaluating the impact of CBCT on changes in management recommendations. A different study design that does not mandate that the lesions be biopsy-confirmed would be more appropriate to evaluate for changes in management recommendations based on CBCT. This would allow for evaluating the efficacy of CBCT at level 4 of Fryback and Thornbury's model.[17]

In attempting to evaluate diagnostic accuracy of PANs and CBCTs, the limitation of this study is that some of the cases demonstrated uncommon pathology. This would affect the likelihood of the observers providing the correct diagnosis. Some of the cases were also recurrent lesions which had radiographic presentations that were not necessarily typical of the original pathology. However, these scenarios are also representative of clinical reality where oral radiologists may be confronted with rare lesions and where not all lesions have classic "textbook" appearances.

As part of the study design, the observers were not provided with any clinical information. This was to avoid distractors, since the focus of this study was on radiographic features. For example, if there was a clinical history of expansion, it may affect the observers' interpretation of this radiographic sign. In addition, memory bias may be introduced by providing a clinical history, as the observers may remember the radiographic signs and differential diagnoses they provided on the other modality. The lack of clinical information may have affected the diagnostic accuracy of the observers, and is not representative of clinical reality.

Although a significant attempt was made to randomize the images, one of the observers provided feedback that some of the PANs and CBCTs belonging to the same case were still placed too closely to each other in viewing sequence. This may have introduced a degree of memory bias into the results. For future improvements, the study protocol should ensure that PANs and CBCTs from the same patient are adequately randomized.

Conclusions

Observers detected differences in radiographic features of lesions on PAN and CBCT with respect to border definition, continuity of corticated borders, effects on incisive or inferior alveolar canals, expansion of surrounding anatomic boundaries, cortical thinning and cortical destruction. However, there was no association between the two modalities and the point at which the correct differential diagnosis was made, nor between the two modalities and weighted confidence levels when controlling for multiple observers and case IDs.

Future directions

In order to improve the statistical power of this study, a larger sample should be used, which would also allow for stratification analysis to be performed. One area where this could be done is in determining whether there are significant differences between PAN and CBCT based on the lesion's location. Our hypothesis is that that CBCT would be more efficacious than PAN for imaging lesions located in the anterior regions of the jaw or in the mid-face. The goal is to identify specific radiographic signs or disease characteristics that may be predictive of when a CBCT is likely to provide maximum diagnostic benefit. This is a critical first step towards developing evidence-based selection criteria for CBCT imaging of oral and maxillofacial pathology. The ultimate goal is to provide care for patients in a manner in which the benefits outweigh any risks undertaken. We hope that this research project provides a starting point for other future studies of a similar nature to be undertaken and that the combined efforts will bring us closer towards that end-goal. Finally, additional studies should be carried out to

evaluate the impact of CBCT for imaging intraosseous pathology at higher levels of the Fryback and Thornbury hierarchy to assess its benefit to clinicians, patients and society.

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Table 1. Overview of cases: Histopathological diagnosis, time-span between PAN/CBCT, location

Case ID	Histopathologic diagnosis	Time between PAN and CBCT (weeks)*	Location description
1	Dentigerous cyst, inflamed	0.0	Inferior to #17
2	Radicular cyst or residual cyst†	2.7	Between #25, 26
3	Keratocystic odontogenic tumor (KCOT)	0.0	Apical to #15
4	Periapical granuloma	-3.7	Apical to #9, 10
5	Periapical granuloma with foreign material	0.0	Apical to #9
6	Keratocystic odontogenic tumor (KCOT), recurrent	0.0	Distal to #18
7	Keratocystic odontogenic tumor (KCOT), recurrent	0.0	Between #4, 6
8	Aneurysmal bone cyst	6.1	Apical to #26
9	Periapical granuloma	6.9	Apical to #8
10	Osteoporotic bone marrow defect	9.9	Superior to #17
11	Fibrous dysplasia	11.4	Anterior mandible
12	Central ossifying fibroma	-12.9	Apical to #10
13	Multiple hyperplastic follicles	9.3	(MF)‡ Between #17, 18
14	Ameloblastoma, recurrent	0.0	Between #19, 20
15	Traumatic bone cyst/Simple bone cyst	0.0	Between #18, 19
16	Focal osseous dysplasia/Periapical cemental dysplasia	14.9	Mesial to #18
17	Root and focal osseous dysplasia/Periapical cemental dysplasia	13.1	Mesial to #18
18	Traumatic bone cyst/Simple bone cyst	6.0	Apical to #23
19	Traumatic bone cyst/Simple bone cyst	9.0	Apical to #31
20	Traumatic bone cyst/Simple bone cyst	16.0	Apical to #26
21	Dentigerous cyst	0.0	Apical to #18
22	Central odontogenic fibroma	9.1	Tooth #32
23	Myospherulosis and reactive bone	0.0	Distal to #31
24	Dentigerous cyst, inflamed	0.0	Apical to #18
25	Keratocystic odontogenic tumor (KCOT), recurrent	-9.3	(MF)‡ Apical to #19
26	Radicular cyst or residual cyst†	-7.1	Apical to #6
27	Keratocystic odontogenic tumor (KCOT)	2.1	(MF)‡ Apical to #14, 15
28	Nasopalatine duct cyst	2.9	Palatal to #8, 9
29	Compound odontoma	15.3	Apical to #28
30	Keratocystic odontogenic tumor (KCOT)	-0.6	Apical to #3
31	Residual cyst, inflamed	7.1	Anterior mandible
32	Keratocystic odontogenic tumor (KCOT)	0.0	Apical to #4
33	Lateral periodontal cyst	2.0	Between #21, 22

*The date that the PAN was acquired was used as the reference. If the CBCT was taken after the PAN, the number of weeks is positive. If the CBCT was taken before the PAN, the number of weeks is negative.

†Case 2 and Case 26: The cystic lesion in each case was centered over an existing tooth and adjacent missing tooth. Therefore, in both of these cases, "residual cyst" was also accepted as a correct diagnosis

‡(MF): Abbreviation for "multifocal". Observers were made aware in the lesion description when the lesion was multifocal. The lesion that they were asked to describe was the one for which the location was provided.

Table 2. Summary of lesions by category

Category	Diagnosis	n=
Benign tumors (n=10)	Keratocystic odontogenic tumor (KCOT)	4
	Keratocystic odontogenic tumor (KCOT), recurrent	3
	Ameloblastoma, recurrent	1
	Central odontogenic fibroma	1
	Central ossifying fibroma*	1
Cysts (n=8)	Dentigerous cyst	1
	Dentigerous cyst, inflamed	2
	Radicular cyst or residual cyst	2
	Residual cyst, inflamed	1
	Nasopalatine duct cyst	1
	Lateral periodontal cyst	1
Lesions of bone (n=5)	Traumatic bone cavity/Simple bone cyst	4
	Aneurysmal bone cyst	1
Inflammatory lesions (n=3)	Periapical granuloma	2
	Periapical granuloma with foreign material	1
Fibro-osseous lesions (n=3)	Focal osseous dysplasia/Periapical cemental dysplasia	1
	Root and focal osseous dysplasia/Periapical cemental dysplasia	1
	Fibrous dysplasia	1
Others (n=4)	Compound odontoma†	1
	Multiple hyperplastic follicles‡	1
	Myospherulosis and reactive bone§	1
	Osteoporotic bone marrow defect‖	1

*Central ossifying fibroma could also be classified as a "fibro-osseous lesion"

†Compound odontoma was classified as a harmatoma

‡Multiple hyperplastic follicle was classified as a developmental condition

§Myospherulosis could be classified as a foreign body reaction, a lesion of bone, or an inflammatory lesion

‖Osteoporotic bone marrow defect was classified as a variance of normal anatomy

Table 3. Overall agreement between PAN and CBCT with respect to lesion features

Qn #	Questions	Overall Kappa (95% CI)	Strength of agreement*
1	What is the lesion's shape?	0.65 (0.51, 0.80)	Substantial
2	Are its borders well-defined?	0.28 (0.07, 0.50)	Fair
3	Are its borders well-corticated in terms of thickness?	0.60 (0.43, 0.77)	Moderate
4	Are its borders continuously corticated?	0.42 (0.21, 0.63)	Moderate
5	The lesion's internal contents are mostly radiolucent/≤Soft tissue density, Mixed or Radiopaque/ ≥Bone density	0.74 (0.59, 0.89)	Substantial
6	Is the lesion multilocular?	0.56 (0.12, 0.99)	Moderate
7	Does it appear to be affecting the incisive canal or the inferior alveolar canal?	0.80 (0.65, 0.94)	Substantial
8	Does it appear to expand the normal surrounding anatomic boundaries?	0.19 (0.06, 0.32)	Slight
9	Does it appear to be causing cortical thinning?	0.10 (0.02, 0.18)	Slight
10	Does it appear to be causing cortical destruction?	0.23 (0.05, 0.42)	Fair
11	Does it appear to be causing tooth displacement?	0.73 (0.54, 0.92)	Substantial
12	Does it appear to be causing root resorption?	0.48 (0.26, 0.69)	Moderate

* Strength of agreement is interpreted as follows: 0.01 – 0.20: Slight, 0.21 – 0.40: Fair, 0.41-0.60: Moderate, 0.61-0.80: Substantial, 0.81-0.99: Almost perfect.

Table 4. Odds ratio of a "Yes" response on CBCT compared to a "Yes" response on PAN

Qn #	Questions	Odds ratio (95% CI)	p-value
2	Are its borders well-defined?	5.45 (1.73, 17.21)	**0.004**
3	Are its borders well-corticated in terms of thickness?	0.77 (0.29, 2.02)	0.59
4	Are its borders continuously corticated?	0.34 (0.13, 0.93)	**0.035**
6	Is the lesion multilocular?	0.50 (0.05, 5.51)	0.57
7	Does it appear to be affecting the incisive canal or the inferior alveolar canal?	6.38 (1.06, 38.43)	**0.043**
8	Does it appear to expand the normal surrounding anatomic boundaries?	18.56 (6.15, 55.98)	**< 0.001**
9	Does it appear to be causing cortical thinning?	30.22 (10.10, 90.41)	**< 0.001**
10	Does it appear to be causing cortical destruction?	9.80 (2.92, 32.86)	**< 0.001**
11	Does it appear to be causing tooth displacement?	1.39 (0.39, 4.90)	0.61
12	Does it appear to be causing root resorption?	0.83 (0.31, 2.22)	0.70

Bolded p-values represent statistically significant differences ($P<0.05$) between PAN and CBCT

Table 5. Intraobserver agreement with respect to all lesion features (% agreement)

Qn #	Questions	Observer 1		Observer 2		Observer 3	
		PAN	**CBCT**	**PAN**	**CBCT**	**PAN**	**CBCT**
1	What is the lesion's shape?	80	80	70	70	90	90
2	Are its borders well-defined?	90	100	70	80	70	100
3	Are its borders well-corticated in terms of thickness?	90	80	100	70	100	90
4	Are its borders continuously corticated?	100	90	90	90	80	80
5	The lesion's internal contents are mostly radiolucent/≤Soft tissue density, Mixed or Radiopaque/ ≥Bone density	100	100	90	80	100	100
6	Is the lesion multilocular?	100	90	100	100	100	100
7	Does it appear to be affecting the incisive canal or the inferior alveolar canal?	90	100	90	100	80	70
8	Does it appear to expand the normal surrounding anatomic boundaries?	100	100	90	90	100	80
9	Does it appear to be causing cortical thinning?	100	100	70	90	100	100
10	Does it appear to be causing cortical destruction?	100	60	70	80	100	50
11	Does it appear to be causing tooth displacement?	100	100	100	90	90	80
12	Does it appear to be causing root resorption?	90	60	80	90	90	90
	Average	95.00	88.33	85.00	85.83	91.67	85.83

Table 6. Interobserver agreement with respect to all lesion features (% agreement)

Qn #	Questions	Observers 1 & 2		Observers 1 & 3		Observers 2 & 3	
		PAN	**CBCT**	**PAN**	**CBCT**	**PAN**	**CBCT**
1	What is the lesion's shape?	64.52	74.19	70.97	70.97	74.19	74.19
2	Are its borders well-defined?	74.19	87.10	83.87	93.55	74.19	87.10
3	Are its borders well-corticated in terms of thickness?	83.87	83.87	74.19	96.77	74.19	87.10
4	Are its borders continuously corticated?	83.87	83.87	51.61	74.19	51.61	70.96
5	The lesion's internal contents are mostly radiolucent/≤Soft tissue density, Mixed or Radiopaque/ ≥Bone density	80.65	87.10	80.65	90.32	83.87	87.10
6	Is the lesion multilocular?	93.55	96.77	100.00	96.77	93.55	100.00
7	Does it appear to be affecting the incisive canal or the inferior alveolar canal?	77.42	87.10	77.42	87.10	77.42	87.10
8	Does it appear to expand the normal surrounding anatomic boundaries?	80.65	67.74	87.10	70.97	70.97	64.52
9	Does it appear to be causing cortical thinning?	74.19	77.42	80.65	80.65	61.29	87.10
10	Does it appear to be causing cortical destruction?	74.19	90.32	93.55	90.32	70.97	87.10
11	Does it appear to be causing tooth displacement?	90.32	80.65	96.77	83.87	93.55	77.42
12	Does it appear to be causing root resorption?	77.42	80.65	80.65	80.65	80.65	80.65
	Average	79.57	83.07	81.45	84.68	75.54	82.53

Table 7. Frequency table of pooled observer responses with respect to **lesion shape**

		CBCT			
		Irregular	Round/ Ovoid	Scalloped	Total
PAN	Irregular	10 (11.63%)	5 (5.81%)	1 (1.16%)	16 (18.60%)
	Round/ Ovoid	5 (5.81%)	45 (52.33%)	5 (5.81%)	55 (63.95%)
	Scalloped	2 (2.33%)	0 (0.00%)	13 (15.12%)	15 (17.44%)
	Total	17 (19.77%)	50 (58.14%)	19 (22.09%)	86* (100.0%)

* Excluded "Cannot tell": n= 7

Table 8. Frequency table of pooled observer responses with respect to **border definition**

		CBCT		
		No	Yes	Total
PAN	No	7 (7.78%)	16 (17.78%)	23 (25.56%)
	Yes	4 (4.44%)	63 (70.00%)	67 (74.44%)
	Total	11 (12.22%)	79 (87.78%)	90* (100.00%)

* Excluded "Cannot tell": n=3

Table 9. Frequency table of pooled observer responses with respect to whether **borders are well-corticated in terms of thickness**

		CBCT		
		No	Yes	Total
PAN	No	46 (51.69%)	8 (8.99%)	54 (60.67%)
	Yes	10 (11.24%)	25 (28.09%)	35 (39.33%)
	Total	56 (62.92%)	33 (37.08%)	89* (100.00%)

* Excluded "Cannot tell": n=4

Table 10. Frequency table of pooled observer responses with respect to **continuity of border cortication**

		CBCT		
		No	Yes	Total
PAN	No	52 (60.47%)	5 (5.81%)	57 (66.28%)
	Yes	14 (16.28%)	15 (17.44%)	29 (33.72%)
	Total	66 (76.74%)	20 (23.26%)	86* (100.00%)

* Excluded "Cannot tell": n=7

Table 11. Frequency table of pooled observer responses with respect to **internal contents**

		CBCT			
		Mixed	Radiolucent	Radiopaque	Total
PAN	Mixed	10 (10.87%)	4 (4.35%)	0 (0.00%)	14 (15.22%)
	Radiolucent	1 (1.09%)	69 (75.00%)	1 (1.09%)	71 (77.17%)
	Radiopaque	2 (2.17 %)	1 (1.09%)	4 (4.35%)	7 (7.61%)
	Total	13 (14.13%)	74 (80.43%)	5 (5.43%)	92* (100.00%)

* Excluded "Cannot tell": n= 1

Table 12. Frequency table of pooled observer responses with respect to **locularity**

		CBCT		
		No	Yes	Total
PAN	No	87 (93.55%)	1 (1.08%)	88 (94.62%)
	Yes	2 (2.15%)	3 (3.23%)	5 (5.38%)
	Total	89 (95.70%)	4 (4.30%)	93 (100.0%)

Table 13. Frequency table of pooled observer responses with respect to **effect on the incisive canal or inferior alveolar canal**

		CBCT		
		No	Yes	Total
PAN	No	59 (69.41%)	6 (7.06%)	65 (76.47%)
	Yes	1 (1.18%)	19 (22.35%)	20 (23.53%)
	Total	60 (70.59%)	25 (29.41%)	85* (100.00%)

* Excluded "Cannot tell": n=8

Table 14. Frequency table of pooled observer responses with respect to **expansion of surrounding anatomic boundaries**

		CBCT		
		No	Yes	Total
PAN	No	31 (34.44%)	38 (42.22%)	69 (76.67%)
	Yes	3 (3.33%)	18 (20.00%)	21 (23.33%)
	Total	34 (37.78%)	56 (62.22%)	90* (100.00%)

* Excluded "Cannot tell": n=3

Table 15. Frequency table of pooled observer responses with respect **to cortical thinning**

		CBCT		
		No	Yes	Total
PAN	No	15 (17.44%)	48 (55.81%)	63 (73.26%)
	Yes	2 (2.33%)	21 (24.42%)	23 (26.74%)
	Total	17 (19.77%)	69 (80.23%)	86* (100.0%)

* Excluded "Cannot tell": n= 7

Table 16. Frequency table of pooled observer responses with respect to **cortical destruction**

		CBCT		
		No	Yes	Total
PAN	No	53 (61.63%)	21 (24.42%)	74 (86.05%)
	Yes	4 (4.65%)	8 (9.30%)	12 (13.95%)
	Total	57 (66.28%)	29 (33.72%)	86* (100.00%)

* Excluded "Cannot tell": n=7

Table 17. Frequency table of pooled observer responses with respect to **teeth displacement**

		CBCT		
		No	Yes	Total
PAN	No	59 (64.13%)	4 (4.35%)	63 (68.48%)
	Yes	3 (3.26%)	26 (28.26%)	29 (31.52%)
	Total	62 (67.39%)	30 (32.61%)	92* (100.00%)

* Excluded "Cannot tell": n=1

Table 18. Frequency table of pooled observer responses with respect to **root resorption**

		CBCT		
		No	Yes	Total
PAN	No	63 (71.59%)	7 (7.95%)	70 (79.55%)
	Yes	8 (9.09%)	10 (11.36%)	18 (20.45%)
	Total	71 (80.68%)	17 (19.32%)	88* (100.00%)

* Excluded "Cannot tell": n=5

Table 19. Pooled frequency table of correct diagnosis on PAN vs CBCT at any differential diagnosis

		CBCT		
		No	Yes	Total
PAN	No	23 (24.73%)	11 (11.83%)	34 (36.56%)
	Yes	9 (9.68%)	50 (53.76%)	59 (63.44%)
	Total	32 (34.41%)	61 (65.59%)	93 (100.00%)

Table 20. Pooled frequency table of correct diagnosis on PAN vs CBCT at the first differential diagnosis

		CBCT		
		No	Yes	Total
PAN	No	37 (39.78%)	9 (9.68%)	46 (49.46%)
	Yes	10 (10.75%)	37 (39.78%)	47 (50.54%)
	Total	47 (50.54%)	46 (49.46%)	93 (100.00%)

Table 21. Average confidence levels of observers about their first differential diagnosis on PAN and CBCT, regardless of whether diagnosis was correct

	PAN	**CBCT**
Observer 1	3.61	3.94
Observer 2	3.55	3.65
Observer 3	3.90	3.90

Table 22. Frequency of change in confidence level of observers from using PAN to using CBCT at the first differential diagnosis regardless of whether diagnosis was correct

	Decrease in confidence	**No change in confidence**	**Increase in confidence**
Observer 1	4	17	10
Observer 2	5	20	6
Observer 3	5	21	5
Total	14	58	21

Figure 1. Representative example of a PAN and a CBCT volume viewed by observers

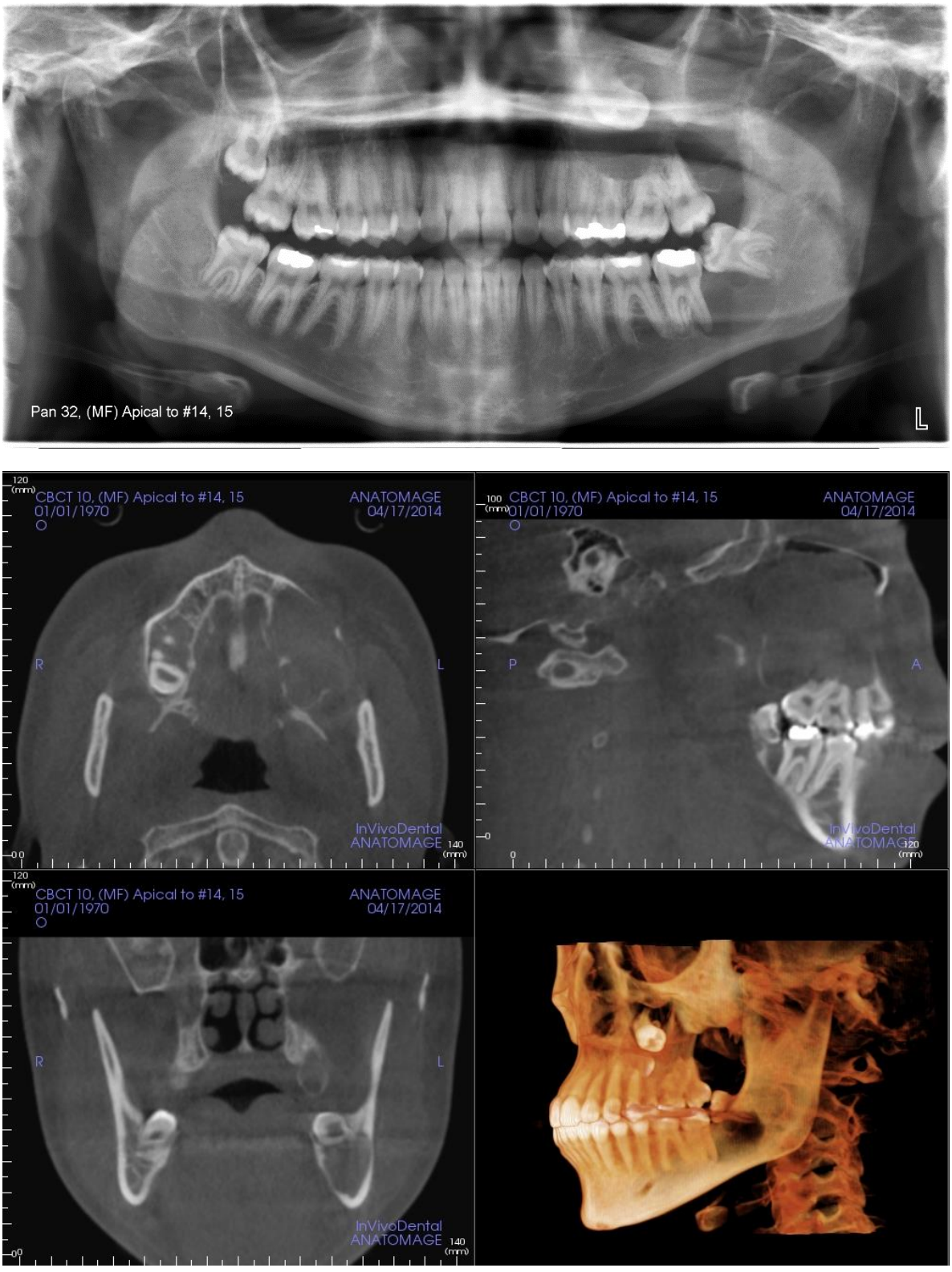


Figure 2. Example of CBCT demonstrating well-defined borders not seen on PAN

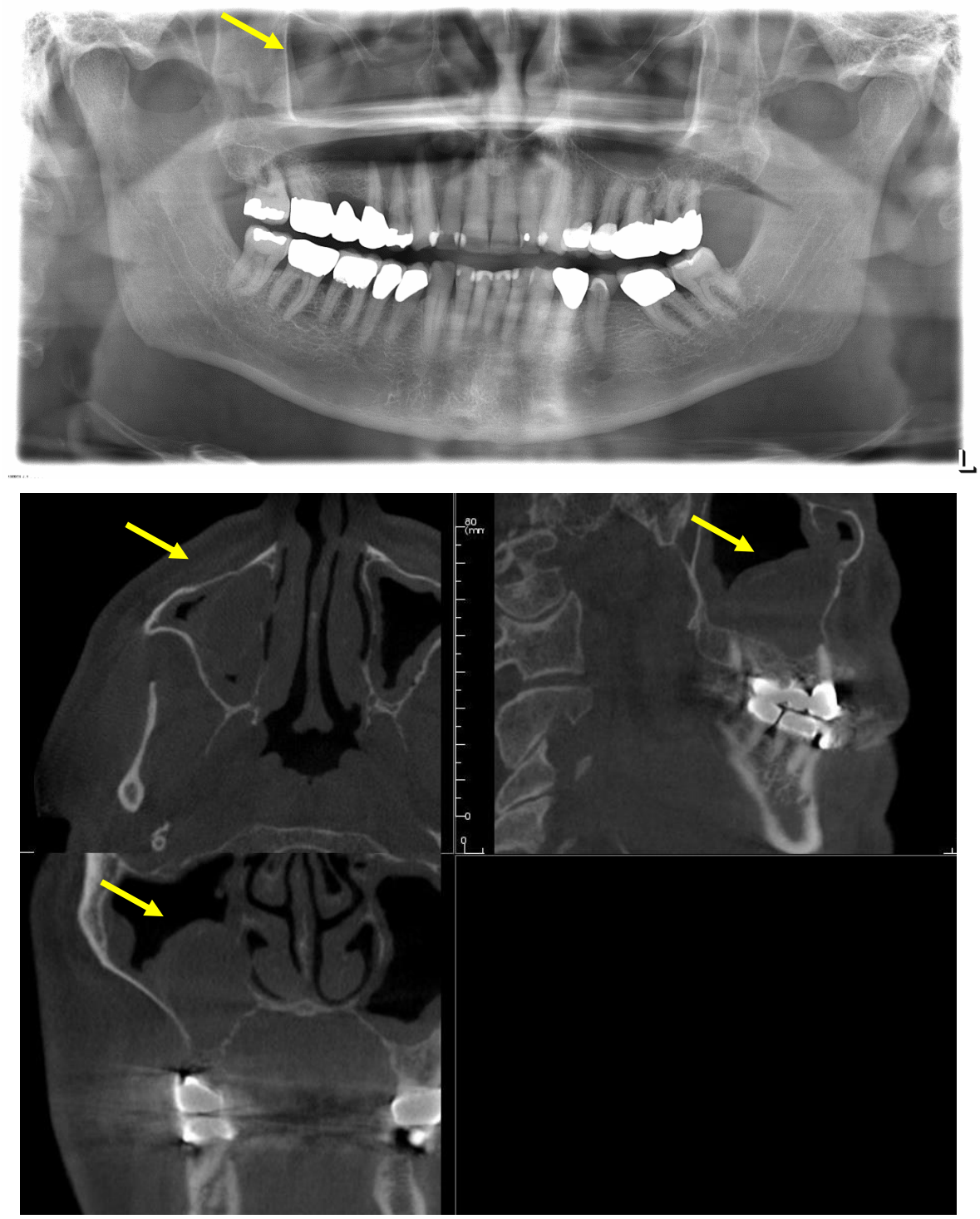


Figure 3. Example of PAN demonstrating continuity of cortication of lesion borders not seen on CBCT

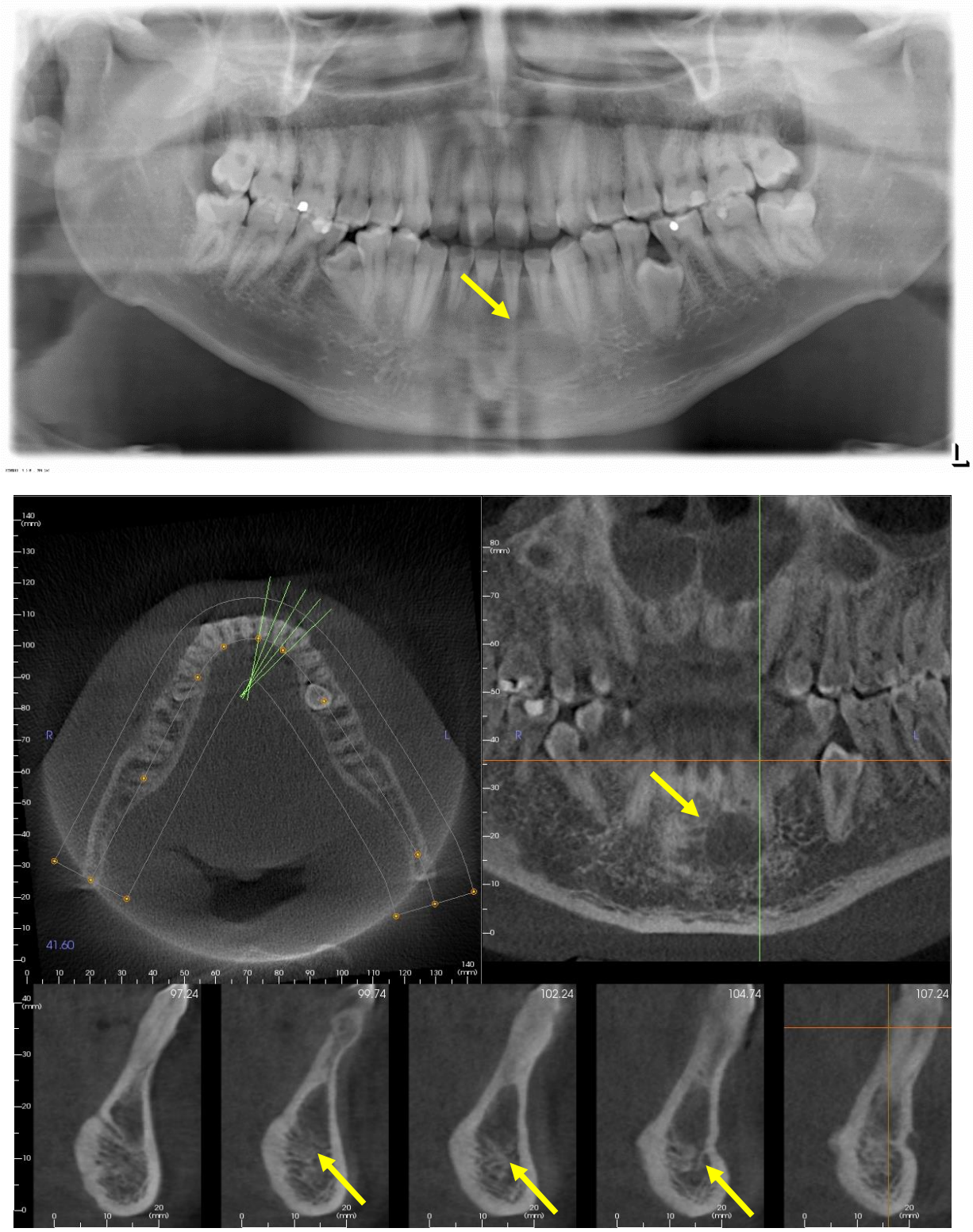


Figure 4. Example of CBCT demonstrating displacement of IAC not seen on PAN

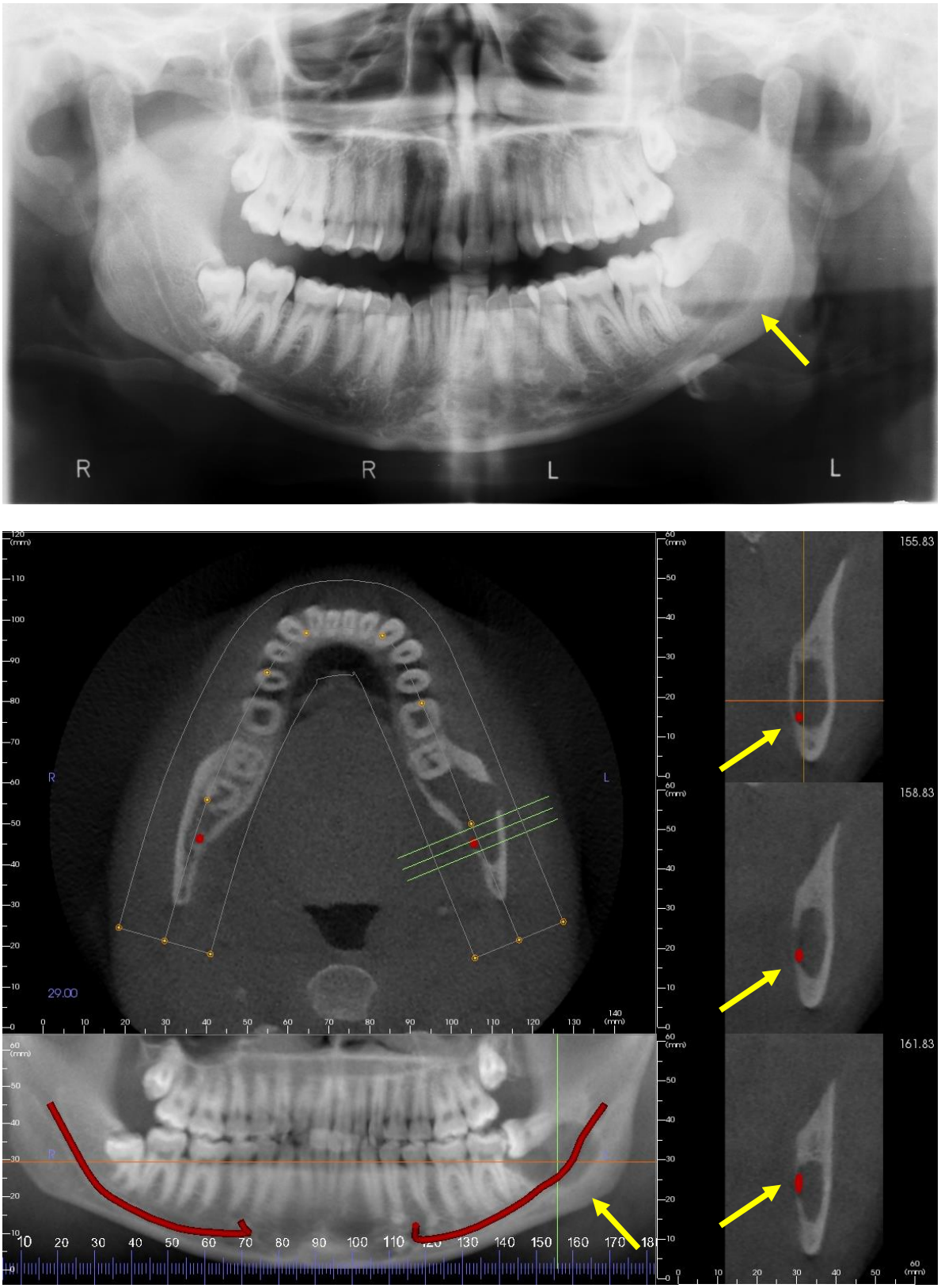


Figure 5. Example of CBCT demonstrating expansion not seen on PAN

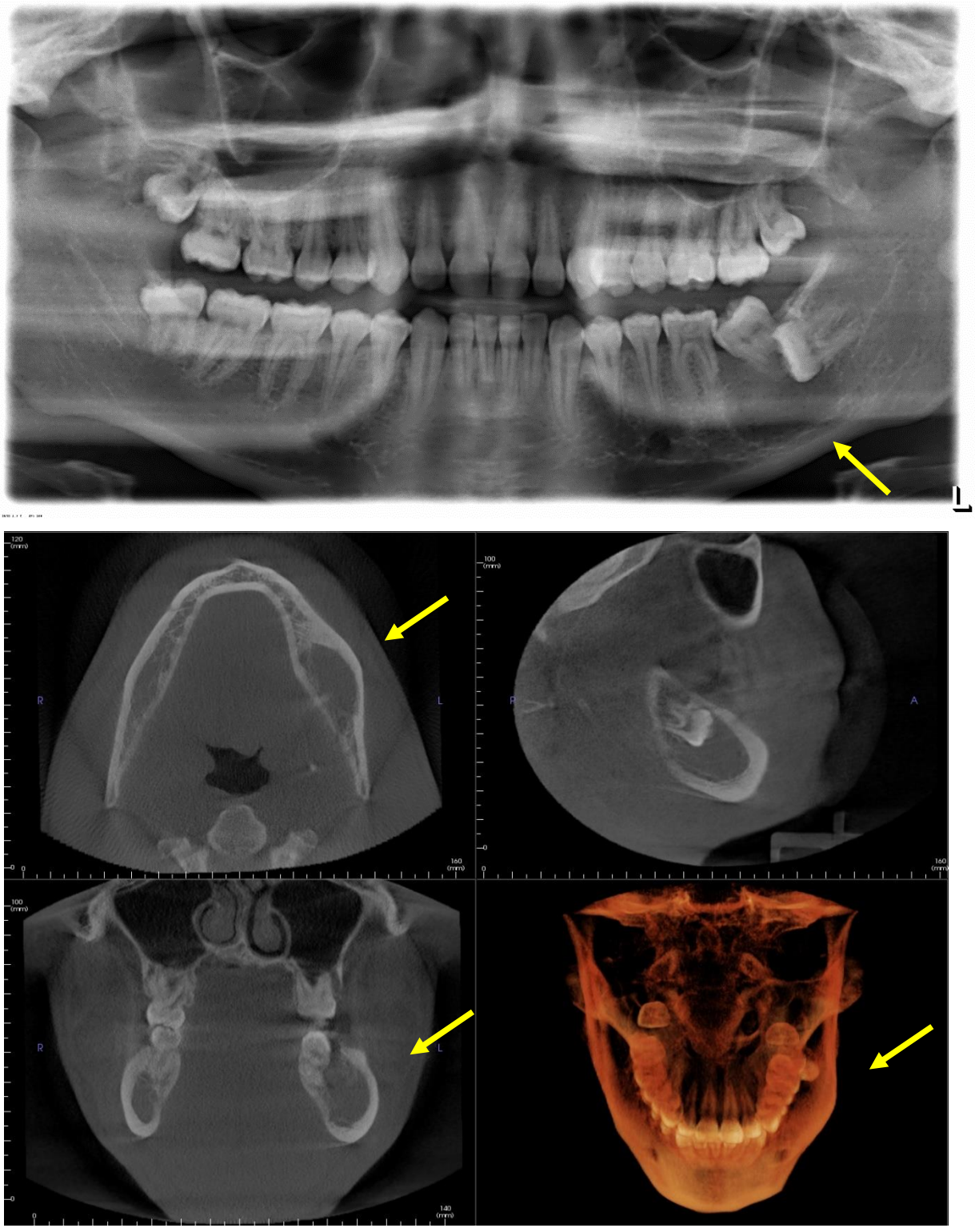


Figure 6. Example of CBCT demonstrating cortical thinning not seen on PAN

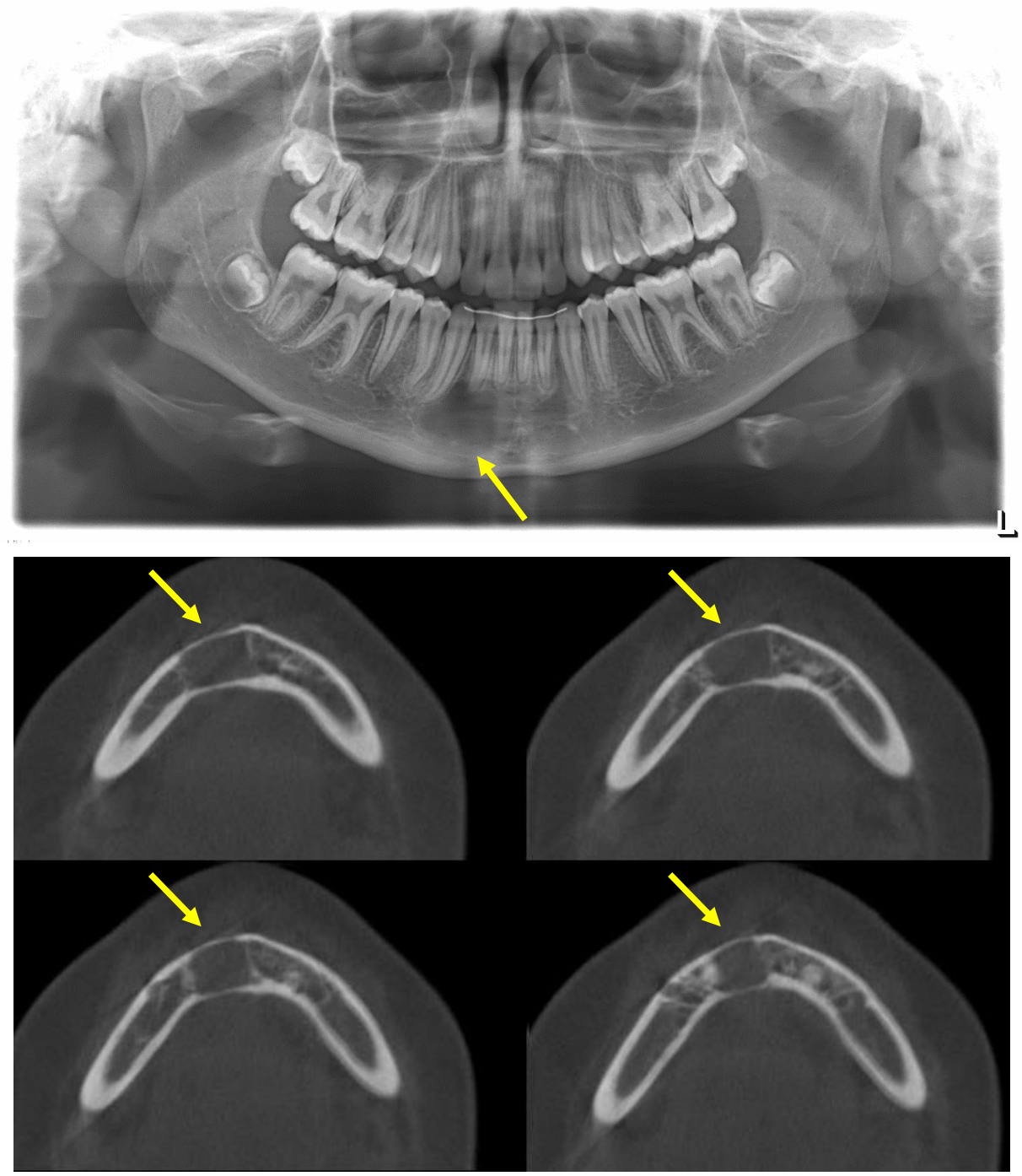
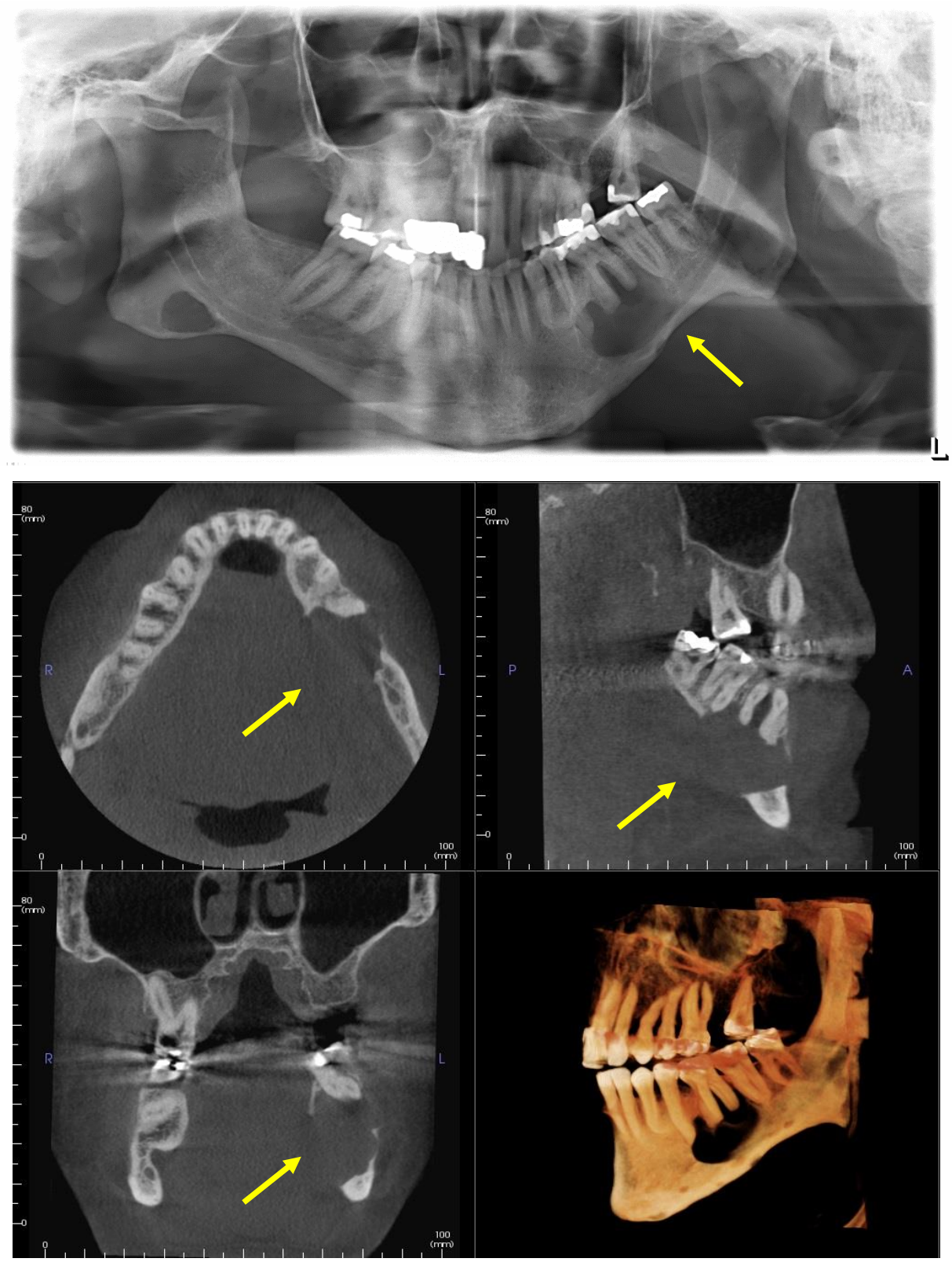


Figure 7. Example of CBCT demonstrating cortical destruction not seen on PAN



APPENDIX 1: SEARCH STRATEGIES FOR ELIGIBLE SUBJECTS

1. Search criteria used by School of Dentistry's Office of Computing and Information Systems (*OCIS*).
    - Date range: 1st January 2000 – 31st March 2016
    - Current Dental Terminology/Current Procedural Terminology (CDT/CPT) codes: Panoramic radiograph (D0330 or 70355) and CBCT (D0322 or D0360 or D0362 or D0363 or D0364 or D0366 or D0367 or D0380 or D0321 or 70486 or 76100) and Biopsy (88305 or 88307)
    - Panoramic radiograph and CBCT must be taken within 3 months of each other
    - Biopsy must not be performed between acquisition of panoramic radiograph and CBCT

2. Cases contributed by Dr. George Blakey, oral and maxillofacial surgeon at UNC School of Dentistry. Search criteria used:
    - Date range: 1st January 2013 – 19th April 2016
    - Current Procedural Terminology (CPT) codes: 21046, 21047, 21048, 21040, 21045

3. Cases contributed by Dr. Glenn Reside, oral and maxillofacial surgeon at UNC School of Dentistry from personal case log of surgery cases, date range 1st January 2013 – 21st April 2016.

4. Search criteria from the UNC School of Dentistry CBCT log
    - Date range: 1st January 2015 – 11th May 2016
    - CBCT indication: Pathology