Evaluation of the Reliability and Accuracy of Using Cone-beam Computed Tomography for Diagnosing Periapical Cysts from Granulomas

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Abstract

Introduction: The purpose of this study was to evaluate the reliability and accuracy of cone-beam computed tomographic (CBCT) imaging against the histopathologic diagnosis for the differential diagnosis of periapical cysts (cavitated lesions) from (solid) granulomas.

Methods: Thirty-six periapical lesions were imaged using CBCT scans. Apicoectomy surgeries were conducted for histopathological examination. Evaluator 1 examined each CBCT scan for the presence of six radiologic characteristics of a cyst (ie, location, periphery, shape, internal structure, effects on surrounding structure, and perforation of the cortical plate). Not every cyst showed all radiologic features (eg, not all cysts perforated the cortical plate). For the purpose of finding the minimum number of diagnostic criteria present in a scan to diagnose a lesion as a cyst, we conducted 6 receiver operating characteristic curve analyses comparing CBCT diagnoses with the histopathologic diagnosis. Two other independent evaluators examined the CBCT lesions. Statistical tests were conducted to examine the accuracy, inter-rater reliability, and intra-rater reliability of CBCT images. Results: Findings showed that a score of 4 positive findings was the optimal scoring system. The accuracies of differential diagnoses of 3 evaluators were moderate (area under the curve = 0.76, 0.70, and 0.69 for evaluators 1, 2, and 3, respectively). The inter-rater agreement of the 3 evaluators was excellent ($\kappa = 0.87$). The intrarater agreement was good to excellent ($\kappa = 0.71, 0.76,$ and 0.77). Conclusions: CBCT images can provide a moderately accurate diagnosis between cysts and granulomas. (J Endod 2013;39:1485–1490)

Key Words

Biopsy, cone-beam computed tomography, differential diagnosis, granuloma, periapical cyst
The use of CBCT scans for endodontic diagnosis is controversial because of concerns relating to a higher exposure of radiation to patients than necessary, long duration of scanning, and expensive cost compared with conventional dental radiographs (15). Although CBCT imaging is widely used in orthodontics (16), dental implant treatment planning (17), and the detection of obstructive sleep apnea (18), the use of gray values in the diagnosis of PA lesions exhibits some disadvantages according to a recent publication (16). Authors of this publication concluded that gray values could be easily affected by the field of view and spatial resolution selections (16), so in our current study we used a set of diagnostic criteria based on the radiologic characteristics of apical cysts instead of using gray values.

The main purpose of the present study was to evaluate a set of diagnostic criteria for differentiating PA cysts from granulomas according to their CBCT imaging characteristics. The criteria were established based on the radiologic characteristics of PA cysts (19, 20). The goals of this study were to evaluate this set of 6 diagnostic criteria and to find out the optimal number of criteria findings necessary for the differential diagnosis of PA cysts (cavitated lesions) versus granulomas; to evaluate the intrarater and inter-rater reliability of 3 independent evaluators using 6 criteria for the differential diagnosis of cysts versus granulomas; and to evaluate the accuracy, specificity, sensitivity, and overall agreement of CBCT diagnosis and histopathological reports for 3 blinded evaluators.

Materials and Methods

Thirty-six PA lesions diagnosed by clinical symptoms and radiographic findings were selected for the study. The inclusion criteria of lesions were a minimum average diameter of 5 mm from sagittal views of CBCT images. The protocol was approved by the Institutional Review Board of the University of Southern California, Los Angeles, CA (#UP-12-00506).

Radiology

PA radiolucency was imaged by Kodak 9000 3D (Carestream Health Inc, Rochester, NY) at the Redmond Imaging Center, University of Southern California. The technician acquired a fixed field of view volume of 3.75 × 5 cm. The pixel size was 76 μm and 15-bit pixels (32,768 gray values). The scanner was operated at 70–90 kV and 8–10 mA. The Digital Imaging and Communications in Medicine format images were exported from Kodak 9000 and imported into InVivo Dental Application 5.1.6 software (Anatomage Inc, San Jose, CA).

Histopathology

Root-end resections were performed per routine clinical protocols. Histopathological specimens were obtained for microscopic examination, stained by hematoxylin-eosin, and analyzed. All histopathological specimens were examined by a board-certified oral pathologist (PS) without prior knowledge of clinical symptoms of patients, CBCT diagnosis, and surgical observation of lesions.

Pathology Microscopic Criteria for the Diagnosis of Cysts versus Granulomas. For a granuloma diagnosis, there had to be no histopathologic evidence of cystic organization; no evidence of squamous lining epithelium as specifically described for cyst diagnosis to follow; the presence of soft connective tissue morphology consistent with granulation tissue; and the presence of inflammatory cell infiltrates, foamy histiocytes, or multinucleated giant cells. For a cyst diagnosis, there had to be histopathologic evidence of fibrous connective tissue with cystic organization and more than 1 definitive foci of stratified squamous lining epithelium comprising ≥50 cohesive cells attached by visible cell-cell junctions on high-power magnification (60 × original) and the presence or absence of inflammatory cell infiltrates within the wall or the lining of the cyst. Epithelial islands or odontogenic rests located or embedded within fibrous connective tissue were not considered evidence of lining cystic epithelium. Overt evidence of keratinaceous debris within an epithelial-lined lumen and the presence of cholesterol clefs and Rushton bodies, erythrocyte extravasation and hemosiderin deposition, and occasional multinucleated giant cells was considered supportive of a cyst diagnosis along with the aforementioned criteria and the acknowledgment that histopathologic findings can overlap between cysts and granulomas, and there is no single pathognomonic feature to discriminate the 2 lesions histopathologically. A second evaluation of all biopsy slides was taken by the same oral pathologist after 2 weeks to calculate the intrarater reliability.

Evaluation of Diagnostic Criteria

For each lesion, we computed a cumulative score 0–6 as explained in the prior section. A score of 1 meant that only 1 of the criteria in Table 1 was determined to be present in the images. Because of the limitations of CBCT scans and the fact that most cysts do not show all 6 characteristics (eg, not all cysts may perforate the cortical plate), all the lesions did not show the 6 radiologic findings. For the purpose of finding the optimal number of diagnostic criteria (scoring system) to determine if a lesion was a cyst, we conducted 6 receiver operating characteristic (ROC) curve analyses (21). ROC provides measures of accuracy, which is constructed from the sensitivity and specificity of a diagnostic test. The measure of accuracy was the area under the curve (AUC), representing the average specificity over all sensitivities (21). For the first ROC curve, a diagnosis of a cyst corresponded to a score ≥1. The diagnosis of a cyst in the sixth analysis corresponded to a score of 6. Therefore, 6 ROC analyses were conducted based on the histopathologic diagnoses from the oral pathologist (cyst = yes/no) and the 6 CBCT diagnoses according to the 6 scoring systems (≥1, ≥2, ..., = 6). The AUC (21) was calculated for each scoring system, ranging in value from 0.5 (chance) to 1.0 (perfect discrimination or accuracy) (21). The largest of the 6 AUCs was selected as the best scoring system and was chosen for the diagnosis of a cyst. Three independent endodontist evaluators (JG, OS, and TC) blinded to the histopathological reports examined the images of 56 lesions using the 6 criteria in Table 1. A

### Diagnostic Criteria

A set of diagnostic criteria (Table 1) for PA cysts was established based on radiologic characteristics (ie, location, periphery, shape, internal structure, effects on surrounding structure, and perforation of the cortical plate) (19, 20). For each lesion, evaluator 1 (JG), without prior knowledge of the patient or the histopathological report, examined the Digital Imaging and Communications in Medicine images and tabulated the data. For each criterion, if radiologic evidence was found, the lesion would be scored 1 point. A cumulative score for each lesion was documented. The final score for each lesion was a number between 0 and 6 according to the number of positive findings.

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**TABLE 1. CBCT Diagnostic Criteria for the Differential Diagnosis of a Cyst**

| Located at the apex of the involved tooth |
| Well-defined corticated border |
| Shape is curved or circular |
| Internal structure of lesion is radiolucent |
| Displacement and resorption of the roots of adjacent teeth |
| with a curved outline |
| Perforation of cortical plate |
Intra- and Inter-rater Reliability

To assess the intrarater reliability of the 3 evaluators, all 36 cases were examined for a second time 6 months later. The intrarater reliability of each evaluator was conducted with Cohen kappa. Cohen kappa assesses the extent to which a rater agrees in 2 evaluations of the same set of cases (22). Agreement was noted as excellent if $\kappa \geq 0.75$, good if $0.60 \leq \kappa < 0.75$, intermediate if $0.4 \leq \kappa < 0.60$, and poor if $\kappa < 0.4$ (22). Interrater agreement between the 3 evaluators was conducted using Cronbach alpha tests. The Cronbach alpha test is used to assess the internal consistency among multiple raters (23). Agreement was noted as excellent if $\alpha \geq 0.80$, good if $0.60 < \alpha < 0.79$, intermediate if $0.40 < \alpha \leq 0.60$, and poor if $\alpha < 0.40$ (23). Figure 1 describes the overall protocol for the study.

CBCT Comparison to Histopathological Reports

Using the best scoring system (\( \geq 4 \) criteria), CBCT imaging was compared with histopathological diagnoses. Sensitivity, specificity, false-positive rate, false-negative rate, overall agreement, and AUCs were calculated for each of the 3 independent evaluators. Accuracy was noted as good if AUC > 0.80, moderate if 0.60 ≤ AUC ≤ 0.80, and poor if AUC < 0.60 (24). SPSS software version 17.0 (SPSS Inc, Chicago, IL) was used in this study with significance accepted at a value of $P < .05$.

Results

The intrarater agreement for the oral pathologist was excellent ($\kappa = 0.93$). Among the 6 AUCs (Fig. 2A), one for each scoring system, a score $\geq 4$ positive findings exhibited the highest AUC (0.76); therefore, it was used in this study for the differential diagnosis of a cyst. A lesion was diagnosed as a cyst if 4 or more of the 6 criteria evaluated were considered as “yes” by the evaluator.

Interrater agreement was good for evaluator 1 ($\kappa = 0.71$) and excellent for evaluators 2 ($\kappa = 0.76$) and 3 ($\kappa = 0.77$). Results of Cronbach alpha indicated that the interagreement between the 3 evaluators was excellent, and it was not caused by chance agreement ($\alpha = 0.87$). When comparing each evaluator’s ratings with the histopathologic diagnosis (PS), we found a high mean overall agreement (mean overall rate = 0.77). For evaluator 1, 30 of 36 lesions had the same diagnosis as the histopathological reports (overall agreement = 0.83, AUC = 0.76, Fig. 2B). For evaluator 2, 27 of 36 lesions were in agreement (overall agreement = 0.75, AUC = 0.70, Fig. 2B), whereas 26 of 36 were in agreement for evaluator 3 (overall agreement = 0.72, AUC = 0.69, Fig. 2B). Table 2 presents the sensitivity, specificity, overall agreement, false-positive rate, false-negative rate, and AUC for all 3 evaluators compared with the histopathological results from the board-certified oral pathologist (Table 2).

Figure 3A–F shows an example of a lesion with consistent diagnoses of a PA cyst by 3 evaluators and the histopathological report. Figure 3G–L shows an example of an inconsistent differential diagnosis between 3 evaluators (a PA granuloma) and the histopathological report (a PA cyst). Figure 3M–R shows an example of a lesion with consistent diagnoses of a PA granuloma by 3 evaluators and the histopathological report.
Figure 3 shows an example of a lesion with inconsistent diagnoses between CBCT evaluation (2 of 3 evaluators diagnosed it as a PA cyst) and the histopathological report (a PA granuloma).

### Discussion

Surgical biopsy and pathological examination are standard procedures when a distinction between a PA cyst and a granuloma is necessary. Nair (2) concluded that 85% of all PA lesions were PA granulomas. Lin et al (25, 26) indicated that most reactive PA lesions (granulomas and radicular cysts) may heal by nonsurgical root canal therapy except apical true cysts. Apical true cysts (PA cavities completely enclosed in epithelial lining), particularly larger lesions, may require surgical intervention because they are self-sustaining and not dependent on the presence or absence of intracanal infection or inflammation (2, 25). However, there is no direct evidence to show that large cysts or granulomas can or cannot heal after nonsurgical root canal therapy; indirect clinical evidence appears to indicate that radicular cysts may heal or regress after nonsurgical root canal therapy, whereas apical true cysts require surgery (25). The key factor in establishing that apical true cysts can or cannot heal after nonsurgical root canal therapy would be the pretreatment identification of an apical lesion as an apical true cyst (25). Currently, there is no predictable method of identifying pretreatment apical lesions as an apical true cyst (25). Currently, there is no predictable method of identifying pretreatment apical lesions as an apical true cyst (25). Pretreatment biopsy alone cannot be used to imply that apical true cysts can or cannot heal after nonsurgical root canal therapy; this determination requires definitive pretreatment identification, which is impossible at this time (25). If we were able to predict the presence of apical true cysts before nonsurgical root canal therapy, we could conduct outcome studies in animals and humans to test the hypothesis of whether inflammatory cysts can or cannot regress after nonsurgical root canal therapy (25). Thus, as a potential step toward this end, we evaluated in the current preliminary study whether CBCT imaging could represent a feasible biopsy-independent alternative for differentiating apical cysts from granulomas.

CBCT imaging has been considered to be a nonsurgical alternative used in the differentiation between apical cysts and granulomas (14). Tsai et al (11) compared CBCT imaging and PA radiographs, and the results showed that CBCT imaging showed excellent accuracy when simulated lesions were larger than 1.4 mm, whereas AP radiographs showed poor accuracy for all lesion sizes. Rodrigues et al (12) used PA radiographs, CBCT scans, and magnetic resonance imaging as methods to evaluate a lymphangioma mimicking AP, concluding that CBCT scans could diagnose well-circumscribed lesions. However, its use is still controversial. CBCT imaging provides gray values rather than Hounsfield units, which are easily affected by field of view, spatial resolution selection, hard beaming, scattering, and the number of basis projections (17). On the positive side, CBCT imaging has advantages in the field of endodontics because of better representation of soft tissue, lower exposure to radiation, and less cost compared with conventional CT imaging (27).

In this study, a set of 6 diagnostic criteria was evaluated to differentiate PA cysts from granulomas. The 6 criteria were based on the radiologic characteristics of a PA cyst (location, periphery, shape, internal structure, and effects on surrounding structure) (20). In some cases, it is difficult to differentially diagnose a PA cyst from a granuloma (20). The reason is that a granuloma might present...
with the same radiologic characteristics as a cyst. Also, not every cyst will show all radiologic features (ie, not all cysts may perforate the cortical plate) (20). Thus, an optimal number of criteria were assessed (highest AUC of 6 diagnostic criteria) in order to differentiate a cyst from a granuloma with the most accuracy. Using ROC analyses to assess the accuracy of each scoring system, we found that 4 or more positive findings (criteria on Table 1) were the optimal choice for a lesion to be diagnosed as a cyst (AUC = 0.76). All 3 evaluators in our study showed moderate accuracy when compared with histopathological diagnoses from the board-certified oral pathologist (AUC = 0.76, 0.70, and 0.69).

In the present study, the results indicate that CBCT images could provide good to excellent accuracy for differential diagnosis between cysts and granulomas with excellent inter-rater (\( \kappa = 0.87 \)) and good to excellent intrarater reliabilities. The mean overall agreement of 3 evaluators was 0.77, which was the same as that in a previous study by Simon et al (14) using CBCT gray values. In that study, 13 of 17 CBCT diagnoses coincided with the biopsy reports (overall agreement = 0.77). According to the authors, in the 4 cases of split diagnosis, the pathological reports were inaccurate to diagnose AP because the biopsy examination might not represent the entire lesion and epithelium may be present but not identified in the viewed sections. The authors concluded that CBCT imaging might be more accurate than biopsy examination.

In a recent study by Rosenberg et al (13), 2 radiologists independently analyzed CBCT images from 45 patients using a set of diagnostic criteria. The results indicated a weak (poor) agreement between 2 radiologists (\( \kappa = 0.14 \)), and an overall accuracy (AUC) of 0.65 for the first radiologist and 0.51 for the second compared with the biopsy results. The moderate to weak agreement between radiologists might be because of the large number of possible diagnoses (eg, cysts, likely cysts, granulomas, likely granulomas, and others), whereas only 2 possible differential diagnoses were taken into account in this article (cyst/granuloma). In this study, we also attempted to reduce uncertainty by reducing the number of criteria to 6 and making the diagnosis of a cyst a quantitative measure (the presence of 4 or more radiologic criteria). In the previous study, radiologists chose the best diagnosis for each lesion based on the diagnostic criteria without a clear scoring system; however, in the present study, evaluators only examined the lesion based on the 6 predefined criteria and reported a cyst diagnosis if 4 or more positive findings were present. The authors believe that this quantitative scoring system reduced uncertainty and increased inter-

![Figure 3](image-url)
rater and intrarater reliability and accuracy compared with prior studies.

One of the limitations in our study was the small sample size. Further studies on a larger number of cases will be required to confirm the findings of the present study. Moreover, the small amount of PA cyst lesions (10/36) also may have contributed to the high rates of false negatives (4/10, 4/10, and 4/10 for the 3 evaluators). Another limitation is the inclusion of only 2 types of PA lesions. On the positive side, the accuracy of all evaluators was moderate, and the inter- and intrarater reliability was good to excellent. Finally, the cross-sectional nature of this study and the level of evidence it represents is insufficient to make any recommendations or claims regarding the clinical usefulness of CBCT imaging for the diagnosis of reactive endodontic lesions. Well-controlled human studies that are longitudinal in nature would be required to show the clinical relevance and efficacy of CBCT imaging in the current context, particularly given the radiologic standard of care (ie, as low as reasonably achievable) for radiation exposure and safety to patients. Accordingly, the current study is not meant to provide clinical evidence or rationale for subjecting patients to the additional radiation of CBCT imaging.

In summary, CBCT images provided a moderately accurate differential diagnosis between cysts and granulomas when the apical lesion presented with a minimum average diameter of 5 mm. CBCT imaging exhibits potential for further research in endodontics for the differential diagnosis of cysts versus granulomas.

Acknowledgments

The authors deny any conflicts of interest related to this study.

References