Original Article

The Association Between the Histopathological Diagnosis and Lesion Volume in Periapical Lesions

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Abstract

To evaluate the association between the histopathological diagnosis, clinical features and lesion volume in human radicular cysts and periapical granulomas. Periapical biopsies histopathologically diagnosed as radicular cysts (n = 30) and periapical granulomas (n = 30) from teeth with periapical lesions were recruited. Pathological diagnosis, patients' age, gender, and location of the periapical lesion were obtained from treatment records. Preoperative CBCT images were obtained from the hospital database for measurement of lesion volume using OnDemand3D™ Dental software. The Mann-Whitney U test or Kruskal-Wallis H test was used to determine the association between lesion volume and pathological diagnosis: radicular cyst and periapical granuloma, and other clinical data. A *P*-value less than 0.05 was considered statistically significant. There was a significant association between lesion volume and pathological diagnosis of the periapical lesions. Radicular cysts showed a significantly higher median lesion volume compared to periapical granulomas, 693.58 (IQR 195.94 - 1449.75) and 67.41 (IQR 41.03 - 185.38), respectively ($P<0.001$). No significant association between the lesion volume of periapical lesions and other variables including the gender, age, and location of the periapical lesions was found. The higher periapical lesion volume was significantly associated with pathological diagnosis as radicular cyst. Gender, age, and location of periapical lesions were not associated with the volume of periapical lesions.

Keywords: radicular cyst, periapical granuloma, lesion volume, CBCT

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Introduction

Periapical lesions such as radicular cysts or periapical granulomas are among the most common pathologies encountered in dentistry. They are primarily caused by bacterial infection of the pulpal tissue with subsequent advancement to the root apex and induce an immune response in the periapical tissue. The intricate interplay between bacteria and the defense mechanisms of the host triggers the production of mediators and proinflam-

matory cytokines by immune cells, ultimately resulting in periapical inflammation and bone resorption. This is a defensive mechanism to prevent the spread of microbial invasion from the root canal to the surrounding tissues.[1] Periapical granuloma represents a granulation tissue, while radicular cyst is a cavity lined by epithelium.[2,3] Previous studies indicated that the proliferation of epithelial rests of Malassez in periradicular tissue is a crucial process in the formation of radicular cysts.[4-6] During periapical inflammation, inflammatory mediators, proinflammatory cytokines and growth factors released from the host cells can stimulate the proliferation of epithelial rests, and possibly develop into a radicular cyst through several theories.[5] Several studies have explained the inflammatory mechanisms in the pathogenesis of periapical granuloma and radicular cyst.[5,7-10]

Previous studies[11-13] have reported a high correlation between the 2-D radiographic size of periapical lesions and prevalence of radicular cysts. Çalışkan *et al.*[11] reported that 82.2 % of lesions with 2–9.9 mm diameter were diagnosed histologically as periapical granulomas and 11.3 % as radicular cysts; whereas 51.6 % of lesions with 10–20 mm diameter were diagnosed as periapical granulomas and 42 % as radicular cysts. Moreover, the prevalence of radicular cyst up to 92 – 100 % was reported for cases with size of periapical lesion more than 200 mm^2 and lesion diameter greater than 20 mm.[12,14] Pitcher *et al.*[15] assessed volume of periapical lesion using CBCT volumetric analysis and reported that the median volume of radicular cysts (179.9, IQR = 77.7 – 430.7) was approximately three-fold that of periapical granulomas (57.4, IQR = 30.7 – 101.7) and indicated that lesion volume was a strong predictor for radicular cyst.

Periapical radiographs are two-dimension (2-D) images that have been commonly used to evaluate the size of periapical lesions. However, periapical radiographs have the well-known limitations as the geometric distortion of the actual lesion size and restrictive information of the relation to surrounding structures. Lesion overlapping with neighboring anatomic structures might be difficult for radiographic interpretation.[16] Information is demonstrated in only two dimensions: a periapical lesion can only be detected in the radiograph when 30 % – 50 % of the mineral content of bone has been lost. In addition, the buccolingual expansion of the lesion cannot be measured with 2-D radiographs.[17]

Considering some limitations on conventional radiography, cone-beam computed tomographic (CBCT) imaging is mainly used for diagnosis, treatment planning, and outcome assessment in surgical endodontics.[18] Previous studies indicated that CBCT images could provide three-dimensional and clinically relevant information such as the relationship of the root apex to adjacent anatomic structures, root canal anatomy, alveolar bone topography, previous procedural complications (i.e., separated instrument, root perforation) and the true size, extent, and location of the periapical lesion.[18,19] In the studies that compared the abilities of periapical radiography and CBCT imaging in detecting periapical lesions, the results showed that CBCT imaging detected and measured periapical lesions more accurately than 2-D radiographs.[20,21]

Despite the previously described advantages of CBCT imaging, the association between three-dimensional measurements of lesion volume and the histopathological diagnosis of periapical lesions has not been sufficiently addressed. Therefore, this study aimed to investigate the association between lesion volume of periapical lesions among the pathological diagnosis: radicular cyst and periapical granuloma, and other clinical features using cone-beam computed tomography image analysis.

Material and Methods

Data collection

The Human Research Ethics Committee of the Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand (HREC-DCU 2021-100) approved the study protocol. The sample size was calculated based on the results of Filho *et al.*[22], considering on an alpha of 0.05 and the power of the test of 90 %. This calculation indicated that a minimum of 24 samples per group would be required. Considering a 20 % compensation for error, the sample size of 30 cases for radicular cyst (n=30) and 30 cases for periapical granuloma (n = 30) were recruited in this study.

The periapical biopsies were obtained during enucleation or from teeth which underwent apicoectomy at the post-graduate endodontic clinic and the oral andmaxillofacial surgery clinic. Periapical lesions histopathologically diagnosed as radicular cyst or periapical granuloma from 2020 were collected backward until the desired number of cases per group (30 cases) was reached.

The biopsy reports during 2018 and 2020 from the Department of Oral Pathology, Chulalongkorn University were reviewed for lesions diagnosed as radicular cyst or periapical granuloma by board-certified oral pathologists who were practicing at the time of surgeries. All histo-pathological slides were reviewed by a board-certified oral pathologist (KD) before including in this study. The histopathological diagnosis was classified as follows[23]:

1. Radicular cyst: Cavity partially or completely lined by non-keratinized stratified squamous epithelium with inflammatory cell infiltrate.

2. Periapical granuloma: Granulation tissue at the apical area of the tooth infiltrated with lymphocytes, plasma cells, and macrophages. Fibrous tissue can be present at the periphery.

Inclusion criteria were as follows:

1. Patients underwent the surgical removal of periapical lesions and the biopsies were histopathologically diagnosed as periapical granuloma or radicular cyst.

2. Pre-operative CBCT images which covered the entire periapical lesion and had been taken before the enucleation of periapical surgery were available.

3. Periapical radiolucencies were observed on the pre-operative CBCT images.

Exclusion criteria were as follows:

1. Patients with incomplete treatment records.

Demographic and clinical characteristics were obtained from treatment records. The clinical data collected were gender, age of patient, location of periapical lesion: anterior maxilla, posterior maxilla, anterior mandible, posterior mandible.

Radiographic Analysis

Preoperative CBCT images were obtained from the hospital database for radiographic analysis. For measurement of lesion volume from CBCT images, the Digital Imaging and Communications in Medicine (DICOM)–based image data were imported into the OnDemand3D™ Dental software (CyberMed, Seoul, Republic of Korea) and performed directly on a computer monitor screen (P2419H flat panel display, Dell, China). The root-associated with the periapical lesion was shown in three planes (axial, coronal, and sagittal). To determine the volume of lesion volume, one researcher (SV); endodontist, supervised by a board-certified oral and maxillofacial radiologist (PS), examined the preoperative CBCT images for the presence of periapical lesions. The volume of interest was determined in square areas selecting the most exterior point of the lesion in all three planes (Fig 1a). The “Profile line” tool was used to determine local threshold at the most exterior point of the lesion. After setting the threshold, the volume of lesion was automatically determined by the program using the “Segmentation” tools, followed by a 3D reconstruction of the radiolucency. Modifications of the lesion border were performed with the “Fine Tuning” and “Sculpt” functions. In case of doubt, SV consulted the board-certified oral and maxillofacial radiologist (PS). The lesion volume was measured in mm^3 (Fig. 1b).

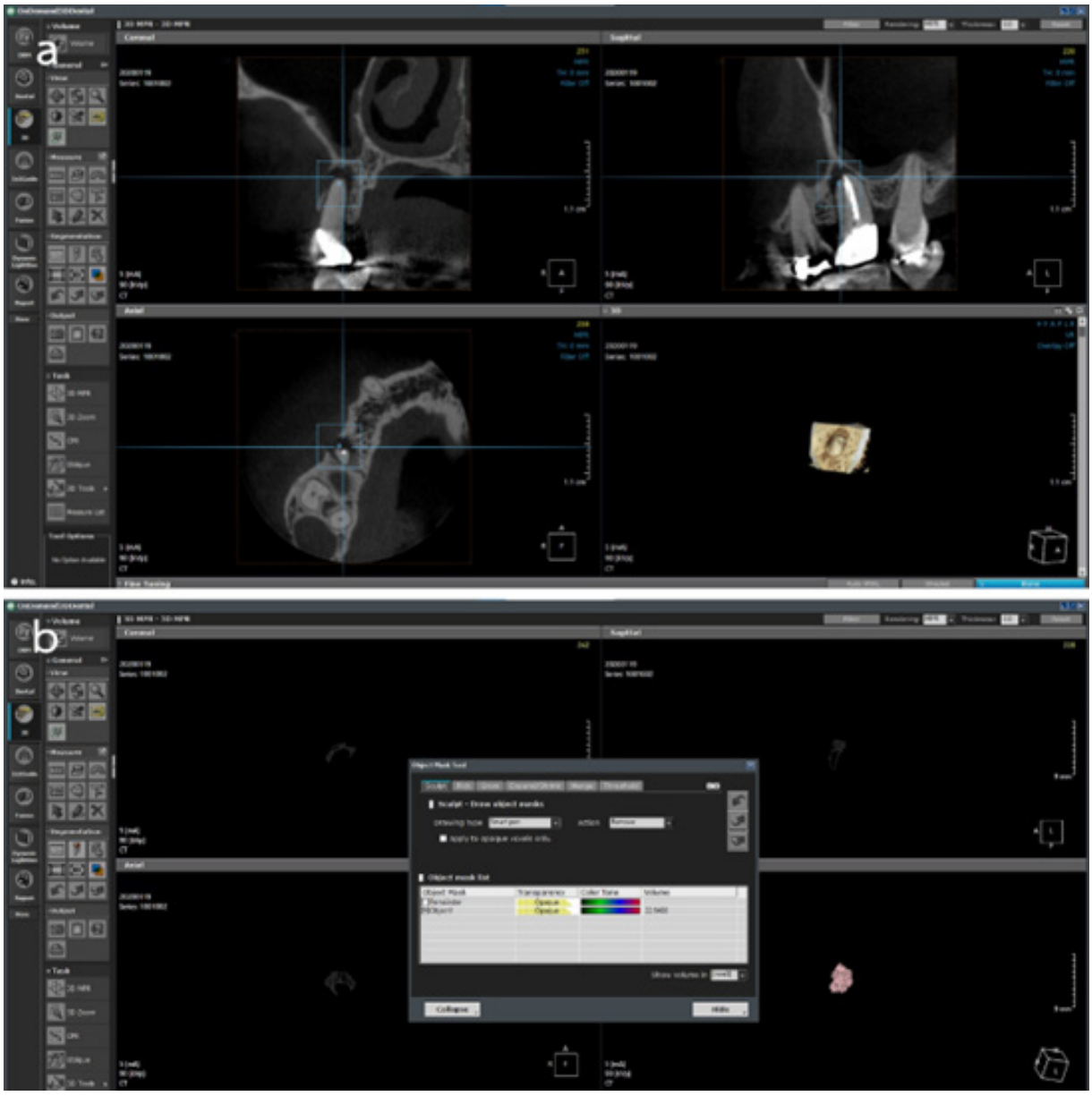

Figure 1 *Segmentation of the periapical lesion of maxillary right second premolar (tooth 15) in coronal, sagittal and axial views. (a) The volume of interest was determined in square areas selecting the most exterior point of the lesion in all three planes. (b) The volume of lesion was automatically measured by the OnDemand3D™ Dental software (CyberMed, Seoul, Republic of Korea) using the "Segmentation" tools, followed by a 3D reconstruction of the radiolucency.*

Statistical Analysis

The distribution of the data was analyzed by the Shapiro-Wilk normality test. Due to a nonparametric data distribution, the lesion volume was presented as median and interquartile range (IQR). The differences in the proportions of the demographic and clinical parameters including gender, age range, and location of periapical lesion between radicular cyst and periapical granuloma were analyzed using Pearson's chi-square test. The Mann-Whitney U test was used to determine the association between the lesion volume and gender as well as pathological diagnosis, while the Kruskal-Wallis H test was used to determine the association between the lesion volume and age range as well as location of periapical lesion. The intra-rater reliability test of lesion volume was done by

reinvestigating 10 randomly selected cases one month apart and was calculated using intraclass correlation coefficients (ICC). The ICC was 0.912, indicating excellent reliability.[24] Statistical analysis was calculated using IBM SPSS statistics for Windows, version 29 (IBM, Armonk, New York). The $P<0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics

A total of 60 periapical biopsies histopathologically diagnosed as radicular cyst (n = 30) and periapical granuloma (n = 30) were included. From the 60 biopsies analyzed, 41.7 % were in males and 58.3 % in females, with mean age of 46.5 ± 14.46 years. Seventy-seven percent of biopsies were in the maxilla and 23 % were in the mandible. (Table 1). There was no statistically significant difference in the proportions of the demographic and clinical parameters including gender, age range, and location of periapical lesion between radicular cyst and periapical granuloma (P = 0.793, 0.145 and 0.492, respectively).

The association between lesion volume and clinical data and pathological diagnosis

The median lesion volume was 194.46 (IQR 63.74-735.01) mm^3. The radicular cysts had median lesion volume of 693.58 (IQR 195.94-1449.75), whereas the periapical granulomas had median lesion volume of 67.41 (IQR 41.03-185.38). Radicular cysts exhibited a significantly higher median lesion volume compared to periapical granuloma ($P < 0.001$) (Table 2). In addition, other investigated variables including gender, age range, and location of periapical lesion demonstrated no statistically significant association with the lesion volume (P = 0.333, 0.429 and 0.273, respectively).

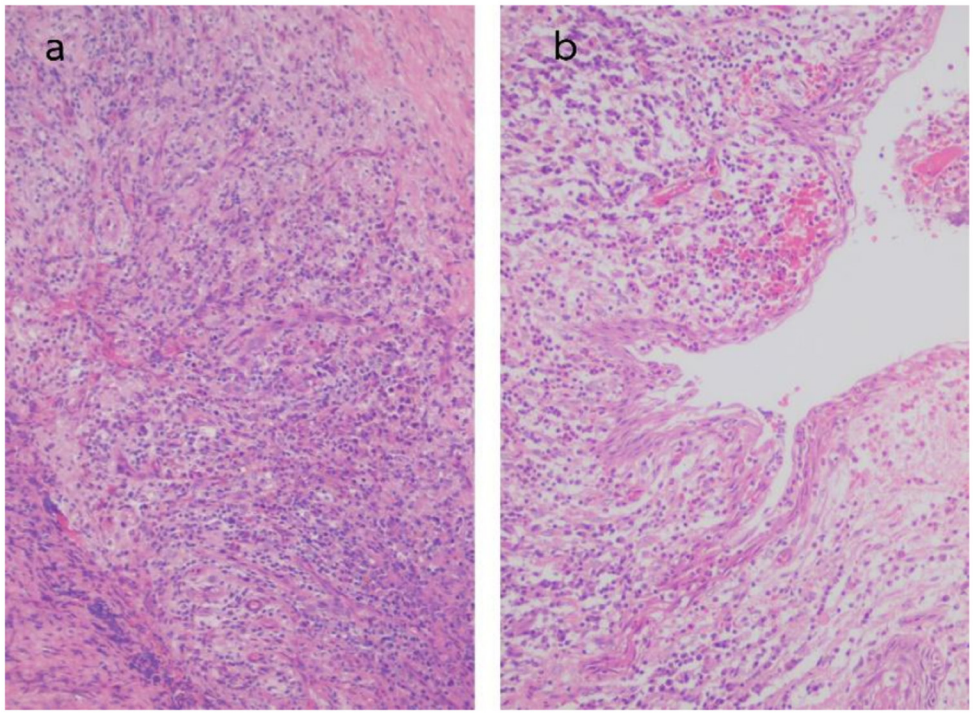

Figure 2 *Representative photomicrographs of (a) periapical granuloma and (b) radicular cyst. (Haematoxylin and Eosin staining, original magnification 100X)*

Table 1 *Demographic and clinical characteristics according to the pathological diagnosis*

	Total (n=60)	Periapical granuloma (n=30)	Radicular cyst (n=30)	*P*-value[a]
Gender, n (%)				0.793
Male	25 (41.7%)	12 (40.0%)	13 (43.3%)	
Female	35 (58.3%)	18 (60.0%)	17 (56.7%)	
Age, n (%)				0.145
15-30	10 (16.7%)	4 (13.3%)	6 (20.0%)	
31-40	13 (21.7%)	7 (23.3%)	6 (20.0%)	
41-50	5 (8.3%)	3 (10.0%)	2 (6.7%)	
51-60	17 (28.3%)	5 (16.7%)	12 (40.0%)	
> 60	15 (25.0%)	11 (36.7%)	4 (13.3%)	
Tooth Location, n (%)				0.492
Anterior maxilla	37 (61.7%)	17 (56.7%)	20 (66.7%)	
Posterior maxilla	9 (15.0%)	6 (20.0%)	3 (10.0%)	
Anterior mandible	8 (13.3%)	5 (16.7%)	3 (10.0%)	
Posterior mandible	6 (10.0%)	2 (6.6%)	4 (13.3%)	

[a]*analysed using Pearson's Chi-Square test*

Table 2 *The associations between investigated variables and the lesion volume in periapical lesions*

Variables	Lesion volume Median (IQR)	*P*-value
Gender		0.333[a]
Male (n=25)	232.38 (58.14-838.51)	
Female (n=35)	170.94 (64.27-712.66)	
Age		0.429[b]
15-30 (n=10)	507.97 (119.20-3141.12)	
31-40 (n=13)	263.80 (55.63-491.45)	
41-50 (n=5)	197.42 (32.45-1671.41)	
51-60 (n=17)	278.31 (109.79-855.55)	
> 60 (n=15)	117.02 (52.71-499.11)	
Pathological diagnosis		**<0.001**[a]
Periapical granuloma (n = 30)	67.41 (41.03-185.38)	
Radicular cyst (n = 30)	693.58 (195.94-1449.75)	
Tooth location		0.273[b]
Anterior maxilla (n=37)	191.51 (58.14-657.99)	
Posterior maxilla (n=9)	70.55 (32.34-556.86)	
Anterior mandible (n=8)	325.81 (94.58-1444.52)	
Posterior mandible (n=6)	605.88 (344.15-3141.12)	

[a]*analysed using Mann–Whitney U test*
[b]*analysed using Kruskal-Wallis H test*
A significant association (P < 0.05) was indicated in bold.

Discussion

This study showed the association between periapical diagnosis and the lesion volume in periapical lesions. Previous clinical studies[15,25] of the lesion volume of radicular cyst and periapical granuloma, measured from CBCT imaging suggested that the CBCT volume of a periapical lesion might be used for predicting radicular cyst and the relationship between the CBCT volume and the pathological diagnosis of the periapical lesions should

be further investigated.[25] This study demonstrated that the higher periapical lesion volume was associated with pathological diagnosis as radicular cyst.

Although the radiographic lesion size was not considered to be a diagnostic sign for the type of periapical lesion, there was a trend towards an increased prevalence of radicular cysts amongst the higher lesion size.[26,27] Previous studies[12,13,27] have reported the association between the size of periapical lesion and pathological diagnosis, especially radicular cyst, but the association between lesion volume and pathological diagnosis of periapical lesion: radicular cyst or periapical granuloma, was insufficient addressed. Mortensen *et al.*[13] and Natkin *et al.*[27] demonstrated that the relative number of radicular cysts increased with increasing size of lesions, whereas the relative number of periapical granuloma decreased. In addition, Lalonde *et al.*[12] indicated that the relation of the radiographic lesion size to pathological diagnosis of periapical lesions. They reported that with a radiographic lesion size of 200 mm^2 or more, the incidence of radicular cysts was almost 100 %. However, limitations of 2D radiographs are well known as the geometric distortion of the actual lesion size and restrictive information of relation to surrounding structures.[16] Conversely, CBCT imaging detects and measures periapical lesions more accurately than 2D radiographs.[20]

This study is one of a few clinical studies[15] evaluating an association between pathological diagnosis of periapical lesions, and the lesion volume measured by CBCT imaging. In the present study, we determined the association between pathological diagnosis of periapical lesion and lesion volume using CBCT analysis and found that a radicular cyst showed a significantly higher lesion volume compared to periapical granuloma. This result is consistent with a previous study.[15] Pitcher *et al.*[15] investigated the predictive validity of a radicular cyst screening method using CBCT volumetric analysis and indicated that lesion volume was the strong predictor for radicular cyst. They reported that if the lesion volume was >247 mm^3, there was 80 % probability of a radicular cyst. Nevertheless, a definitive diagnosis of a radicular cyst can only be attained by biopsy and histopathological evaluation.[28,29]

In addition, CBCT imaging has been used for assessing the outcome of endodontic treatment.[18] Kim *et al.*[30] investigated parameters of preoperative periapical lesions using CBCT images. They reported that the volume of the periapical lesion was a significant predictor on the outcome of endodontic microsurgery. Periapical lesions larger than 50 mm^3 in volume had a reduced percentage of success, whereas lesions smaller than 50 mm^3 in volume were significantly associated with successful treatment outcomes. These results are in agreement with Kreisler *et al.*[31] who evaluated the effect of related factors on the outcome of apical surgery and found that the periapical lesion volume was one of significant predictors. They found that teeth with lesion volume above 60 mm^3 had a significantly lower success rate after apical surgery.

In the present study, the median (IQR) of overall lesion volume was 194.46 (IQR 63.74-735.01) mm^3, which was quite large since samples did not only come from Postgraduate Endodontic clinic, but also from Oral and Maxillofacial Surgery clinic which mostly operated on large periapical lesions. The limitation of the present study is that the whole lesion was not always collected for histopathological examination during the surgery. Because of the limitations of the clinical study, the biopsy included in this study could not observe the relationships of periapical lesions with the root apex, inflamed area, and surrounding bones.

In the present study, there was no statistically significant difference in the demographic and clinical parameters including gender, age range, and location of periapical lesion between radicular cyst and periapical granuloma (P = 0.793, 0.145 and 0.492, respectively). Banomyong *et al.*[25] determined the association between clinical characteristics including history of fistula, swelling, pus, exudate, tooth mobility, pain on percussion and histopathological diagnosis of periapical granuloma and radicular cyst, and reported that there was no significant association of clinical characteristics between periapical granuloma and a cyst. In addition, the association between

the volume of periapical lesions and clinical data: gender, age of patient, location of periapical lesion was not found in this study. No previous clinical studies have reported the relationship between gender, patient's age, location of periapical lesion and lesion volume of radicular cyst or periapical granuloma. Nonetheless, radicular cysts are the most common odontogenic cystic lesions that occur in jaws.[32-34] Radicular cysts occur in tooth-bearing sites of the jaw, but more frequently in the anterior maxilla, than the mandibular region.[32,33] Incidence of radicular cyst is most commonly occur between the third and sixth decade of life, showing a predominance in males.[32,33]

Based on our findings, the volume of periapical lesions might be used to provide the differential diagnosis between the periapical granuloma and a radicular cyst, be helpful in treatment planning, and probably imply the prognosis of treatment.

Conclusions

There is a significant association between the histopathological diagnosis and lesion volume in periapical lesions. Radicular cysts exhibited a significantly higher lesion volume compared to periapical granuloma. Gender, age of patient, and location of periapical lesion were not associated with volume of periapical lesion.

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