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Analysis of Periapical Biopsies Submitted for Histopathological Evaluation: A Retrospective Study

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Analysis of Periapical Biopsies Submitted for Histopathological Evaluation: A Retrospective Study

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2. Abstract

Apical periodontitis, a result of pulp infection, is the most common pathological process in the periapical region. Disciplined clinical and radiographic evaluations and appropriate diagnostic tests can detect lesions related to apical periodontitis. Aside from this, lesions mimicking pulp-related pathology but unrelated to pulpal infection and necrosis are occasionally discovered in the periapical region. Teeth that are refractory to routine endodontic therapy are often managed with endodontic surgery, by which diseased periapical tissue is surgically removed. The objective of this study was two-fold: (1) to determine the prevalence of diverse periapically located pathological entities, and (2) to apply that information to evaluate the rationale for routine submission of surgically obtained tissue for histological examination and diagnosis.

Methods: A 5-year retrospective analysis of pathology reports from the UCONN Oral Pathology biopsy service was conducted. Periapical lesions were categorized as (a) odontogenic inflammatory, (b) odontogenic non-inflammatory, (c) non-odontogenic non-neoplastic, or (d) non-odontogenic neoplastic in nature, respectively, and the prevalence of lesions in each pathologic category was determined. The correlations among prevalence of specific lesions, patient demographic data and anatomic location in the jaws were analyzed. Also, the correlation between the final diagnoses and the general category of submitting clinicians' provisional diagnoses was assessed to determine the efficacy of clinicians' index of suspicion.

Results: A total of 21649 pathology reports were reviewed, of which 2979 lesions (13.8%) met the criterion of being located at the apices of teeth. Of these, 2693 lesions (90.4%) carried diagnoses associated with apical periodontitis. A total of 286

cases (9.6%) from the periapical region represented a wide range of pathological conditions unrelated to apical periodontitis. Periapical granuloma was the most common odontogenic inflammatory lesion (51.5%); odontogenic keratocyst was the most common odontogenic non-inflammatory lesion (2.08%); and nasopalatine canal cyst was the most common non-odontogenic periapical lesion (1.1%). Six malignant neoplasms were diagnosed in periapical locations. Periapical pathology was more common in the maxilla than the mandible. There was no correlation among specific periapical pathological entities, age and gender. A majority (84%) of the final diagnoses were in the general category of the provisional clinical diagnoses provided by the clinicians; 16% of clinical impressions were inconsistent.

Conclusions: In the course of assessing a tooth for non-surgical endodontic therapy, careful clinical evaluation aids in diagnosing a large majority of odontogenic inflammatory lesions. However, lesions unrelated to apical periodontitis also occur in the periapical region. Histopathologic examination of periapical specimens remains the gold standard for establishing accurate diagnoses and differentiating amongst the various periapical pathoses. Routine submission of periapical biopsies is required to establish a specific diagnosis **any time** a recoverable amount of tissue can be removed from a periapical surgical site. In addition to dictating further management, histopathologic examination helps to rule out uncommon, potentially destructive and/or life-threatening lesions.

3. Review of Literature

3.1 Introduction

The practice of dentistry is centered around the diagnosis and management of diseases that afflict teeth as well as the surrounding hard and soft tissues. Dental caries and periodontal disease are the most common infectious and inflammatory conditions that dentists manage on an everyday basis. Apical periodontitis, a potential sequela of dental caries, is the most commonly encountered pathological process resulting from carious involvement of dental pulpal tissue. Dentists are responsible for its clinical evaluation, initial diagnosis and management. In addition, dentists occasionally encounter other pathological conditions that affect the oral and maxillofacial complex. Several pathological conditions unrelated to pulpal disease can mimic apical periodontitis clinically and radiographically. Therefore, it is essential for all dental practitioners to be familiar with the pathogenesis and the classic historical, clinical and radiographic features of apical periodontitis, in order to distinguish it from other odontogenic or non-odontogenic lesions that can present in the periapical region. In the following sections, the salient features of apical periodontitis will be described. The criteria and clinical tools used in the diagnosis of apical periodontitis will be reviewed. The prevalence of odontogenic inflammatory lesions and other odontogenic or non-odontogenic pathoses presenting in the periapical area will be discussed. Additionally, the rationale for obtaining additional laboratory tests for diagnostic confirmation, treatment planning and surgical management of apical periodontitis will be discussed.

3.2 Apical periodontitis

Apical periodontitis is an inflammatory process that occurs in the periodontal tissues surrounding the apex of a tooth with an infected, necrotic pulp. Teeth that have undergone carious breakdown or previously traumatized can undergo pulpal necrosis, secondary to microbial colonization and inflammation. The resulting necrotic pulpal and microbial debris can exit the root canal system through the apical foramen and instigate an inflammatory response around the root tip. The inflammatory response represents a biological attempt to "wall off" the microbial and necrotic debris. The resulting destruction of the periodontal soft tissue and alveolar bone immediately surrounding the root tip presents itself radiographically as a well-demarcated lytic change often with a corticated border. This is a relatively common occurrence in daily dental practice, for which treatment options include endodontic therapy or extraction of the involved teeth. Prior to treatment planning, proper diagnostic evaluation is essential. Therefore, clinicians' familiarity with the pathogenesis, history and characterization of apical periodontitis, is critical for effective diagnostic evaluation and management.

3.2.1 Pathogenesis of pulp necrosis

Microorganisms endogenous to the oral cavity have been shown to play a key role in pulp necrosis. A large proportion of the microbes involved in pulpal necrosis that eventuates in apical periodontitis are bacteria. Bacteria enter the pulp through the dentinal tubules via deep carious lesions, microfractures in traumatized teeth, or iatrogenic exposures of dentin. Bacteria can directly or indirectly affect the integrity of the pulp. In general, a pulpal response is evident in teeth with early carious lesions even before bacteria reach the dentin-pulp complex (Brännstrom and Lind 1965). Bacteria can release

active enzymes and metabolites that cause direct damage to the pulp. Lipopolysaccharides (LPS) on the microbes' outer cell membrane are strong chemotactic agents that trigger instigation and regulation of the inflammatory response (Bergenholtz 1990). Similarly, other bacterial extracellular and intracellular components can induce an inflammatory reaction within the pulp (Bergenholtz 1977). Upon recognition of LPS and other bacterial products, antigen presenting cells (APCs) resident within the odontoblastic layer of the pulp initiate an intrapulpal inflammatory cascade. This results in pulpal infiltration with acute and eventually, chronic inflammatory cells; the closed pulpal environment is rich with cytokines, various inflammatory mediators and cytotoxic enzymes. If the overlying carious process is left untreated, or if the localized pulpal inflammation is not addressed, it eventually leads to pulpal necrosis and creates an optimal milieu for further microbial colonization and tissue destruction.

3.2.2. Apical periodontitis: history of characterization and pathogenesis

Over the decades, several studies have characterized the role of microorganisms and their byproducts in apical periodontitis. As far back as 1894, Miller demonstrated the presence of different bacterial species within root canal spaces of diseased teeth (Miller 1894). In 1965, a seminal research study by Kakehashi and colleagues demonstrated the critical role that bacteria play in pulpal and periapical inflammation. They studied the fate of surgically exposed pulps of rats in a normal control population to oral microorganisms and compared it with germ-free rats. In the teeth of rats in the control population complete pulp necrosis, lack of pulpal repair, and formation of periapical lesions were evident. In contrast, pulps of germ-free rats were vital, showed signs of dentinal bridging and no evidence of periapical pathology (Kakehashi et al. 1965). In another study that

highlighted the role of bacteria in periapical pathogenesis, Bergenholtz detected bacteria in traumatized teeth with necrotic pulps and no evidence of obvious pulpal exposure. Analysis of the contents of traumatized teeth with non-vital pulps and radiographically detectable periapical lesions revealed the presence of bacterial growth (Bergenholtz 1974). Sundqvist reported similar findings and further characterized the role of microbes, especially anaerobic bacteria, in the pathogenesis of apical periodontitis. Anaerobic culturing methods were used to evaluate the nature of bacterial colonization in traumatized, non-vital teeth. It was observed that in teeth with radiographically appreciable periapical lesions, anaerobic bacterial colonies were consistently grown out from intracanal samples. By contrast, pulpal content from teeth with no appreciable radiographic bone destruction did not yield anaerobic bacteria, lending support to their role in the destruction of investing soft and hard periapical tissues (Sundqvist 1976). The microbial nature of apical periodontitis in primates was first studied by Möller et al. (Möller et al. 1981). This study involved aseptically necrotized pulpal tissue in monkey teeth. Teeth in one group were infected by indigenous oral flora, whereas teeth in another group were kept bacteria-free. After 6-7 months, bacteria induced an inflammatory reaction in the apical region of infected teeth and there was radiographic evidence of bone destruction. Sterile teeth were confirmed radiographically to lack evidence of apical bone destruction (Möller et al. 1981). The specific antigenic components of bacteria that instigated periapical inflammatory reactions and the nature of resulting tissue destruction were elucidated in subsequent research studies. Bacterial LPS of different species was shown to play a role in inducing inflammation within the pulps and at the apices of teeth using several animal models. In one study, it was observed that LPS induced

inflammation eventuated in pulpal necrosis and formation of periapical lesions comparable to those observed in human beings (Dwyer and Torabinejad 1981). In addition to LPS, several other endogenous oral microbial by-products and components can cause inflammation, pulpal necrosis and subsequent periapical lesions (Dahlén et al. 1981; Pitts et al. 1982). Over time, other investigators have elucidated the role that by-products of endogenous oral microorganisms play in causing pulp necrosis and consequent apical periodontitis.

The pathogenetic mechanisms leading up to apical periodontitis have been well characterized. As described above, bacterial metabolites and byproducts from a necrotic pulp leach out into the apical periodontal area and the surrounding bone through the apical foramen. Following antigen detection by local antigen presenting cells (APC), polymorphonuclear leukocytes (PMNs) and other inflammatory cells migrate towards the site of infection in response to bacterial elements and other local factors. PMNs internalize and destroy bacteria through release of highly active enzymes contained in their cytoplasmic granules. In the process of bacterial elimination, these enzymes cause collateral damage and destroy the surrounding normal bone and extracellular matrix. With the accumulation of infectious and necrotic debris, a chronic inflammatory process ensues. Lymphocytes, macrophages and fibroblasts migrate and attempt to eliminate the infectious debris and "wall off" the area. In addition, macrophages release proinflammatory cytokines and mediators such as IL-1, TNF-α, prostaglandins, and leukotrienes, which potentiate the effect of other immune cells (Artese et al. 1991). These proinflammatory mediators activate dormant osteoclasts. This results in osseous

destruction observable as a radiographically lucent lesion at the apex of a tooth with a necrotic pulp (Wiebe et al. 1996).

3.2.3 Role of microbial biofilms in apical periodontitis

The oral cavity harbors large numbers of microorganisms. Initially, pulpal infection is polymicrobial and dominated by facultative bacteria. When pulps of teeth become devitalized as a consequence of caries or trauma, necrotic tissues in the root canals provide an environment that is conducive to anaerobic bacterial growth (Sundqvist 1976). Anaerobic bacteria selectively proliferate and populate the root canal system; they thrive on necrotic pulpal tissue, components of saliva, and bacterial metabolites (Siqueira et al. 2002). As described above, several anaerobic species have been implicated in apical periodontitis. These bacterial species "co-aggregate" to form complex, often intricate, metabolically integrated communities called biofilms (Nair 1987). The detailed nature of these biofilms has been further characterized over the years by other investigators (Siqueira and Lopes 2001; Chavez de Paz 2007; Ricucci and Siqueira 2010). In contrast to planktonic bacterial growth, being part of a co-aggregated, integrated community is clearly advantageous to the diverse bacterial species that populate the root canal system. In the root canal system a multitude of anaerobic bacterial species is connected by an intricate meshwork of extracellular polysaccharide matrices: this provides a physical barrier against bactericidal enzymes (Costerton 1999), and superior protection from antimicrobial agents (Brown and Gilbert 1993; Chavez de Paz et al. 2007). In addition, there are several distinct features of biofilm-based growth that are conducive to their persistence and "success". (1) Microorganisms in a biofilm dwell in a symbiotic relationship that allows the distribution of nutrients to nutrient-deprived ecosystems

(Mayer et al. 1999). Efficient nutrient exchange and metabolic cooperation enhances bacterial survival in an already nutrient-depleted environment. (2) The variegated nature of the biofilm structure allows for differences in levels of nutrients, pH, oxygen tensions, and metabolic products, thus creating selective micro-environments. These micro-environments provide micro-niches where selective species of bacteria thrive and survive (Socransky and Haffajee 2000). (3) The exchange of genetic material between bacterial species allows them to acquire new traits via subpopulation communication or "quorum sensing" (Davies et al. 1998; Socransky and Haffajee 2002). This tends to enhance their pathogenicity and renders them resistant to multiple chemical agents. Furthermore, it has also been shown that the mutually protective nature of biofilms provides a safe haven for pathogens such as *Actinomyces israelii,* which under normal circumstances are destroyed by neutrophilic infiltrates. Therefore, complex bacterial biofilms that thrive in root canals of non-vital teeth demonstrate a distinctive survival advantage in a harsh environment. This, in turn, makes their eradication a clinical challenge.

3.3 Clinical evaluation and diagnosis of apical periodontitis

Establishing an accurate clinical diagnosis is the cornerstone of successful endodontic therapy. Clinicians should follow a systematic, disciplined diagnostic protocol prior to assessing whether a tooth requires endodontic therapy. Following a review of the patient's chief complaint, medical, dental and social histories, a comprehensive orofacial examination is conducted. Additionally, appropriate radiographic imaging and chair-side diagnostic tests must be performed to determine the pulp vitality status of a tooth with a periapical lesion. This clinical diagnostic step is

critical: it enables the clinician to determine whether the observed radiographic lesion is due to pulp necrosis, and therefore inflammatory in nature. While conventional radiographs and pulp-vitality tests remain the mainstay of clinical diagnosis in endodontics, additional imaging modalities are available for further evaluation of periapical lesions that pose a diagnostic dilemma. Regardless of the tests and imaging used, the overall goal of diagnostic evaluation remains the same: (i) paying attention to the patient's signs and symptoms and (ii) reproduction of the patient's chief complaint. One must never waver from the above principles in evaluating a tooth for potential endodontic therapy. The steps in the clinical and radiographic evaluation methods are discussed further below.

3.3.1 Orofacial examination and evaluation

Following a review of the patient's chief complaint, medical and dental histories, a comprehensive extra- and intraoral exam is performed. The orofacial area is evaluated for the presence of extraoral swelling, draining fistulae, lymphadenopathy, masticatory muscle and TMJ function. Intraorally, the attached and movable mucosal surfaces are examined and evaluated for changes in color, surface texture, consistency and irregularities.

The offending tooth, the adjacent teeth and their respective investing soft tissues and attached mucosae overlying alveolar bone are then examined. The alveolar process overlying the apex of the offending tooth and adjacent teeth are palpated to detect any appreciable swelling or bony expansion. The teeth are evaluated for mobility, and sensitivity to touch and percussion. Gingiva and associated periodontal tissue are evaluated for inflammation and pocket depths. Generalized deep periodontal pocketing

and bleeding upon probing may indicate a periodontal etiology. Fractured or cracked roots can be detected by evaluating periodontal pocket depths and bite-based diagnostic instruments (Tooth Slooth®). Following this protocol, the offending tooth and surrounding teeth are evaluated for pulp vitality status.

3.3.2 Diagnostic pulp-testing: thermal, electric and other methods

Several methods are available to assess pulp vitality of teeth, including thermal and electric modalities. Thermal tests are among the most commonly used diagnostic pulpal tests. They are relatively safe and have been proven by many studies to be generally consistent and effective during endodontic evaluation. It should be pointed out that results from thermal tests merely confirm evidence of pulpal nerve function, but do not provide information on the actual health of the pulp. Thermal tests have been used since the early 20th century. As far back as 1933, Reiss and Furedi stated that "dentists should not be interested in just the condition of the nerves in the pulp but in the condition of the pulp itself" (Reiss and Furedi 1933).

The thermal method that is most commonly used is "cold testing", in which a cold agent such as ice, ethyl chloride, frozen carbon dioxide or tetrafluoroethane (Endo-Ice®) refrigerant spray are applied to a tooth surface. The introduction of a sudden temperature change, and the corresponding patient response and reaction time, provide information as to the vitality status of a given tooth. Over the decades, several research studies have evaluated the efficacy of cold thermal tests in the diagnosis of pulpal disease and have shown them to be relatively reliable (Augsburger and Peters 1981; Petersson et al. 1999; Jones et al. 2002). Warm or hot thermal testing is not used as frequently as cold testing. Warm agents such as hot water or heated gutta percha may be used as part of a diagnostic

evaluation that attempts to reproduce a patient's complaint of sensitivity or pain to hot liquids. Heated instruments (ball burnishers and rubber wheels) have been occasionally used as thermal testing tools, but have not been adopted universally due to inconsistency in the ability to consistently gauge the temperature produced on tooth surfaces. More regulated systems like the System B (Sybron Endo®) thermal tester allow the clinician to set specific temperatures without the risk of causing irreversible tooth or pulpal damage. Irrespective of the thermal tests utilized, one must test each tooth carefully and separately to minimize false positive or negative responses of adjacent teeth.

In addition to thermal tests, electric pulp testing (EPT) devices are commonly used to evaluate pulp vitality. The EPT method utilizes a probe that generates a small electrical current delivered with a water or petroleum based medium, of which toothpaste is the one most commonly used. When clinicians employ this method, the tooth in question is generally dried, isolated and the crown contacted by the EPT probe with the patient's hand over part of the instrument to close the circuit. When the patient feels a "tingling" or warm sensation, he or she releases the instrument, thus breaking the circuit and ending the tingling sensation. EPTs are based on the principle that A-delta nociceptors in the pulpal nerves that are stimulated upon contact with an electrical probe transmit only pain, but not proprioception or thermal sensations. As with thermal tests, EPT only gives clinicians information about whether or not there is pulpal nerve function. It does not provide any information on the overall vascular health of the pulp and/or the presence of inflammation (Gazelius et al. 1986; Schnettler and Wallace 1991). Several studies highlight the inconsistencies in the ability of EPT readings to predict the true vitality status and health of pulpal tissue (Reynolds 1966; Chilton and Fertig 1972). Notably,

EPT is less reliable in assessing pulpal status of immature teeth with open apices (Fuss et al. 1986).

The results from studies comparing these pulp-vitality assessment tools do not demonstrate any significant differences in their reliability in adult patients (Fuss et al. 1986; Peters et al. 1994; Chen and Abbott 2011). The common finding across these studies is the comparative consistency and reliability of cold thermal testing methods over electric pulp-testing methods (Fuss et al. 1986; Moody et al. 1989; Peters et al. 1994; Petersson et al. 1999). Other possible methods for assessing pulp vitality are laser Doppler flowmetry and pulse oximetry (Schnettler and Wallace 1991; Chen and Abbott 2011). In selected cases where thermal and electric tests are equivocal, cavity tests can be utilized.

In view of the inconsistencies in reliability of the above-mentioned testing methods, a combination of thermal and electric pulp testing is recommended for assessment of pulp-vitality status (Pitt Ford and Patel 2004). In a majority of cases, a combination of these two tests yields accurate diagnostic results. This enables practitioners to differentiate between teeth with vital or necrotic pulps, and minimizes the potential for misdiagnoses of radiolucent periapical lesions.

3.3.3 Radiographic evaluation of apical periodontitis

Radiographic imaging has been an integral part of diagnostic evaluation of dental hard tissues. As with the pulp-testing instruments, a non-invasive and consistently reproducible imaging modality is desirable. Periapical radiographs are among the first radiographs employed during treatment planning. They provide adequate detail of the dental hard tissues and the surrounding alveolar bone, including the health of the

periodontal ligament (PDL) area. Any small changes in the width of the PDL spaces and periapical tissues are easily identified. Given the amount of detail obtained from this relatively simple test, periapical radiographs have been extensively studied in attempts to correlate particular radiographic features of periapical lesions with their respective histological diagnoses. Such investigations have had inconclusive results. In a clinical case series, Blum illustrated the difficulties in accurately diagnosing periapical lesions relying solely on periapical radiographic findings (Blum 1952). Priebe and colleagues failed to find any significant correlation between provisional clinical diagnoses based in the radiographic appearances of periapical lesions and their corresponding microscopic diagnoses. They studied observers' ability to distinguish between periapical cysts and granulomas, based exclusively on findings in periapical radiographs. The investigators reported a huge discrepancy among four independent observers; only 13% of periapical cysts were accurately identified radiographically. Observers that provisionally diagnosed periapical granulomas based on radiographic features alone were 59% accurate (Priebe et al. 1954). A similar study comparing the diagnostic capabilities of radiologists and endodontists further illustrated the overall inability of both groups to accurately diagnose periapical lesions based solely on periapical radiographic findings (Baumann and Rossman 1956). This has proved to be a recurring theme in several similar studies over ensuing years [Wais – 26% accurate (Wais 1958), Mortensen 48% accurate (Mortensen et al. 1970; Oehlers 1970; Hirsch et al. 1979)]. While periapical radiographs provide important information relative to diagnosis and evaluation of dental hard tissues, the fact remains that histopathological examination is the only way to distinguish between the various lesions associated with apical periodontitis.

Several other radiographic imaging technologies have been evaluated to determine their correlation with histopathological diagnoses. Studies comparing diagnostic specificity of periapical radiographic density have shown no observable differences between periapical cysts and periapical granulomas (Shrout et al. 1993; White et al. 1994; Ricucci et al. 2006). Ricucci concluded that the presence or absence of a (radiopaque) lamina dura did not help to differentiate between inflammatory periapical lesions, confirming again that histopathology remains the "gold-standard" of accurate periapical pathology diagnosis (Ricucci et al. 2006). Furthermore, it was found that there is no correlation between lesion size and specific periapical diagnosis (Carrillo et al. 2008). The conclusion of the overwhelming majority of the radiographic features-based diagnostic studies is that periapical radiography alone is not reliable for determining specific periapical pathology.

With the availability of more sophisticated imaging technology, computerized tomography was also studied in an attempt to differentiate between periapical cysts and granulomas. Trope and others showed that images of periapical cysts and periapical granulomas taken by computerized tomography (CT) show different radiographic densities. They proposed utilizing computerized tomography as a noninvasive method to distinguish between periapical cysts and granulomas (Trope et al. 1989). Aggarwal and co-workers clinically diagnosed 12 periapical lesions that were later submitted for histopathologic examination after endodontic surgery. They demonstrated excellent correlation between clinical diagnoses based on computed tomography scan and ultrasound with power Doppler flowmetry, and histopathologic diagnoses (Aggarwal et al. 2008). With the advent of cone-beam computed tomography (CBCT) which provides

higher resolution images and lower radiation dose compared to conventional CT, investigators have explored its use in the diagnosis of apical pathology. One study concluded that it was possible to diagnose periapical pathology based on CBCT findings without the need for histopathological examination (Simon et al. 2006). Contrary to these findings, a subsequent CBCT-based study reached very different conclusions (Rosenberg et al. 2010). These investigators noted that in addition to diagnostic inconsistencies, small numbers of cases and potential observer variability, the large amount of radiation required for (conventional CT or CBCT) imaging limit its practical clinical use. The risks associated with the radiation doses that patients are exposed to far outweigh the purported diagnostic benefits.

3.3.4 Non-radiographic evaluation of apical periodontitis

Other non-radiographic methods have been proposed in an attempt to clinically differentiate between periapical pathoses. Morse and colleagues utilized polyacrylamide-gel electrophoresis to detect albumin levels in root canal fluids from teeth with necrotic pulps showing evidence of apical pathosis. Upon completion of root canal treatment, periapical lesions were surgically removed and submitted for histopathologic evaluation. Different albumin patterns were detected in teeth associated with periapical granulomas compared to periapical cysts. The biochemical method was highly accurate in determining the type of periapical lesions, which were confirmed histologically (Morse et al. 1973). Given the technical challenge associated with the collection of root canal fluid samples, the limitation of the testing method to evaluate root canal content of teeth contaminated with blood or saliva, or that of teeth that have been previously treated and are associated with periapical pathology, this methodology has not been widely adopted

for routine diagnostic use. In another study, Morse and colleagues developed a chair side, colorimetric method to differentiate between periapical granulomas and cysts based on quantification of protein content of root canal fluids (Morse et al. 1976). Fluid samples that were aspirated from non-vital teeth were tested using the Schacterle and Pollack colorimetric method for protein quantification. Fluids that contained varying amounts of protein tested along a spectrum of light blue (low protein) to dark blue to blue-black (high protein). The Morse study reported that histologically confirmed periapical granulomas were consistently along the light blue end of the spectrum, whereas histologically confirmed periapical cyst showed shades of darker blue (medium blue to dark blue range) (Morse et al. 1976). Again, observer variability in the interpretation of the colorimetric tests could compromise diagnostic reliability, resulting in misdiagnoses. Another limitation of colorimetric testing is that it cannot be used in the presence of saliva and/or blood.

Other imaging methods investigated in the evaluation of periapical pathology include ultrasound (Cotti et al. 2003) and magnetic resonance imaging. A recent study compared the diagnostic accuracy of ultrasound to conventional and digital radiography in conjunction with histopathological diagnoses. The percentage accuracy for the three methods was as follows: conventional radiography was 48%, digital radiography was 58%, and ultrasound was 95% (Raghav et al. 2010). The variable density of cortical bone in the periapical and surrounding alveolar areas limits the routine use of this technology in diagnosing lesions of the jaws.

3.4 Clinical management of apical periodontitis

3.4.1 Non-surgical treatment of apical periodontitis

The rationale of endodontic therapy is to prevent, treat and inhibit the progression of apical periodontitis, the primary focus being disinfection of the root canal. Non-surgical root canal treatment is performed in teeth with necrotic pulps that are periodontally sound and considered restorable. Following adequate isolation, surface disinfection and dental caries excavation, the tooth is evaluated for restorability and/or the presence of cracks or fractures. Subsequently, the root canal space is accessed and chemo-mechanical preparation is carried out followed by intracanal medicament placement. At a subsequent visit, the practitioner obturates the root canal system to provide a hermetic seal and prevent future bacterial leakage. Isolating the apical zone and preventing the seepage of further necrotic or bacterial debris allows the body to successfully resolve the inflammatory response in the periapical tissues. This results in eventual regeneration and repair of the surrounding periapical osseous tissue. Non-surgical endodontic therapy is considered "successful" when re-evaluation reveals resolution of clinical symptoms and radiographic evidence of periapical bone healing and restoration of normal PDL space architecture (Bergenholtz et al. 1979; de Chevigny et al. 2008). Different scales such as the Strindberg criteria (Strindberg 1956) or the Periapical Index (Orstavik et al. 1986) are frequently used to evaluate treatment success. Using strict antimicrobial principles and proper chemo-mechanical preparation, several studies report success rates of non-surgical root canal treatment as ranging between 86% and 100% (Strindberg 1956; Sjögren et al. 1990; Marquis et al. 2006). It has been demonstrated that improper sterile technique and coronal microleakage results in

intracanal bacterial recolonization. This eventually leads to periapical re-infection and is the most common reason for post-treatment failures (Nair 2006).

Prior to proceeding with retrograde surgery of teeth with endodontic therapy-failure, non-surgical re-treatment methods should be considered. The rationale behind re-treatment remains the same as conventional endodontic therapy; to rid the root canal system of microbes. Re-treatment is initiated by removing the old restoration, post and core material and/or root canal filling material. Chemo-mechanical preparation is repeated, with placement of intracanal medicament and eventual obturation. When performed properly, several studies report success rates of ~ 83% for non-surgical re-treatment (Bergenholtz et al. 1979; de Chevigny et al. 2008).

3.4.2 Surgical treatment of apical periodontitis

Surgical endodontic therapy should be considered when conventional endodontic therapy is unsuccessful and when re-treatment is not feasible. The specific indications for periradicular surgery are:

i. Failure of nonsurgical re-treatment

ii. Conventional re-treatment is not feasible or practical (presence of adequate coronal restoration with an irretrievable post, separated instrument, non-negotiable ledge, root perforation, and symptomatic overfilling)

iii. When non-pulp related pathology is considered in the clinical differential diagnosis and a biopsy is indicated.

Surgical endodontic therapy is conducted upon obtaining direct access to the periapical area through a bony window. The periapical area is curetted to remove any

remnant pathologic tissue around the affected root tip. The root tips are generally resected, prepared and filled with a retrograde, inert filling material. This procedure aims to remove the inflammatory and necrotic or infected tissue from around the root tip, facilitating the growth of new bone in the area. Success rates for contemporary periapical surgical techniques are reported in the range of 92-97% (Rubinstein and Kim 1999; Maddalone and Gagliani 2003). The American Association of Endodontists recommends routine submission of tissue curetted from this area for histopathological evaluation and diagnosis. Microscopic evaluation of periapical tissue determines the precise nature of the pathological process and distinguishes odontogenic inflammatory lesions from other odontogenic and non-odontogenic pathoses that can mimic apical periodontitis clinically and radiographically (Newton 1999).

3.5 Periapical pathology - categorization

In order to understand the pathogenesis of some commonly encountered pathologic odontogenic conditions (inflammatory and non-inflammatory), it is important to be familiar with early tooth formation. Odontogenesis generally begins on day 11 of embryogenesis and is characterized by focal thickenings of the ectodermal tissue that surfaces the developing stomodeum that eventuates in the dental lamina. The dental lamina, an invagination of the overlying ectoderm into the underlying primitive ectomesenchyme, eventually gives rise to the enamel organ and, in time, the tooth crown. The ectomesenchyme condenses below the primitive enamel organ to form the *dental papilla*, which eventually gives rise to dentin and pulpal tissue. At the end of the so-called “Bell Stage”, with enamel and coronal dentin formation well on their way to being

complete, the inner and outer enamel epithelia come together to form a bilaminar sheet of epithelium referred to as “Hertwig’s root sheath”. At the same time, the ectomesenchymal cells surrounding this area begin to form the primitive tissues of the cementum, periodontal ligament and the surrounding alveolar bone. The above root sheath provides a scaffold, the inside of which serves as the framework for the root canal dentin. The external surface of the root sheath provides a scaffold for the development of the periodontal ligament and cementum formation. Upon root completion and formation of the periodontal ligament and cementum, the root sheath involutes and its remnants remain within the periodontal ligament space as odontogenic epithelial rests (Cell rests of Malassez) (Nanci 2007).

The ectoderm and ectomesenchyme are essential components of odontogenesis. Any developmental or inflammatory dysregulation of the formative elements of the above tissues can give rise to pathological changes. Developmental disturbances during odontogenesis can result in certain odontogenic cysts or hamartomas. Acquired somatic mutations in these developing tissues in children or adults can lead to the formation of benign neoplasms of odontogenic origin. Most often, in the setting of apical periodontitis, inflammatory infiltrates that are rich in cytokines and growth factors can also cause tissue destruction and stimulate odontogenic epithelial rests, which can give rise to inflammatory odontogenic cysts. It is also well to note that non-odontogenic lesions are occasionally found in the periapical region. The categorization and selected examples of the various lesions encountered in the periapical region are presented in **Table 1**.

3.5.1 Odontogenic inflammatory pathology

As described above, caries and trauma can cause pulpal necrosis and the efflux of bacteria and their by-products into the periapical area, resulting in apical periodontitis. Another condition associated with inflammation of the periradicular tissues is severe periodontal disease, which on occasion can extend to involve the bone surrounding the entire length of the root. In the apical or lateral radicular regions, lesions resulting from apical periodontitis are the most commonly encountered inflammatory pathoses. Depending on the microscopic findings, the lesions of apical periodontitis are diagnosed as one of the following:

a) periapical granuloma

b) periapical cyst

c) periapical abscess

d) periapical scar

Periapical granulomas consist of granulation tissue infiltrated predominantly by chronic inflammatory cells. It is instigated by bacteria and their by-products exiting the apical foramina of teeth with necrotic pulps. Varying degrees of fibrosis can be seen apparently in an attempt by the body to "wall-off" the infectious and necrotic debris at the periapex. In addition, occasional strands or nests of odontogenic epithelium (remnants of Hertwig's root sheath) can be seen among the elements of periapical granuloma (Summers 1974; Summers and Papadimitriou 1975; Block et al. 1976; Leonardi et al. 2005; Ricucci et al. 2006). Untreated, periapical granulomas can remain dormant, or scar, or develop into cysts. In some instances, they can become symptomatic and present with abscess formation (Abbott 2004).

A periapical cyst is an odontogenic inflammatory cyst. They are epithelium lined cavities that may be filled with fluid; their walls typically demonstrate varying degrees of inflammatory infiltration; hemorrhagic debris, cholesterol crystals and fibrosis may also be seen. Inflammatory cytokines, mediators, and growth factors present in the inflammatory infiltrate of a periapical granuloma can stimulate the proliferation of nearby cell rests of Malassez thus leading to the formation of a cyst (Nair 1998). Two theories have been proposed to explain the formation of periapical cysts (i) the nutritional deficiency theory and (ii) the abscess theory (Nair 1998). According to the former theory, central cells die as the epithelial nests proliferate and expand. It is thought that the avascular nature of epithelium contributes to necrosis of centrally located cells, leading to cavitation and subsequent cyst formation. The latter theory proposes that epithelial cells proliferate to wall-off inflammatory aggregates that form at the apical periodontium of a tooth secondary to efflux of necrotic or infectious debris through the apical foramen. Experimental evidence in an animal model seems to support the "abscess theory" (Nair 2006; Nair et al. 2008), while the exact cellular mechanisms remain elusive. Depending on the exact location and association of cyst lumina with the overlying teeth, periapical cysts may be termed "bay/ pocket" cysts or "true" in nature. It was observed, in a study of periapical tissue obtained in *en bloc* sections of teeth and surrounding bone, that some periapical cysts were contiguous with the overlying root canal systems containing infected necrotic pulps and termed "bay or pocket" cysts. A subset of cysts that were separate, with no apparent communication with the overlying tooth were termed "true" periapical cysts (Simon 1980). The actual clinical significance of this delineation is a subject of much debate. Regardless, it should be noted that these cysts are inflammatory

in origin, with any differences being observed only upon surgical bloc sections of the roots, as opposed to routine endodontic surgical curettage, which is a more conservative approach.

Acute inflammatory exacerbation of periapical pathology can lead to the formation of a periapical abscess. This may be accompanied by formation of a sinus tract that can track through the bone and communicate with the oral cavity or cutaneous surface. Persistence of a chronic inflammatory focus and/or repair of the tissues in the area can result in fibrous organization and scar formation. Clinically and radiographically, periapical scars can look identical to any other lesion of apical periodontitis.

3.5.1. (i) Prevalence of odontogenic inflammatory pathology

Periapical tissue obtained during surgical endodontic therapy is usually submitted for histopathological examination. Lesions of apical periodontitis are ultimately diagnosed as periapical granuloma, cyst, abscess, or scar. The prevalence of each of the lesions associated with apical periodontitis has been extensively studied and reported in the literature. The details are presented in **Table 2** and are discussed below.

In 1956, Bauman and Rossman published one of the earliest studies to report on the prevalence of specific periapical pathologies (Baumann and Rossman 1956). They examined 121 periapical lesions and reported a high prevalence of periapical granulomas - 73.5% (89/121); periapical cysts were less common - 26.5%(38/121). Bhaskar examined 2308 cases of periapical lesions submitted by 314 contributors for histopathologic evaluation. Retrospective analysis revealed 1118 (48%) periapical granulomas, 969 (42%) periapical cysts, 58 (2.5%) periapical scars, 26 (1%) periapical

abscesses, and 23 (1%) foreign body reactions to exogenous materials such as fragments of gutta percha, silver points, cotton fibers, and lipid material (Bhaskar 1966). Over the years several other small and large retrospective studies have reported on the prevalence of specific odontogenic periapical pathology: Wais – 74% periapical granulomas (74/100), Mortensen – 59% granulomas (232/396), Stockdale and Chandler – 77.3% (856/1108) (Wais 1958; Mortensen et al. 1970; Stockdale and Chandler 1988). In the latter study, Stockdale and Chandler also reported on the prevalence of periapical cysts (17%, 186/1108), periapical scars (4.5%, 50/1108) and foreign body reaction (0.5%, 5/1108). In 1998, Nair reported a similarly high prevalence of periapical granulomas in his study of periapical lesions removed *en bloc* with their respective teeth. Given that *en bloc* sections were available, a delineation between the specific types of periapical cysts was made. Serial sectioning of the blocs revealed 39 periapical cysts (15%), which were further sub-classified based on their association with the root apex as apical "true" and "pocket" cysts, respectively; 24 true cysts and 15 pocket cysts (Nair et al. 1996). The details from other similar studies reporting on the prevalence of apical pathology are presented in **Table 2** (Lalonde and Luebke 1968; Block et al. 1976; Hirsch et al. 1979; Winstock 1980; Nobuhara and del Rio 1993; Kuc et al. 2000; Ricucci et al. 2006; Carrillo et al. 2008; Love and Firth 2009).

Very few studies have reported a higher prevalence of periapical cysts over granulomas. Priebe et al. reported a prevalence of 54.5% for periapical cysts, compared to 45.5% granulomas or abscesses (Priebe et al. 1954). Seltzer et al., reported 58% cysts in a study of 87 periapical specimens (Seltzer et al. 1967a; Seltzer et al. 1967b). To

summarize, an overwhelming majority of studies reported periapical granulomas as the most common apical lesions diagnosed, followed by periapical cysts and others.

3.5.2 Odontogenic non-inflammatory pathology

Non-inflammatory lesions of odontogenic origin near or at the apices of teeth can mimic the radiographic appearance of apical periodontitis. They usually do not present with the same clinical features or responses to thermal and/or electric pulp tests as a tooth with pulpal necrosis. Inadequate initial diagnostic evaluation can lead to misdiagnosis of a non-inflammatory lesion as apical periodontitis. This, in turn, can eventuate in inappropriate and unnecessary endodontic therapy. Most non-inflammatory odontogenic lesions are developmental cysts and benign tumors of odontogenic origin. These lesions are usually asymptomatic, and in many cases, are discovered incidentally on routine radiographic examination. Radiographically, lesions noted in the vicinity of the apices of asymptomatic teeth with vital pulps should raise suspicion of possible non-inflammatory odontogenic pathology. Diagnosis of such lesions can be challenging if they are proximal to, or involve, a tooth that has already been endodontically treated.

3.5.2. (i) Prevalence of odontogenic non-inflammatory pathology

A broad scope of non-inflammatory odontogenic lesions can be encountered in the periapical area. These lesions have the potential to cause bone destruction and present with radiolucent lesions that can appear similar to apical periodontitis. They range from non-inflammatory hyperplastic lesions, developmental odontogenic cysts, odontogenic neoplasms and others. Among these, the odontogenic keratocyst (OKC) and the ameloblastoma are the most clinically significant lesions. OKC can present as a uni- or

multilocular cystic radiolucency. Due to its potentially destructive behavior and its occasional association with the Basal Cell Nevus syndrome linked to mutations in the PTCH gene, it has been recently reclassified by the WHO as a cystic odontogenic tumor and consequently renamed "keratinizing cystic odontogenic tumor" (KCOT). This reclassification has not changed the approach to surgical management and follow-up (Philipsen 2005). OKC/ KCOTs are generally slow growing, painless intraosseous processes that can cause jawbone swelling. They can present in lateral periodontal and periapical locations. Ameloblastoma is a slow growing benign neoplasm of odontogenic epithelium. It shares many clinical and radiographic features with OKC/ KCOTs. Despite being classified as a benign neoplasm, ameloblastoma's lack of encapsulation underlies its characteristic capacity for intraosseous infiltration. Early detection, diagnosis and relatively radical surgical management of OKC/ KCOTs and ameloblastomas is indicated due in view of their locally destructive behavior and potential for recurrence. Conservative management is often associated with high recurrence rates (Neville and Damm DD 2009).

As seen in **Table 3**, the literature is replete with reports of various odontogenic non-inflammatory lesions in the periapical region. In addition to the 28 cementoblastomas reported in a retrospective analysis of 2308 apical lesions (Bhaskar 1966), there have been variable numbers of OKCs (Stockdale and Chandler 1988; Carrillo et al. 2008; Schulz et al. 2009), odontomas (Spatafore et al. 1990), lateral periodontal cysts, odontogenic myxomas and other non-inflammatory odontogenic cysts and neoplasms **(see Table 3)** (Nobuhara and del Rio 1993; Kuc et al. 2000; Ortega et al. 2007). In addition, there are several case reports and series reporting on periapically

located non-inflammatory odontogenic pathology (Cohen et al. 1984; Gunhan et al. 1991; Nohl and Gulabivala 1996; Cunha et al. 2005; Faitaroni et al. 2008; Pace et al. 2008; Daskala et al. 2009; Estrela et al. 2009; Nikitakis et al. 2010). The significant morbidity resulting from the radical surgical procedures associated with several of the above pathological conditions underscores the importance of early detection and establishment of a specific diagnosis.

3.5.3. Non-odontogenic pathology

Non-odontogenic pathological entities are occasionally encountered in a periapical location. Although they can mimic apical periodontitis radiographically, they are unrelated to pulpal necrosis. Careful evaluation of the history and attention to the clinical diagnostic work-up can aid in the early detection and differentiation of these lesions from apical periodontitis. The non-odontogenic lesions can be broadly categorized into non-neoplastic and neoplastic processes. Benign hyperplastic lesions, developmental cysts and benign neoplastic processes in the periapical region generally present themselves as well-demarcated, often corticated radiolucencies (with or without internal opacification), with potential for localized hard and soft-tissue destruction. They may be incidental radiographic findings or associated with painless, slow growing masses. Malignant neoplasms tend to be more aggressive, and present as ill-defined radiolucencies (with or without opacification). Malignant neoplasms are uncommon in the maxilla and mandible. They tend to occur in patients with a prior history of either a local or distant primary cancer, and are rarely the first manifestation of metastatic disease to the jaw. Affected patients usually complain of other cancer-related signs and

symptoms including tooth mobility, pain, paresthesia and a rapidly growing mass. Irrespective of the type of non-odontogenic lesion (benign, developmental or malignant process), the associated tooth or teeth respond positively to a combination of pulp testing methods. Endodontic therapy should not be considered if the historical, clinical, radiographic and pulp-testing results are not supportive of apical periodontitis.

3.5.3. (i) Prevalence of non-odontogenic pathology

There are published reports of benign developmental and reactive lesions that mimic apical periodontitis radiographically. They include giant cell lesions (Bhaskar 1966; Dahlkemper et al. 2000; Venkatesh and Nandini 2009), fibrous dysplasia (Seltzer et al. 1967a), traumatic bone cyst, nasopalatine canal cysts (Spatafore et al. 1990; Kuc et al. 2000; Rodrigues and Estrela 2008), chronic sinusitis and periapical cemento-osseous dysplasia (Ortega et al. 2007). **Table 4** summarizes the spectrum of non-odontogenic lesions that have been reported in periapical locations.

Non-odontogenic neoplasms, both benign and malignant, have also been reported **(Table 5)**. These include individual case reports and case series of ossifying fibromas (Piattelli 1996; de Moraes Ramos-Perez et al. 2010), hemangiomas (Orsini et al. 2000), antral carcinomas (Copeland 1980), adenoid cystic carcinomas (Burkes 1975), metastatic lesions (Milobsky et al. 1975; Selden et al. 1998; Fujihara et al. 2010; Khalili et al. 2010), malignant lymphomas, and plasmacytomas (Spatafore et al. 1990; Kuc et al. 2000; Saund et al. 2010). All of these lesions occurred in periapical locations.

3.6 Periapical lesions: patient demographics and anatomical location

Numerous studies attempted to correlate specific periapical pathoses and patient demographics. Demographic elements most often studied were age, gender and specific histopathological diagnosis of the lesion in question. Additionally, correlation between periapical lesions and anatomic location within the jaw was evaluated. In the following section, reports in the literature evaluating the correlation between periapical lesions of all kinds and the above elements will be discussed.

3.6.1. Gender

A survey of the literature reveals no correlation between specific inflammatory odontogenic periapical pathology and gender. Bhaskar reported an increased predilection of cysts in males as compared to females (605 vs. 327) (Bhaskar 1966), whereas no gender-predilection were reported in other studies (Lalonde and Luebke 1968; Stockdale and Chandler 1988; Spatafore et al. 1990; Love and Firth 2009) **(Table 6)**.

Two studies evaluated the correlation between odontogenic non-inflammatory lesions and gender. Bhaskar reported more cementoblastomas in females (24/28) as compared to males (4/28) (Bhaskar 1966). Ortega and associates reported 8 cases of OKC in females and 3 cases in males (Ortega et al. 2007). The observed differences were interpreted as insignificant given the small number of cases reviewed.

3.6.2. Age

Investigators have reported on the correlation between specific periapical inflammatory pathoses and age (Table 7). Bhaskar reported that most periapical

granulomas and cysts were diagnosed in the 3rd decade of life. Periapical scars tended to be discovered more frequently in the 5th decade. A wide age range was noted for periapical abscesses (Bhaskar 1966). Spatafore et al., reported the highest prevalence of inflammatory periapical pathology in the 4th decade of life (Spatafore et al. 1990). Similar results were reported independently by other investigators (Stockdale and Chandler 1988; Love and Firth 2009). Given the differences in the reported data, there appears to be no definitive correlation between specific periapical inflammatory pathoses and age.

One study reported on the correlation between odontogenic non-inflammatory lesions and age. In a series of cementoblastomas, Bhaskar reported a high prevalence in the 4th decade of life (Bhaskar 1966).

3.6.3. Anatomical location in the jaws

Several studies report conflicting results on the correlation between periapical pathology and particular anatomical location in the jaws **(Table 8)**. Given the variations in the morphology and shape of specific teeth, certain teeth and locations are associated with particular periapical lesions more often than others. Bhaskar found that lesions of apical periodontitis were significantly more common in the maxilla than in the mandible: (i) granulomas (796:237, maxilla:mandible), (ii) cysts (798:82, maxilla:mandible) and others **(Table 8)** (Bhaskar 1966). Lolande and Luebke reported more granulomas in the maxillary anterior region, followed by the mandibular posterior region (149:79, maxillary anterior:mandibular posterior) **(Table 8)** Similar results were observed with periapical cysts **(Table 8)** (Lalonde and Luebke 1968), with other investigators reporting minor

differences in the distribution (Mortensen et al. 1970; Stockdale and Chandler 1988). A review of the literature reveals general correlation between the prevalence of apical periodontitis lesions and the maxillary arch. It is possible that the increased correlation is a result of inherent bias of the samples analyzed, given that maxillary teeth tend to be surgically treated more often. The increased prevalence of periapical pathology in the maxillary anterior region may be a function of the teeth in this area being more prone to trauma, alongwith patients' desire to retain anterior teeth for esthetic reasons.

Among the non-inflammatory lesions, it is well known and confirmed in the literature that cementoblastomas occur most commonly in the posterior mandible (Bhaskar 1966).

3.7 Correlation between clinical provisional diagnosis and histopathologic diagnosis

The overall prevalence of periapical lesions among all oral pathology samples submitted for histological examination ranges from 2.9 - 6-6% (Bergstrom et al. 1987; Odesjo et al. 1990; De Moor et al. 2000). These authors reported that the majority of periapical lesions are related to apical periodontitis. With a reasonably thorough clinical work-up, the generation of a provisional diagnosis is within the scope of any dentist's practice. A short list of four likely provisional diagnoses can provide sufficient justification for further workup, including additional imaging and/or a tissue biopsy. Kuc et al., conducted a retrospective study to investigate the correlation between contributors' provisional clinical diagnoses of periapical lesions and their final histopathological diagnoses (Kuc et al. 2000). They categorized 805 periapical lesions into 3 groups based on their histopathologic diagnoses. These groups were 1) sequelae of pulpal necrosis, 2) complicated sequelae of pulpal necrosis, and 3) periapical lesions unrelated to pulpal necrosis. The investigators concluded that endodontists were significantly more accurate in the clinical evaluation of periapical pathology related to pulpal necrosis as compared to their general dentist or oral surgery counterparts. Drastic differences observed between the general category of provisional diagnoses and the final histopathological diagnosis tended to reflect inadequate clinical and diagnostic evaluation, or an unusual presentation of a disease process inconsistent with its typical ("classic") features. In any case, it is well to note that a provisional diagnosis is at best, a well-educated guess. While provisional diagnoses can frame treatment planning and management guidelines, the gold standard for diagnosis of periapical pathology remains microscopic evaluation.

4. Objectives and Specific Aims

The objective of this study was to assess the pathological spectrum of periapically-located lesions in order to determine whether routine submission of tissue obtained for histopathological review and diagnosis during endodontic surgery is justified. The specific aims of this study were:

Specific Aim 1: To determine the prevalence of periapically located lesions submitted for histopathological examination

Specific Aim 2: To investigate the correlation between patient demographics, anatomical location in the jaws, and specific histological diagnoses

Specific Aim 3: To analyze the differences between the final histological diagnoses and the clinicians' submitted provisional diagnoses.

5. Materials and Methods

The study protocol was reviewed and approved by the Institutional Review Board (IRB # 11-122-1) at the University of Connecticut Health Center.

5.1 Retrospective review

A total of 21649 Pathology reports from the archives of the University of Connecticut (UCONN) Oral Pathology Biopsy service between 2006 and 2010 were reviewed. The pathology reports contained information about the patient's gender, age, specific anatomic location of surgical or biopsy site, clinicians' provisional diagnosis (or diagnoses), gross and microscopic description and the final diagnosis. In accordance with the UCONN-IRB guidelines, patient identifier data were excluded during data collection and recording. Given the narrow scope of our study, only reports that met the following criteria were included in the study. Cases were included only if the biopsy report stated that the submitted specimen:

1) was located at the apex of a primary or permanent tooth based on clinicians' description.

2) was from the apex of an extracted tooth

3) was obtained during endodontic surgery or other periapical surgical procedure

A report was excluded from the study if:

1. it did not specify the exact anatomic location of the lesion in the jaw
2. the lesion did not involve the periapical area
3. the lesion was obtained in the area of an impacted tooth
4. the lesion was reported as being residual or in the region of previously extracted teeth
5. the lesion was from the third molar area
6. the report lacked a specific histopathological diagnosis

If the biopsy report met the study criteria, the following clinical data were inserted into a password-protected, Microsoft Excel (Microsoft Co, Redmond, WA, USA), document:

1) Tooth number/ numbers or specific anatomic location

2) Patient's age

3) Patient's gender

4) Submitting clinician's specialty

5) Significant patient history

6) Provisional or differential diagnoses, if provided

7) Final histopathological diagnosis

Pathology accession numbers and medical record numbers were de-identified. Random de-identification numbers were created using an online research randomizer (http://www.randomizer.org) and arbitrarily assigned to each report. The extracted data were saved in a password-protected Microsoft Excel (Microsoft Co, Redmond, WA, USA) document.

5.2 Categorization of lesions and demographic correlation and anatomical location

Based on the final diagnosis, the reports were categorized into 4 groups **(Tables 1 and 10)**: odontogenic inflammatory, odontogenic non-inflammatory, non-odontogenic non-neoplastic and non-odontogenic neoplastic. Final diagnoses of the submitted periapical specimens were also broadly categorized as those (i) related to pulp-necrosis (PRPN), (ii) unrelated to to pulp-necrosis (PUPN), and (iii) non-pathological tissue (NPT). Furthermore, specimens that revealed essentially normal findings or non-pathological tissue were excluded from the final analysis **(Table 15c)**

Correlations between specific diagnoses and demographic data were evaluated. The lesions from each of the above 4 groups were further subcategorized by:

i. Gender
ii. Age (in years): < 20, 20-50 and > 50
iii. Anatomic location (broad): maxillary or mandibular
iv. Specific anatomic location or tooth (sextant): maxillary or mandibular
    a. anterior
    b. premolar
    c. molar

5.3 Index of clinical suspicion

The provisional diagnoses provided by the submitting clinicians on the biopsy requisition forms were recorded and categorized according to the 4 categories discussed

above. They were compared with the category of final histopathological diagnosis to evaluate the consistency of the submitting clinicians' index of suspicion (IOS). A clinician's IOS was recorded as consistent if the category of final diagnosis on the pathology report was in the general category of any of the provided provisional diagnoses. IOS was recorded as "inconsistent" if the provisional diagnoses were in a different category of disease than the final diagnosis. Those reports that did not have a clinician's provisional diagnosis were included in the analysis as being "inconsistent". In addition, the IOS for individual dental specialties was assessed.

6. Results

6.1. Demographics, anatomical locations and contributors

A total of 21649 biopsy reports from the UCONN Oral Pathology Biopsy service between 2006 and 2010 were reviewed. Of these, 2979 lesions met the inclusion criteria set forth for this study. Information on patient demographics, specific anatomical location and specialties of submitting clinicians is summarized in **Table 9**.

6.2 Prevalence of all periapical lesions

Periapical lesions constituted 13.8% (2979/21649) of all specimens submitted to the UCONN Oral Pathology Biopsy service; this includes all intraosseous and soft-tissue lesions submitted for diagnosis. Periapical lesions that met the inclusion criteria were further categorized into 4 groups as described earlier **(Table 1):** odontogenic inflammatory, odontogenic non-inflammatory, non-odontogenic non-neoplastic and non-odontogenic neoplastic. The prevalence of all periapically located pathology is presented in **Table 10**. The most commonly encountered periapical lesions in descending order are: (i) periapical granuloma (51.5%), (ii) periapical cyst (32.9%), (iii) periapical scar (4.8%), (iv) OKC/ KCOT (2.1%), (v) lateral periodontal cyst (1.2%), (vi) nasopalatine canal cyst (1.1%), (vii) benign fibro-osseous lesions (1.0%), (viii) periapical abscess (0.9%), (ix) traumatic bone cyst (0.6%)and (x) odontoma (0.5%). A total of 6 periapical lesions were associated with primary teeth: 3 periapical cysts, 2 odontomas, and 1 central odontogenic fibroma, respectively.

6.3 Odontogenic inflammatory pathology

The overall prevalence of odontogenic inflammatory pathology in the periapical location was 90.4% (2693 of 2979 specimens). The prevalence of individual odontogenic inflammatory lesions, their respective anatomical distribution, and demographic data (gender and age) are presented in **Tables 11a and 11b**. Lesions associated with apical periodontitis accounted for 99% (2684 of 2693) of all odontogenic inflammatory pathology in the apical region. Periapical granulomas were the most prevalent periapical lesion accounting for 57% (1534 of 2693) of all inflammatory odontogenic pathology. Most periapical granulomas were seen in adults between the age groups of 20-50 (590 of 1534) and > 50 (888 of 1534), with an overall prevalence of 96% in adults above the age of 20 **(Table 11a)**. The frequency of periapical granulomas was higher in the maxilla than in the mandible (1106:428, maxilla: mandible). Analysis of the specific teeth involved (by sextant) revealed that the highest prevalence of periapical granulomas was in the maxillary anterior region (474 of 1564; 30.3%). The mandibular premolars showed the lowest prevalence (70 of 1564; 4.4%).

Periapical cysts were diagnosed in 981 cases (36%) of the 2693 odontogenic inflammatory lesions **(Table 11a)**. No significant differences in frequency were observed between male and female patients. Periapical cysts were again noted to be most prevalent in patients aged between 20-50 years (447 of 981) and in patients older than 50 (477 of 981). The latter two age groups accounted for 94% of all periapical cysts. More periapical cysts were found in association with maxillary teeth (579:402, maxillary:mandibular). Similar to periapical granulomas, teeth in the maxillary anterior region (278 of 1051; 26.4%) and mandibular molar sextants (244 of 1051; 23.2%) were the most likely areas

to demonstrate periapical cysts; the mandibular premolar showed the lowest prevalence (84 of 1051; 8%) **(Table 11b)**.

A total of 143 periapical scars and 26 periapical abscesses were diagnosed, accounting for roughly 6% of all pathologic manifestations of apical periodontitis. Again, maxillary teeth were more commonly affected with no significant gender predilection. A majority of periapical scars and abscesses were diagnosed in patients older than 20 years. The maxillary anterior sextant was the most common anatomic site. Other odontogenic inflammatory lesions consisted of periodontitis, foreign body reaction, condensing osteitis, and non-specific odontogenic cyst. To summarize, a preponderance of odontogenic inflammatory periapical lesions (granulomas, cysts, scars or abscesses) are seen in individuals older than 20 years of age with a predilection for maxillary anterior teeth.

6.4 Odontogenic non-inflammatory pathology

The prevalence of odontogenic non-inflammatory pathology in the periapical location was 5.1% (151 of 2979 specimens). The prevalence of individual odontogenic non-inflammatory lesions, their respective anatomical distribution, and demographic data (gender and age) are presented in **Tables 12a and 12b**. Odontogenic keratocysts (OKC/KCOT) were the most prevalent non-inflammatory odontogenic lesion in the periapical region (62 of 151; 41%). Overall, they accounted for 2.08% of all periapical pathology (62 of 2979 periapical biopsies).

OKC/ KCOTs were most common in males over 50 years of age. The maxilla and the mandible were equally affected. The teeth most common associated with periapically

located OKC/ KCOTs were mandibular premolars (22 of 83), followed by mandibular and maxillary anterior teeth (19 of 83 and 18 of 83, respectively). Of note, the molar region considered a classic location for OKC/ KCOTs, accounted for less than 15% of periapically located OKC/ KCOTs.

Lateral periodontal cysts (LPCs) were diagnosed in 37 (24.5%) of the odontogenic non-inflammatory lesions. LPCs affected males and females equally and were seen mostly in patients over 20 years of age. LPCs were diagnosed more often in the mandible than the maxilla (32:5, mandible: maxilla). As shown in **Table 12b**, most LPCs were associated with teeth in the mandibular premolar and anterior sextants (46 of the total 55 sextant areas).

Other significant non-inflammatory lesions of odontogenic origin of the 151 located at the apices of teeth included 7 (5%) ameloblastomas, 4 (3%) odontogenic myxomas and 3 (2%) cementoblastomas**.** Other odontogenic non-inflammatory lesions discovered in the periapical region are listed in **Tables 12a and b** with specific information on location and demographic data.

6.5. Non-odontogenic non-neoplastic pathology

The prevalence, demographic data and anatomical distribution of non-odontogenic non-neoplastic lesions are presented in **(Tables 13a and b)**. Of the 120 non-odontogenic non-neoplastic lesions, 33 (22%) were nasopalatine canal cysts (NPCs). NPCs were more common in males (24:9, males: females) and favored patients older than 20 years of age. As expected, all NPCs were located in the anterior maxillary region; one large NPC extended to the premolar sextant **(Table 13b)**. Benign fibro-osseous lesions

(32 cases, 21%) represented the second most common non-odontogenic non-neoplastic pathosis. These lesions had a predilection for middle-age females and were usually located in the mandibular molar region. Clinical-pathological correlation in these cases favored diagnoses consistent with focal cemento-osseous dysplasia. Eighteen (12%) traumatic bone cysts (TBCs) were diagnosed in the periapical region. Twelve of 18 cases were diagnosed in patients under the age of 20, with no gender predilection. Traumatic bone cysts occurred eight times as often in the mandible as in the maxilla, and the largest number of TBCs occurred in the mandibular posterior region. Other non-odontogenic non-neoplastic lesions included central giant cell lesions, developmental cysts, bone sequestra, surgical ciliated cyst, bone marrow defect and 1 case of a giant cell lesion ultimately diagnosed as a lesion of cherubism.

6.6. Non-odontogenic neoplastic pathology

The prevalence, demographic data and anatomical distribution of non-odontogenic neoplastic lesions are presented in **Tables 14a and 14b**. In the periapical region, neoplastic lesions of non-odontogenic origin are rare. They account for < 1% of all periapical lesions (15 of 2979 lesions). Of the 15 non-odontogenic neoplastic lesions that met the criteria for this study, 9 were benign and 6 were malignant.

Ossifying fibromas were seen in 5 cases, diagnosed initially as benign fibro-osseous lesions on the basis of histopathologic features exclusively. However, radiographic and clinical correlations were consistent with a benign fibroosseous neoplasm. All 5 ossifying fibromas were diagnosed in young adults between 20-50 years

of age; there was no gender predilection nor preference noted for either arch. The other benign neoplasms included 2 intraosseous hemangiomas, 1 leiomyoma and 1 osteoma.

Of note, 6 malignant neoplasms were discovered in the periapical region. Two of them were primary in origin (2 *de novo* osteosarcomas) and one the resulted from local intraosseous invasion of primary squamous cell carcinoma. Two malignant neoplasms (1 adenocarcinoma, 1 malignant lymphoma) with periapical radiographic findings represented the first manifestation of malignant disease in the respective patients: there was no previous history of cancer. One case of multiple myeloma in the apical region was in the setting of recurrent system-wide disease.

6.7. Prevalence of periapical pathology in relation to pulpal-status

In this retrospective analysis, 90.4% of the lesions reviewed were of odontogenic inflammatory origin. Gender predilection was not observed. Patients in the age groups of 20-50 and older were more likely to present with periapical pathology. Periapical pathology was twice as likely to present in the maxilla (1929:1050, maxilla: mandible). Alternatively, it is possible that lesions in the maxilla were twice as likely to be submitted for histopathological examination **(Tables 15a and 15b)**. Periapical pathology is seen most often in the anterior maxillary region and least often in in the mandibular premolar region **(Table 15b)**.

The final diagnoses of several specimens in each of the 4 categories **(Tables 10)** represented findings considered within normal limits, or lacking significant pathology. In light of this, 31 specimens that were considered non-pathological (NPT) were separated from the group of 2979 specimens for analysis. The remaining 2948 periapical lesions

were broadly categorized into two groups, one related to pulpal necrosis (PRPN) and the other unrelated to pulpal necrosis (PUPN) **(Table 15c).** Exclusion of specimens diagnosed as NPT did not change the overall prevalence results. Pathology related to pulpal necrosis accounted for 90.4% of all periapical specimens, whereas pathology unrelated to pulp-necrosis was reported in 255 (8.6%) of the cases **(Table 15c)**.

6.8 Consistency of the index of clinical suspicion

Information on the submitting clinician's specialty of practice was recorded from the review of archived biopsy reports. A majority of periapical specimens were submitted by endodontists (1465 of 2979) and oral and maxillofacial surgeons (1289 of 2979) followed by other specialties **(Table 9)**. Within these groups, the consistency of clinicians' index of suspicion (IOS) was analyzed by comparing the final tissue diagnosis with submitted provisional diagnoses. When the final diagnosis reflected one of the general pathological categories listed in the provisional diagnosis, the overall IOS of all submitting clinicians was 84% (2511 of 2979). Endodontists' and oral surgeons' IOS were comparable at 85% and 84%, respectively. This suggests that the final diagnosis for each of the above specialties was in an entirely different category of disease 15% and 16% of the time, respectively. General dentists' IOS was similar to that of endodontists and oral surgeons (85%). **Tables 16a and b** present the consistency of the index of suspicion and the prevalence of periapical pathology (by category) submitted by different contributors. A majority of non-odontogenic lesions were submitted by oral surgeons (88.5%; 119 of 135).

7. Discussion

The overall objective of this study was to determine the prevalence of various periapically located pathological conditions in order to evaluate the rationale for routine submission of tissue for histopathological diagnosis following endodontic surgery. As part of the overall objective, correlations among between specific periapical pathoses, patient demographics and anatomical locations were examined. Also, the correlation between provisional clinical diagnoses prior to biopsy and final histopathological diagnoses was assessed. A total of 21649 pathology reports were reviewed, of which 2979 lesions (13.8%) met the key inclusion criterion: an association with the apices of teeth. The findings reveal that the overwhelming majority of periapical lesions, 2693 of 2979 (90.4%) periapical biopsies were associated with apical periodontitis resulting from infected necrotic pulps. This is consistent with what has been reported in the literature. The remaining 286 of 2979 cases (9.6%) represented a wide range of pathological conditions. These included odontogenic cysts or neoplasms, non-odontogenic inflammatory lesions, and systemic or neoplastic processes. Furthermore, fewer than 0.5% of the submitted periapical specimens demonstrated essentially normal tissue and were therefore diagnosed as exhibiting no obvious pathology. There was no correlation among the various periapical lesions and the recorded demographic data and anatomic locations. The results obtained from comparing submitted provisional clinical diagnoses to the final histopathological diagnoses proved to be the most enlightening. The clinicians' overall index of suspicion as measured by their submitted provisional diagnoses, was consistent roughly 85% of the time and inconsistent approximately 15% of the time. This finding raises questions about the importance, the efficacy of and the

consistency with which the clinical diagnostic work-up is conducted prior to considering endodontic therapy. The fact that the final histopathological diagnoses of submitted specimens were in completely different categories of pathological processes than the clinicians' impressions, highlights the importance of a thorough, multi-pronged approach to clinical diagnosis. Additionally, it underscores the importance of routine submission of biopsies obtained from the periapical area.

7.1 The overwhelming majority of periapical lesions are the result of pulp necrosis

Periapical granuloma, periapical cyst, periapical scar, or periapical abscess is diagnosed following microscopic examination. The literature reports a wide range in the prevalence of each of the above diagnostic entities. Our results revealed that 90.4%, an overwhelming majority (2693 of 2979) of periapical biopsy specimens, were diagnosed as secondary to apical periodontitis. Of these, 1534 (57%) were diagnosed as periapical granulomas, while periapical cysts represented 981 (36%) of cases. These results are consistent with the findings in the literature reporting a higher prevalence of periapical granulomas than cysts (Baumann and Rossman 1956; Wais 1958; Lalonde and Luebke 1968; Mortensen et al. 1970; Hirsch et al. 1979; Stockdale and Chandler 1988; Spatafore et al. 1990; Nobuhara and del Rio 1993; Nair et al. 1996; Kuc et al. 2000; Ricucci et al. 2006; Carrillo et al. 2008; Love and Firth 2009; Schulz et al. 2009).

The 36% prevalence of periapical cysts in our retrospective analysis is comparable to, albeit slightly higher than, the average prevalence of 26% (range – 6-54.5%) for periapical cysts reported in the literature. Several authors have investigated

and discussed the reasons for the wide prevalence range (6-54.5%) reported. In a study conducted by Nair and colleagues that evaluated periapical lesions obtained *en bloc* with the tooth root, it was suggested that the observed differences in prevalence may be a result of differences in the criteria used to diagnose periapical cysts. For example, it was suggested that the relatively small, crushed tissue fragments curetted out during endodontic surgery did not allow for adequate assessment of the epithelial lining and its "true relationship" with the apical foramen. They argue that unless periapical tissue is collected and submitted *en bloc* with the tooth root, accurate distinction between periapical granulomas and periapical cysts cannot be established. A review of the literature reveals differences in the criteria that investigators use in distinguishing periapical granulomas and periapical cysts. In some reports, a diagnosis of periapical cyst is rendered only when a distinct cystic cavity completely enclosed by an epithelial lining is present (Simon 1980; Nair et al. 1996). This is a very stringent definition and restricts the diagnosis of cysts to those periapical lesions submitted *en bloc*. Other soft tissue fragments containing epithelial elements but without distinct lumen formation are diagnosed as "periapical granuloma with epithelium". These strict criteria may not be applicable in everyday clinical endodontics but they provide insight into the pathogenesis and progression of periapical pathology. The identification of a stratified squamous epithelial lining, with or without an enclosed cystic lumen, associated with inflamed granulation tissue are sufficient criteria for diagnosis of a periapical cyst. This is the most likely reason for the wide prevalence range observed in the literature relative to periapical cysts.

The lesions of apical periodontitis usually resolve with conventional endodontic therapy. Those periapical lesions refractory to conventional treatment and/or re-treatment are likely to persist as a result of persistent apical inflammation or infection, or on occasion, non-inflammatory pathology. Persistent evidence of periapical disease justifies endodontic surgery. In some studies (Simon 1980; Nair et al. 1996) the authors note that "true" periapical cysts (as opposed to "pocket or bay" cysts) that are non-contiguous with the root apices are more often refractory to conventional endodontic therapy and thus require surgical endodontic treatment. Given the limitations of the currently available clinical diagnostic tests and the inability of imaging tools to distinguish amongst different periapical pathoses, surgical removal of periapical tissue associated with refractory teeth remains the only viable option short of extracting the tooth. Consequently, for teeth that have failed to respond to conventional root canal treatment or re-treatment, surgical endodontic treatment is the more desirable option. Therefore we conclude that any discussion about the prognostic significance of a diagnosis of periapical granuloma versus cyst (true or pocket/ bay type), versus scar or abscess is a purely academic exercise. It is based in studies conducted in research settings, where *en bloc* sectioning of roots and surrounding tissue were routinely carried out. This is certainly neither practical, desirable nor possible in actual clinical practice.

7.2 Lesions unrelated to apical periodontitis can mimic apical periodontitis

The results from our retrospective study revealed that 90.4% of periapical biopsies were found to be associated with apical periodontitis following microscopic analysis. Conversely, 9.6% of specimens taken from lesions that presented as apical radiolucencies were unrelated to pulpal pathology. The latter represented a range of pathological processes that included developmental cysts, benign neoplasms and a few malignant neoplasms. Some lesions were odontogenic in origin, while others were not **(Table 12a, 13a and 14a)**. As discussed in the introduction, periapical lesions unrelated to pulpal necrosis do not present with the same clinical features as those associated with teeth with apical periodontitis. They respond differently to the thermal and/or electrical clinical diagnostic tests of pulp vitality. In light of this, the discovery of such a relatively high percentage of non-pulpal related pathology located at root apices is noteworthy.

Among the lesions unrelated to pulpal necrosis, we reported 151 (5%) cases of odontogenic non-inflammatory lesions. These lesions included 62 (2%) odontogenic keratocysts/ keratocystic odontogenic tumors (OKC/KCOT); 37 (1%) lateral periodontal cysts; 7 (0.2%) ameloblastomas; 4 (0.1%) myxomas; and others **(Table 12a)**. Our results are comparable to those reported in several studies that demonstrated similar numbers of OKC/ KCOTs in their periapical samples (Stockdale and Chandler 1988; Spatafore et al. 1990; Ortega et al. 2007; Carrillo et al. 2008; Schulz et al. 2009). Similar frequencies of lateral periodontal cysts were also reported in the literature (Nobuhara and del Rio 1993; Kuc et al. 2000; Ortega et al. 2007). Two retrospective studies reported ameloblastomas and myxomas in periapical locations and the authors commented on the relative

infrequency of these lesions mimicking apical periodontitis (Kuc et al. 2000; Ortega et al. 2007). That developmental cysts and benign neoplasms of odontogenic origin have been found in the periapical region should raise clinicians' awareness. In this way, such lesions can be included in the clinical differential diagnosis, where indicated.

Non-odontogenic pathology was represented in 135 (4.5%) of 2979 periapical lesions. The diagnoses included nasopalatine canal cysts, benign fibro-osseous lesions (cemento-osseous dysplasias), traumatic bone cysts, and developmental cysts **(Table 13a)**. In addition, several benign and malignant neoplasms were discovered **(Table 14a)**. Similar results were reported in three other retrospective studies (Spatafore et al. 1990; Kuc et al. 2000; Ortega et al. 2007). In addition to some non-odontogenic benign neoplasms (ossifying fibroma, hemangioma, leiomyoma), we found 6 (0.2%) malignant neoplasms, predominantly metastatic in nature. This is consistent with reports in the literature of exceedingly low occurrence of malignancies at the apices of teeth. There have been individual case reports of metastatic malignancies at the apices of teeth mimicking pulpal disease. However, in each case it should be noted that the periapical lesions were often accompanied by other clinical and historical findings that would be considered suspicious for malignancies prior to the evaluation to rule out pulpal disease. Findings that are commonly associated with malignancy include a documented history of primary cancer, evidence or signs of metastatic spread to other sites in the body, unexplained weight loss, fatigue, and others. It should be pointed out that despite causing bone destruction around teeth, malignant neoplasms do not devitalize teeth. Patients frequently report a progressive mass, pain, paraesthesia and tooth mobility. They present with radiographic findings that are in many respects the diametric opposite of those

associated with apical periodontitis namely, ill-defined borders in the former vs. well defined with or without corticated borders in the latter instances. There have been case reports of metastatic carcinomas, malignant lymphomas, osteogenic sarcomas and other various neoplasms in periapical locations (Spatafore et al. 1990).

The prevalence (8.6%) of periapical lesions unrelated to pulpal necrosis in our study can be considered relatively high. It is possible that this is a product of the broad inclusion criteria set out at the beginning of this study. For comparison, a study of 805 periapical biopsy specimens conducted by Kuc et al., revealed only 8 cases (<1%) unrelated to pulpal necrosis. While both studies excluded lesions from the third molar region, the study by Kuc and co-investigators only included cases that were clinically tested for pulpal vitality and suspected as being related to pulp necrosis, whereas the current study included biopsy reports of all lesions in the periapical region; pulp vitality information was not available for all of the cases.

With the knowledge that pathology unrelated to pulpal necrosis can and does occur at tooth apices, more emphasis and time should be expended in the initial diagnostic work-up of a tooth prior to proceeding with endodontic treatment. It behooves clinicians to be constantly mindful of the fundamental principles of the endodontic diagnostic work-up, by paying close attention to patient history, clinical signs and symptoms, recognition of radiographic features associated with diverse pathological processes, and appropriate thermal and/or electric pulp testing.

7.3. Are clinical evaluation and diagnostic tests consistently reliable?

As presented in the introduction, the rationale of endodontic therapy is to eradicate microorganisms and debris present within a necrotic root canal system, thereby allowing for repair of inflamed periapical tissues. In the lead up to root canal therapy, it is critical to evaluate the tooth for restorability, periodontal health and most importantly, to determine whether endodontic therapy is actually indicated. In addition to clinical evaluation, replicating a patient's complaint, radiographic examination and periodontal evaluation, the decision to proceed with endodontic therapy is dependent on the results of clinical diagnostic tests using thermal and electric pulp testing instruments. To that end, it would be interesting to review the reliability and efficacy of these testing devices.

Several investigations have demonstrated highly reproducible results using the currently available thermal and electric pulp vitality test instruments to distinguish between vital and necrotic pulps (Fuss et al. 1986; Peters et al. 1994; Chen and Abbott 2011). The evidence suggests that a combination of the two testing methods offers greater accuracy and reliability in assessing pulp-vitality status. Our results revealed that the large majority of periapical pathoses are a result of pulpal necrosis, yet 9.6% of lesions were unrelated to pulpal pathology. Given the reported reliability of the available tests, clinicians should be able to diagnose pulp-related pathology if a disciplined diagnostic approach is employed. The discovery of a periapical lesion that mimics the radiographic features of apical periodontitis near the apex of a tooth with a vital pulp, should automatically trigger further investigation. This should include obtaining a periapical biopsy to establish diagnosis. A lack of diagnostic discipline early on in the process could lead to misdiagnosis and unnecessary endodontic treatment of a vital tooth. This may

result in further complications, including persistence and progression of a non-pulp related pathological process associated with an endodontically treated tooth. Another consideration is that two distinct pathological processes can be present in the same location. Hence, clinicians should be aware that other pathological processes can arise at the apices of teeth that have already been endodontically treated. While acknowledging some of the limitations of pulp-testing instruments including their inability to evaluate for actual health of pulpal tissue, their importance in the endodontic diagnostic work-up cannot be sufficiently emphasized.

7.4. Provisional clinical diagnoses are provisional

In our study 2693 of 2979 periapical biopsies from of a total 21649 oral pathology reports reviewed over a 5-year period revealed diagnoses attributable to apical periodontitis. This represented about 14% of all of the oral pathology specimens reviewed. These findings confirm that the large majority of periapical lesions are a result of pulpal necrosis. The evidence revealed through this study should inform a clinicians' index of suspicion when teeth with periapical radiographic findings are being evaluated. However, the marked prevalence of pulp-related apical pathology could potentially inflate clinicians' confidence or foster a low index of suspicion than warranted when a periapical radiographic lesion is discovered. In general, after the initial work-up including review of relevant radiographs and diagnostic tests, clinicians either arrive at a specific diagnosis without the need for further tests or they consider several provisional diagnostic possibilities. The nature of the provisional diagnoses can justify further imaging and/or testing, including a periapical biopsy. In our study, the provisional diagnoses provided by the submitting clinicians in 2979 biopsy reports were reviewed and compared to the final histological diagnoses.

Our results revealed that the overall index of suspicion based in the provisional diagnoses provided was positive in 84% of cases **(Table 16a)**. Of the contributing clinicians, endodontists and oral surgeons submitted a majority of the periapical lesions. Clinical provisional diagnoses that were in the general category of pathological process represented by the final histopathological diagnosis (**see 4 categories in Table 1**) were recorded as being positive. Reflective of their index of suspicion, provisional diagnoses provided by contributing endodontists and oral surgeons were similar: 85% and 84%,

respectively. A previous investigation concerning the consistency of submitting clinicians' indices of suspicion showed similar results (Kuc et al. 2000). These authors demonstrated that the provisional diagnoses provided by endodontists were significantly more consistent with the final histopathological diagnoses, as compared to those provided by oral surgeons and general dentists. The finding that endodontists' clinical diagnostic impressions were more consistent with the final diagnoses could be attributable to either: (i) their more organized, disciplined diagnostic work up of periapical lesions or (ii) the relatively narrow scope of their practice which addresses periapical related pathoses most of the time. There were some differences in consistency between our study and that of Kuc et al. Those differences could be attributable to the larger number of cases reviewed in our study. Moreover, different criteria were used to evaluate the consistency of the submitting clinicians' index of suspicion in the respective studies. Despite the high overall consistency of the clinicians' indices of suspicion, 16% of the submitted cases reviewed revealed different diagnoses following histopathological examination than the ones that were expected provisionally. Sixteen percent of the provisional diagnoses were in a completely different category of pathological process. In addition to emphasizing the importance of a disciplined clinical diagnostic work-up, this observation underscores the importance of obtaining a specific final diagnosis through routine biopsy submission of obtained periapical tissues. To state the obvious, "Provisional diagnoses are just that: provisional".

7.5 Routine submission of tissue obtained during endodontic surgery is justifiable

The requirement that periapical tissue obtained from apicoectomy procedures be submitted ***routinely*** for histopathological examination has been, and remains, the subject of much debate. While the guidelines recommend routine submission of surgically obtained periapical tissue for histological diagnosis, this practice is not followed universally.

In an editorial by Walton (Walton 1998), the rationale for routine submission of endodontic periradicular surgical specimens was challenged. He argued that routine submission of biopsies was an exercise, "that may be of academic interest but is of no advantage to the patient and not worth the additional cost to the patient or insurance carrier". The following reasons for non-submission of periapical tissues were cited:

1. Careful clinical and radiographic evaluation and vitality tests aid in detecting the large majority of odontogenic inflammatory lesions.
2. Clinicians are unable to consistently submit curetted periapical tissues in their entirety to establish specific diagnoses (i.e. cyst vs. granuloma), and the often crushed nature of the submitted tissues hampers pathologists' ability to render accurate diagnoses.
3. Exceedingly small numbers of non-endodontic pathological lesions occur at the apices of teeth that have been confidently diagnosed using presurgical clinical tests. Any entity other than an endodontic inflammatory lesion discovered in this location could well be a chance occurrence.

This rhetorical sounding opinion may be well meaning. The author does appear to emphasize the importance of a thorough clinical diagnostic work-up that highlights the tools available to the clinician. However the given rationale fails to consider several key points, including the reason for the performance of periapical surgery in the first place. Surgery is indicated when conventional, nonsurgical root canal therapy has not resolved the lesion. A non-healing lesion by itself is considered "atypical". It warrants further management and exploration. Surgery should not be a technical exercise, based in the assumption that the tissue at the apex is merely inflammatory in nature. The risk-benefit ratio of submitting a biopsy is strong. As stated in a response to Walton's editorial, "If an endodontist's clinical judgment can justify an expensive invasive surgical procedure, how can verification of that judgment through histopathologic examination **not be** justified?" (Ellis 1999).

The challenge to submitting periapical biopsies routinely has been countered by several authors (Baughman 1999; Ellis 1999; Newton 1999). We would offer a further challenge, noting that "accurate clinical diagnosis" is almost entirely dependent on individual clinicians' discipline coupled with the assumption that thermal and/or electric pulp testing instruments are 100% reliable. However, published studies have demonstrated that such presumptions are not based on reality. Furthermore, notwithstanding the value of the provisional clinical diagnosis in guiding treatment decisions, an unconfirmed provisional diagnosis is not without its limitations. Indeed, as our study revealed, provisional diagnoses and final diagnoses were inconsistent in 16% of cases. Therefore, given the prevailing debate, the current American Association of

Endodontists (AAE) recommendations (Newton 1999), under the "Appropriateness of Care and Quality Assurance, Third Edition" guidelines state the following:

"A biopsy is appropriate if any of the following clinical conditions exist:

a. When *a recoverable amount of tissue or foreign material can be removed from the periradicular surgical site.*

b. Unusual or persistent pathosis is noted on clinical or radiographic examination.

c. Medical history indicates the merits of biopsy"

It goes on to reiterate and state that "it is appropriate to establish a diagnosis by microscopic examination ***any time*** a recoverable amount of tissue can be removed from the periapical surgical site". This is in addition to clinical situations listed in statements (b.) and (c.). Additionally, the guidelines state that histopathological assessment should be viewed "…not as an academic exercise, but as a completion or closure to the management of a heretofore unsuccessful case" (Newton 1999).

Our results revealed that several non-endodontic pathological lesions occur in the periapical region (286/2979). They included developmental cysts, OKC/ KCOTs, ameloblastomas and other benign and malignant neoplasms. The possibility of pathology, other than that related to pulpal inflammation and necrosis, aggressive or not, is a risk that justifies routine submission for histological diagnosis.

Standard-of-care issues are frequently a subject of debate, both in clinical practice as well as in a medico-legal setting. In addition to the patient-centered approach discussed above, legal considerations could well justify the need to routinely submit

collected periapical tissue for histopathologic evaluation. While professional liability suits involving periapical tissues are uncommon, the example cited below illustrates the pitfalls of discarding tissue. In the case *O'Brien vs. Stover* (433 F 2d 1013, CCA 8 1971), a dentist was sued for non-submission of tissue from the apex of a tooth in an area that demonstrated bone deterioration. Subsequent biopsies of the non-healing socket revealed a malignant neoplasm. The patient died from complications relating to the malignant neoplasm (Holder 1973).

While acknowledging the rarity of such occurrences, it is important to ask where one "draws the line" to call a procedure meaningful or justifiable. Does detecting and diagnosing a single metastatic carcinoma at the periapical location in the entire lifetime of a single endodontist's practice qualify as "justifiable"? When is submission of a biopsy "worth it"? Should endodontic clinical practice be defined by cost-effectiveness or driven by a strong desire to provide the best healthcare for patients? We believe that prevalence of a few non-endodontic lesions (listed below), which were discovered during our retrospective analysis, answers this question unequivocally:

TOTAL Periapical Pathology	**2979**	**Nature of lesion**
OKC/ KCOT	62	**Locally destructive cyst/ neoplasm**
Ameloblastoma	7	**Benign neoplasm**
Myxoma	4	
Ossifying fibroma	5	
Venous hemangioma	2	
Osteoma (Intra-osseous)	1	
Squamous cell carcinoma	1	**Malignant neoplasm**
Osteosarcoma	2	
Multiple myeloma	1	
B-cell Non-Hodgkin Lymphoma	1	
Metastatic adenocarcinoma	1	

8. Summary and conclusions

Retrospective analysis of 21649 pathology reports from the UCONN Oral Pathology Biopsy service over a 5-year period revealed that 2979 (13.8%) of lesions were located in the periapical region. The results from this study can be summarized as follows:

1. A majority of periapical lesions (90.4%) are related to pulpal necrosis and subsequent apical periodontitis.
2. The remainder showed either non-pathological tissue (1%) or pathological changes unrelated to pulpal necrosis (8.4%). This included several significant pathological entities, including OKC/ KCOT, ameloblastoma and odontogenic myxomas.
3. Non-odontogenic pathology in the periapical location is uncommon, but does occur (4.5% of 2979 biopsies). It comprised cysts, benign neoplasms and a few sporadic malignant neoplastic lesions. Additionally, the submitting clinicians' index of suspicion was inconsistent in 16% of the cases.
4. Disciplined clinical, radiographic and diagnostic testing can aid in the detection and diagnosis of pathology unrelated to pulpal necrosis. In circumstances where vitality tests are equivocal or if the medical history is suggestive, further evaluation may be indicated.
5. Endodontic surgery is generally indicated when conventional nonsurgical root canal therapy has not resolved the lesion. When clinical impressions justify an invasive intraosseous surgical procedure for resolution of a refractory

periapical problem, diagnostic confirmation through tissue biopsy provides a sense of closure for both the clinician and patient alike.

6. Currently available non-invasive imaging methods cannot provide nor confirm specific tissue diagnoses. Therefore, histopathologic examination of periapical specimens remains the gold standard to accurately diagnose and differentiate amongst various periapical pathological lesions. In addition to providing closure and a guideline for further management, the routine submission of periapical tissues for histopathological examination helps to rule out uncommon, destructive and potentially life-threatening diseases.

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10. Tables and Figures.

Table 1: Categorization of periapical pathology and selected examples

Lesion category	Examples
Odontogenic inflammatory pathosis	Periapical granuloma Periapical cyst Periapical scar Periapical abscess Periodontitis Condensing Osteitis
Odontogenic non-inflammatory pathosis	Developmental odontogenic cysts • Odontogenic keratocyst (OKC/ KCOT) • Lateral periodontal cyst Benign Odontogenic noeplasms: • Ameloblastoma • Cementoblastoma • Odontoma • Myxoma
Non-odontogenic non-neoplastic pathosis	Nasopalatine canal cyst Traumatic bone cyst Benign fibro-osseous lesions • Cemento-osseous dysplasia Focal bone marrow defects Central giant cell lesions
Non-odontogenic neoplastic pathosis	Ossifying fibroma Hemangioma/ vascular malformations Intraosseous invasion of primary squamous cell carcinoma Metastatic disease Malignant lymphoproliferative diseases – lymphoma etc.

Table 2: Prevalence of odontogenic inflammatory pathology

Author, Year	Total	Granuloma (%)	Cyst (%)	Scar (%)	Abscess (%)	Foreign body (%)	Biopsy source
Priebe et al., **1954**	**101**	45.5	54.5				Periapical surgery
Baumann and Rossman, **1956**	**121**	73.5	26.5				Periapical surgery
Sommer et al., **1956**	**170**	83	7				Not specified
Wais, **1958**	**100**	74	20				Periapical surgery
Bhaskar, **1966**	**2308**	48	42	3	1	1	Not specified
Seltzer et al., **1967**	**87**	45	51	2			Extraction and periapical surgery
Lalonde and Luebke, **1968**	**800**	45	44	0.5		1.5	Not specified
Mortensen et al., **1970**	**396**	59	41				Extraction and periapical surgery
Block et al. **1976**	**230**	94	6				Periapical surgery
Hirsch et al. **1979**	**648**	68	29	3			Periapical surgery
Winstock **1980**	**9804**	83	8		2	6	Periapical surgery
Stockdale & Chandler, **1988**	**1108**	77	17	4		0.5	Periapical surgery
Spatafore et al., **1990**	**1659**	52	42	2			Not specified
Nobuhara & Del Rio, **1993**	**150**	59	22	12	1	0.5	Periapical surgery
Nair et al., **1996**	**256**	50	15		35		Extraction
Kuc et al., **2000**	**805**	50	46		2		Not specified
Ricucci et al., **2006**	**57**	61	18		21		Extractions and periapical surgery
Love and Firth, **2008**	**100**	77	18	2	3		Periapical surgery
Carrillo et al., **2008**	**70**	66	6	26			Periapical surgery
Schulz et al., **2009**	**119**	70	23	1	5		Periapical surgery

Table 3: Prevalence of Odontogenic Non-inflammatory Pathology

Author, year	Total	Pathology	Number
Bhaskar, **1966**	**2308**	Cementoblastoma	28
Stockdale and Chandler, **1988**	**1108**	OKC	1
Spatafore et al., **1990**	**1659**	Cementoma	N/S
		Odontoma	
		OKC	
Nobuhara and del Rio, **1993**	**150**	LPC	3
		Myxomatous tissue	1
Kuc et al., **2000**	**805**	LPC	1
		Pindborg tumor	1
		Myxoma	1
Ortega et al.. **2007**	**4006**	OKC	11
		COC	1
		LPC	1
		Ameloblastic fibroma	1
		Squamous odontogenic tumor	1
Carrillo et al., **2008**	**70**	OKC	1
Schultz et al., **2009**	**119**	OKC	1

OKC = Odontogenic keratocyst
LPC = Lateral periodontal cyst
COC = Calcifying odontogenic cyst

N/S = Not specified

Table 4: Prevalence of non-odontogenic non-neoplastic pathology

Author, year	Total	Pathology	Number
Bhaskar, **1966**	**2308**	Central giant cell lesion	2
Seltzer et al., **1967**	**87**	Cholesteatoma	1
		Fibrous dysplasia	1
Winstock, **1980**	**9804**	Central giant cell lesion	20
Spatafore et al., **1990**	**1659**	Traumatic bone cyst	N/S
		Nasopalatine canal cyst	N/S
		Central giant cell granuloma	N/S
Kuc et al., **2000**	**805**	Central giant cell lesion	2
		Nasopalatine canal cyst	1
Ortega et al., **2007**	**4006**	Chronic sinusitis	3
		Central giant cell lesion	3
		Nasopalatine canal cyst	1
		Cemental dysplasia	1
		Amalgam tattoo	1

N/S = Not Specified

Table 5: Prevalence of non-odontogenic neoplastic pathology

Author, year	Total	Pathology	Number
Spatafore et al., **1990**	1659	Central ossifying fibroma	N/S
		Lymphoma	N/S
Kuc et al, **2000**	805	Plasmacytoma	1
Ortega et al, **2007**	4006	Hemangioma	1

N/S = Not specified

Table 6: Correlation between gender and odontogenic inflammatory pathology

Author, year	Pathology	Male	Female
Bhaskar, **1966**	Periapical granuloma	550	558
	Periapical cyst	605	327
	Periapical scar	29	26
	Periapical abscess	16	10
Lolande and Luebke, **1968**	Periapical granuloma	162	192
	Periapical cyst	164	183
Stockdale & Chandler, **1988**	Periapical granuloma	398	458
	Periapical cyst	99	87
	Periapical scar	21	29
Love and Firth, **2009**	Periapical granuloma	37	40
	Periapical cyst	6	12
	Periapical scar	1	1
	Periapical abscess	1	2

Table 7: Correlation between age and odontogenic inflammatory pathology

Author, year	Pathology	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
Bhaskar, **1966**	Periapical granuloma	17	182	226	138	118	71	35	13	1
	Periapical cyst	31	213	232	195	145	45	47	19	0
	Periapical scar	1	8	5	9	18	7	6	0	0
	Periapical abscess	2	7	5	1	5	4	1	1	0
Stockdale & Chandler, **1988**	Periapical granuloma		33	238	269	175	139			
	Periapical cyst		12	52	65	33	24			

Table 8: Correlation between anatomical location and odontogenic inflammatory pathology

Author, year	Pathology	Maxilla	Mandible	Maxilla		Mandible	
				Ant	Post	Ant	Post
Bhaskar, **1966**	Periapical granuloma	796	237	N/S	N/S	N/S	N/S
	Periapical cyst	798	82	N/S	N/S	N/S	N/S
	Periapical scar	39	18	N/S	N/S	N/S	N/S
	Periapical abscess	17	9	N/S	N/S	N/S	N/S
Lolande & Luebke, **1968**	Periapical granuloma	199	133	148	46	47	79
	Periapical cyst	199	139	143	41	37	92
Mortensen et al, **1970**	Periapical granuloma	121	111	55	66	29	82
	Periapical cyst	97	67	41	56	14	53
Stockdale & Chandler, **1988**	Periapical granuloma	723	133	632	91	114	19
	Periapical cyst	163	23	153	10	18	5
Spatafore et al., **1990**	Periapical granuloma	613	251	414	199	122	129
	Periapical cyst	454	242	322	132	94	148
	Periapical scar	24	9	18	6	8	1
Love and Firth, **2009**	Periapical cyst	16	2	14	2	2	0
	Periapical scar	1	1	0	1	1	0

N/S = Not specified

Table 9: Results of retrospective analysis of 2979 periapical pathology reports. Demographics, anatomical distribution and contributors

		n	%
Gender			
	Female	1527	51.3
	Male	1452	48.7
	TOTAL	**2979**	**100**
Age			
	< 20	173	5.8
	20-50	1224	41.1
	>50	1582	53.1
	TOTAL	**2979**	**100**
Anatomical distribution (Arch)			
	Maxilla	1929	64.8
	Mandible	1050	35.2
	TOTAL	**2979**	**100**
Permanent dentition - Anatomical distribution (Tooth type)			
	Maxillary anterior	897	20.8
	Maxillary premolar	476	15.1
	Maxillary molar	658	28.4
	Mandibular anterior	274	19.3
	Mandibular premolar	245	7.8
	Mandibular molar	611	8.7
	TOTAL	**3161**	**100**
Primary dentition - Anatomical distribution (Tooth type) *			
	Maxillary anterior	2	33.3
	Maxillary molar	1	16.7
	Mandibular anterior	1	16.7
	Mandibular molar	2	33.3
	TOTAL	**6**	**100**
Contributors			
	Endodontist	1465	49.18
	Oral Surgeon	1289	43.27
	General Dentist	139	4.67
	Periodontist	76	2.55
	Pathologist consult	7	0.23
	Pediatric dentist	2	0.07
	Otolaryngologist	1	0.03
	TOTAL	**2979**	**100**

* Periapical lesions associated with primary teeth were excluded in the final analysis

Table 10: Retrospective analysis of 2979 periapical biopsy reports.
Prevalence of specific pathological lesions

Lesion category	Histologic diagnosis	Prevalence	%
Odontogenic inflammatory	Periapical granuloma	1534	51.49
	Periapical cyst	981	32.93
	Periapical scar	143	4.80
	Periapical abscess	26	0.87
	Sinus tract (fistula)	4	0.13
	Periodontitis	2	0.07
	Foreign body reaction	1	0.03
	Condensing osteitis	1	0.03
	Inflamed odontogenic cyst (non-specific)	1	0.03
Odontogenic non- inflammatory	OKC/ KCOT	62	2.08
	Lateral periodontal cyst	37	1.24
	Odontoma	16	0.54
	Tooth or root fragments (NPT)	10	0.34
	Ameloblastoma	7	0.23
	Myxoma	4	0.13
	Cementoblastoma	3	0.10
	Central odontogenic fibroma	2	0.07
	Hypercementosis	2	0.07
	Calcifying odontogenic cyst	2	0.07
	Adenomatoid odontogenic tumor	1	0.03
	Ameloblastic fibro-odontoma	1	0.03
	Ameloblastic fibroma	1	0.03
	Dental follicle	1	0.03
	Orthokeratotic odontogenic cyst	1	0.03
	Primordial cyst	1	0.03
Non-odontogenic non-neoplastic	Nasopalatine canal cyst	33	1.11
	Benign fibro-osseous lesion	32	1.07
	Bone (NPT)	20	0.67
	Traumatic bone cyst	18	0.60
	Developmental cyst	5	0.17
	Central giant cell lesion	4	0.13
	Sequestrum	2	0.07
	Surgical ciliated cyst	2	0.07
	Bone marrow defect	1	0.03
	Giant cell lesion consistent with cherubism	1	0.03
	Inflamed antral mucosa	1	0.03
	Mature adipose tissue (NPT)	1	0.03
Non-odontogenic neoplastic	Ossifying fibroma	5	0.17
	Osteosarcoma	2	0.07
	Venous hemangioma	2	0.07
	Squamous cell carcinoma	1	0.03
	Multiple myeloma	1	0.03
	B-cell Non-Hodgkin Lymphoma	1	0.03
	Leiomyoma	1	0.03
	Metastatic adenocarcinoma	1	0.03
	Osteoma (Intra-osseous)	1	0.03
	TOTAL	**2979**	**100**

NPT = Non pathological tissue/ within normal limits

Table 11a: Prevalence and demographics of odontogenic inflammatory pathology - Gender, Age, Anatomical location

Specific diagnosis	n	%	Gender		Age distribution			Anatomical location	
			Male	Female	<20	20-50	>50	Max	Man
Periapical granuloma	1534	56.96	693	841	56	590	888	1106	428
Periapical cyst	981	36.43	525	456	57	447	477	579	402
Periapical scar	143	5.31	69	74	6	61	76	104	39
Periapical abscess	26	0.97	10	16	4	12	10	14	12
Sinus tract (fistula)	4	0.15	2	2	0	3	1	2	2
Periodontitis	2	0.07	1	1	0	1	1	1	1
Foreign body reaction	1	0.04	1	0	0	0	1	0	1
Condensing osteitis	1	0.04	0	1	0	0	1	0	1
Inflamed odontogenic cyst	1	0.04	1	0	1	0	0	0	1
TOTAL	2693	100	1302	1391	124	1114	1455	1806	887

Table 11b: Anatomical location of specific odontogenic inflammatory pathology (sextants):

Specific diagnosis	UM	UP	UA	LM	LP	LA	Total
Periapical granuloma	378	272	474	281	70	89	1564
Periapical cyst	202	141	278	244	84	102	1051
Periapical scar	32	20	55	20	6	14	147
Periapical abscess	7	3	6	7	2	1	26
Sinus tract (fistula)	0	0	2	2	0	0	4
Periodontitis	1	0	0	1	0	0	2
Foreign body reaction	0	0	0	0	1	0	1
Condensing osteitis	0	0	0	0	1	0	1
Inflamed odontogenic cyst	0	0	0	1	1	0	2
TOTAL	620	436	815	556	165	206	2798 *

**** 2798 lesions includes those obtained from apices of multiple teeth***

UM = maxillary molar; **UP** = maxillary premolar; **UA**= maxillary anterior;
LM = mandibular molar; **LP** = mandibular premolar; **LA =** mandibular anterior

Table 12a: Prevalence and demographics of odontogenic non-inflammatory pathology - Gender, Age, Anatomical location

Specific diagnosis	n	%	Gender		Age distribution			Anatomical location	
			Male	Female	<20	20-50	>50	Max	Man
OKC/ KCOT	62	41.06	43	19	0	13	49	27	35
Lateral periodontal cyst	37	24.50	22	15	2	13	22	5	32
Odontoma	16	10.60	8	8	13	3	0	8	8
Tooth or Root fragments	10	6.62	3	7	1	8	1	9	1
Ameloblastoma	7	4.64	4	3	2	2	3	1	6
Myxoma	4	2.65	3	1	1	3	0	2	2
Cementoblastoma	3	1.99	2	1	1	1	1	1	2
Central odontogenic fibroma	2	1.32	1	1	1	1	0	0	2
Hypercementosis	2	1.32	0	2	0	2	0	1	1
Calcifying odontogenic cyst	2	1.32	1	1	1	0	1	2	0
AOT	1	0.66	1	0	1	0	0	1	0
AFOD	1	0.66	1	0	1	0	0	0	1
AFO	1	0.66	0	1	1	0	0	0	1
Dental follicle	1	0.66	0	1	1	0	0	1	0
OOC	1	0.66	1	0	0	0	1	0	1
Primordial cyst	1	0.66	1	0	1	0	0	0	1
TOTAL	151	100	91	60	27	46	78	58	93

OKC = Odontogenic keratocyst; **AOT** = Adenomatoid odontogenic tumor; **AFOD** = Ameloblastic fibroodontoma
AFO = Ameloblastic fibroma; **OOC** = Orthokeratinized odontogenic cyst

Table 12b: Anatomical location of specific odontogenic non-inflammatory pathology (sextants)

Specific diagnosis	UM	UP	UA	LM	LP	LA	Total
OKC/ KCOT	5	11	18	8	22	19	83
Lateral periodontal cyst	0	2	5	2	24	22	55
Odontoma	1	2	6	2	4	3	18
Tooth or Root fragments	5	4	1	0	1	0	11
Ameloblastoma	0	0	1	4	3	2	10
Myxoma	2	2	1	1	1	1	7
Cementoblastoma	0	1	1	2	0	0	3
Central odontogenic fibroma	0	0	1	0	1	1	2
Hypercementosis	1	0	1	1	0	0	2
Calcifying odontogenic cyst	1	1	1	0	0	0	3
AOT	0	1	1	0	0	0	1
AFOD	0	0	1	0	0	1	1
AFO	0	0	1	0	0	1	1
Dental follicle	0	0	1	0	0	0	1
OOC	0	0	1	1	0	0	1
Primordial cyst	0	0	1	0	1	1	2
TOTAL	**15**	**24**	**42**	**21**	**57**	**51**	**201***

**** 201 lesions includes those obtained from lesions involving apices of multiple teeth***

UM = maxillary molar; **UP** = maxillary premolar; **UA**= maxillary anterior;
LM = mandibular molar; **LP** = mandibular premolar; **LA =** mandibular anterior
OKC = Odontogenic keratocyst; **AOT** = Adenomatoid odontogenic tumor; **AFOD** = Ameloblastic fibroodontoma
AFO = Ameloblastic fibroma; **OOC** = Orthokeratinized odontogenic cyst

Table 13a: Prevalence and demographics of non-odontogenic non-neoplastic pathology - Gender, Age, Anatomical location

Specific diagnosis	n	%	Gender		Age distribution			Anatomical location	
			Male	Female	<20	20-50	>50	Max	Man
Nasopalatine canal cyst	33	21.85	24	9	2	16	15	33	0
BFOL-COD	32	21.19	3	29	2	24	6	3	29
Bone	20	13.25	4	16	4	6	10	8	12
Traumatic bone cyst	18	11.92	10	8	12	3	3	2	16
Developmental cyst	5	3.31	3	2	0	2	3	3	2
Central giant cell lesion	4	2.65	1	3	1	2	1	1	3
Sequestrum	2	1.32	1	1	0	0	2	0	2
Surgical ciliated cyst	2	1.32	1	1	0	1	1	2	0
Bone marrow defect	1	0.66	1	0	0	0	1	0	1
Giant cell lesion (CHER)	1	0.66	0	1	1	0	0	0	1
Inflamed antral mucosa	1	0.66	0	1	0	1	0	1	0
Mature adipose tissue	1	0.66	1	0	0	1	0	1	0
TOTAL	120	100	91	60	27	46	78	58	93

BFOL-COD = Benign fibro-osseous lesion, cemento osseous dysplasia
CHER = Cherubism

Table 13b: Anatomical location of specific nonodontogenic non-neoplastic pathology (sextants)

Specific diagnosis	UM	UP	UA	LM	LP	LA	Total
Nasopalatine canal cyst	0	1	33	0	0	0	34
BFOL-COD	5	0	2	14	5	8	34
Bone	3	3	3	10	3	1	23
Traumatic bone cyst	4	3	3	6	9	4	29
Developmental cyst	1	1	2	0	1	1	6
Central giant cell lesion	1	1	1	1	2	1	7
Sequestrum	0	0	0	2	0	0	2
Surgical ciliated cyst	2	0	0	0	0	0	2
Bone marrow defect	0	0	0	0	1	0	1
Giant cell lesion (CHER)	0	0	0	0	1	1	2
Inflamed antral mucosa	1	1	0	0	0	0	2
Mature adipose tissue	1	0	0	0	0	0	1
TOTAL	18	10	44	33	22	16	143 *

**** 143 lesions includes those obtained from lesions involving apices of multiple teeth***

UM = maxillary molar; **UP** = maxillary premolar; **UA**= maxillary anterior;
LM = mandibular molar; **LP** = mandibular premolar; **LA =** mandibular anterior
BFOL-COD = Benign fibro-osseous lesion, cemento osseous dysplasia
CHER = Cherubism

Table 14a: Prevalence and demographics of non-odontogenic neoplastic pathology - Gender, Age, Anatomic location

Specific diagnosis	n	%	Gender		Age distribution			Anatomical location	
			Male	Female	<20	20-50	>50	Max	Man
Ossifying fibroma	5	33.3	3	2	0	5	0	3	2
Osteosarcoma	2	13.3	1	1	0	0	2	2	0
Venous hemangioma	2	13.3	2	0	0	1	1	2	0
Multiple myeloma	1	6.7	1	0	0	0	1	0	1
Lymphoma – NHBCL	1	6.7	1	0	0	0	1	1	0
Leiomyoma	1	6.7	0	1	0	1	0	1	0
Metastatic adenocarcinoma	1	6.7	1	0	0	0	1	1	0
Osteoma	1	6.7	1	0	0	1	0	0	1
Squamous cell carcinoma	1	6.7	0	1	0	0	1	1	0
TOTAL	15	100	10	5	0	8	7	11	4

NHBCL = Non-Hodgkin's B-Cell Lymphoma

Table 14b: Anatomical location of specific non-odontogenic neoplastic pathology (sextants)

Specific diagnosis	UM	UP	UA	LM	LP	LA	Total
Ossifying fibroma	0	3	2	0	1	1	7
Osteosarcoma	2	0	0	0	0	0	2
Venous hemangioma	0	0	2	0	0	0	2
Multiple myeloma	1	0	0	0	0	0	1
Lymphoma – NHBCL	1	1	0	0	0	0	2
Leiomyoma	0	0	1	0	0	0	1
Metastatic adenocarcinoma	0	1	0	0	0	0	1
Osteoma	0	0	0	1	0	0	1
Squamous cell carcinoma	1	1	0	0	0	0	2
TOTAL	5	6	5	1	1	1	19*

UM = maxillary molar; **UP** = maxillary premolar; **UA**= maxillary anterior;
LM = mandibular molar; **LP** = mandibular premolar; **LA =** mandibular anterior

NHBCL = Non-Hodgkin's B-Cell Lymphoma

**** 19 lesions includes those obtained from apices of multiple teeth***

Table 15a: Prevalence and demographics of periapical lesions by category - Gender, Age, Anatomic location

Category of periapical pathology	n	%	Gender		Age distribution			Anatomical location	
			Male	Female	<20	20-50	>50	Max	Man
Odontogenic inflammatory	2693	90.4%	1302	1391	124	1114	1455	1806	887
Odontogenic non-inflammatory	151	5.1%	91	60	27	46	78	58	93
Non-odontogenic non-neoplastic	120	4.0%	49	71	22	56	42	54	66
Non-odontogenic neoplastic	15	0.5%	10	5	0	8	7	11	4
TOTAL	**2979**	**1**	**1452**	**1527**	**173**	**1224**	**1582**	**1929**	**1050**

Table 15b: Anatomical location of periapical lesions by category (sextants):

Category of periapical pathology	UM	UP	UA	LM	LP	LA	Total
Odontogenic inflammatory	620	436	815	556	165	206	2798
Odontogenic non-inflammatory	15	24	33	21	57	51	201
Non-odontogenic non-neoplastic	18	10	44	33	22	16	143
Non-odontogenic neoplastic	5	6	5	1	1	1	19
TOTAL	**658**	**476**	**897**	**611**	**245**	**274**	**3161 ***

**** 3161 lesions includes those obtained from apices of multiple teeth***

UM = maxillary molar; **UP** = maxillary premolar; **UA**= maxillary anterior;
LM = mandibular molar; **LP** = mandibular premolar; **LA =** mandibular anterior

Table 15c: Prevalence of periapical pathology in relation to pulp-infection status

Pathology	n	%
Pathology related to pulp-necrosis (PRPN)	2693	90.4%
Pathology unrelated to pulp-necrosis (PUPN)	255	8.6%
Non-pathological tissue (NPT)	31	1.0%

Table 16a: Contributors' index of suspicion – correlation between submitted provisional diagnoses and final histopathological diagnosis

Contributor	Provisional Dx consistent		Provisional Dx inconsistent		Total
	n	%	n	%	n
Endodontist	1251	85	214	15	1465
Oral Surgeon	1077	84	212	16	1289
General Dentist	118	85	21	15	139
Periodontist	58	76	18	24	76
Pathologist	5	71	2	29	7
Pediatric dentist	1	50	1	50	2
Otolaryngology	1	100	0	0	1
TOTAL	**2511**	**84**	**468**	**16**	**2979**

Table 16b: Prevalence of periapical pathology submitted by contributors

Category of periapical pathology	ENDO	OMFS	GD	PERI	PATH	PEDO	ENT	Total
Odontogenic inflammatory	1450	1048	131	58	3	2	1	2693
Odontogenic non-inflammatory	11	122	5	12	1	0	0	151
Non-odontogenic non-neoplastic	4	106	3	5	2	0	0	120
Non-odontogenic neoplastic	0	13	0	1	1	0	0	15
TOTAL	**1465**	**1289**	**139**	**76**	**7**	**2**	**1**	**2979**

ENDO = Endodontist; **OMFS =** Oral surgeon; **GD** = General dentist; **PERI** = periodontist;
PATH = pathologist; **PEDO** = pediatric dentist; **ENT** = otolaryngologist