QUANTITATIVE DIGITAL ASSESSMENT OF PERIAPICAL HEALING

A THESIS

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Dedication

To Kristi,

To my parents,

To my parents in-law

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Introduction

Root canal therapy allows patients the ability to maintain their natural teeth in the event disease threatens the health of the pulp of their tooth. As clinicians, we are constantly striving and refining our procedures to provide our patients with more predictable and successful treatments. Evidence based dentistry heavily influences this decision making process. Our ability to correlate clinical research to clinical outcomes is vital when we are considering the best treatment for our patients. In an evidenced based practice, careful and accurate evaluation of these outcome studies is crucial, and radiographic data is often required.

Evaluation of dental treatment is often assessed through radiographic interpretation, and the use of radiographs have become indispensible for diagnosis and treatment planning. Radiographic records are readily available, relatively inexpensive, transferable, and archivable. Radiographs are a critical component of endodontic outcome studies as evidenced by their use in the primary research that makes up larger scale systematic reviews (Ng et al., 2007).

Data standardization of any scientific study is always a critical component. Attempts have been made to standardize radiographic interpretation in endodontics to correlate different treatments with different outcomes. One of these methods is the Periapical Index introduced by Orstavik in 1986 (Orstavik et al., 1986). Subtraction technology has also been advocated to evaluate outcomes (Tyndall et al., 1990). These methods either oversimplify the data by separating possible outcomes into only five groups such as with the Periapical

Index, or require complicated image acquisition and software processing to extract data, such as with image subtraction methods. In this study, we aim to introduce a method that utilizes the positive attributes from each of these techniques.

Review of the Literature

History of Radiography in Dentistry and Endodontics

In Germany in 1895, Wilhelm Konrad Roentgen produced and detected the first electromagnetic radiation of a wavelength in the range of what we today define as X-rays. Fourteen days later Dr. Otto Walkott exposed the first recorded dental radiograph. The radiograph, captured on small glass photographic plates of Dr. Walkott's own tooth, required an exposure time of 25 minutes. It wasn't until 1899 that Dr. C. Edmund Kells applied these radiographic techniques to endodontics. Dr. Kells also is credited with introducing the paralleling technique later made popular by Dr. Gordon Fitzgerald (Ennis, 1959; Walton, 2008). Over 8 decades later, Dr. Francis Mouyen patented the first solid-state digital radiography system.

X-Rays are made up of electromagnetic radiation that has a wavelength of 10 to .01 nanometers. A voltage potential is set up across a partially evacuated tube containing a cathode on one end and an anode at the other end that produces the X-rays. The cathode consists of a filament, though which current is run, providing a source of electrons. The anode is a tungsten target placed at an angle to provide a "target" for electrons. When the accelerated electrons reach the tungsten target, two main types of useful electromagnetic radiation are created. When high-energy electrons directly hit or nearly miss a tungsten atom, general radiation is produced. A direct electron hit ejects that electron out of the K shell and an electron from the L shell drops into the K shell, which produces characteristic radiation. The number of electrons, and hence X-rays produced can be increased by increasing the current (mA) across the filament. X-rays with more penetrating power can be produced by increasing the voltage (kVp) across the cathode and anode (Ennis, 1959; Farman et al., 2008).

Images are captured by either radiographic film or digital images. Conventional dental films consist of a polyester or triacetate base. On both sides, an emulsion of silver halide crystals and gelatin creates a thin coating on the base. When exposed to X-rays, the crystals hold a latent image. Once developed, these exposed silver halide crystal precipitate metallic silver. Fixation washes the undeveloped crystals away making these areas clear, and precipitated sliver blocks light when viewed on a viewbox (Farman et al., 2008).

Digital images are generally captured by one of two ways, photostimulable phosphor plates, or solid-state complementary metal oxide semiconductor active pixel technology (CMOS-APS) and charge coupled device (CCD) sensors. First, photostimulable phosphor plates capture images by ionizing europium atoms in the phosphor crystalline lattice. When scanned with a red laser, electrons are liberated to recombine with the europium atoms and liberate blue light. This blue light is scanned and converted to a digital image. CMOS-APS or CCD sensors are silicon imbedded electronic circuits that are split up into thousands of photosensitive pixels. In CCDs, each pixel functions as an electron reservoir. When a photon of sufficient energy strikes the silicon, the covalent bonds of the silicon are broken and the charge is transmitted to the pixel reservoir. This charge is then converted to a digital electronic signal for processing. CMOS-APS devices use active transistors built into each pixel. This allows 100 times less power to be used to power the system. Most digital systems today use CMOS-APS technology (Farman et al., 2008).

Methods for Studying Endodontic Outcomes

In endodontics, our ability detect the presence of disease is of paramount importance to our practice. For diagnosis, medical and dental history are recorded, and a clinical exam is performed, which includes pulp testing, percussion, palpation and periodontal probing in conjunction with radiographic evaluation. The poor correlation between our pulp testing and the histological state of the pulp (Bhaskar, Rappaport, 1973; Seltzer et al., 1963a, 1963b) suggests the need for better evaluation methods. Equally important is our ability to evaluate treatments as success or failure. Various methods have been used as criteria for classification of success and failure. In 1956, Strindberg et al introduced a strict set of guidelines that only allowed a case to be classified as successful if it displayed both lack of clinical symptoms and radiographic signs of persistent disease (Strindberg, 1956). On the other end of the spectrum, Seltzer and Bender's criteria introduced in 1967 allowed various radiographic interpretations of radiographic appearance. This meant that a tooth treatment may be considered successful while having a radiographic lesion that is non-progressive or stable as long as the patient was free of clinical symptoms and the patient did not suffer from a loss of function

(Seltzer et al., 1967a, 1967b). In 2002, Friedman introduced an evaluation method that combined radiographic findings and clinical symptoms in a more biological approach. His criteria suggested replacing "success" and "failure" with "healed," "healing," and "persistent disease" (Friedman, 2002). Friedman's criteria required a lack of clinical symptoms combined with a normal or progressively improving radiographic interpretation to place the treatment in either the "healed" or "healing" category (Friedman, 2002). Regardless of the criteria used to evaluate treatment, radiographic interpretation is a common component (Ng et al., 2007).

Radiography as a Component to Outcomes Studies

Epidemiological studies evaluate distributions of prevalence and specific causes of disease (Eriksen et al., 2002). The ability to link specific disease processes or risk factors and treatments or their methodology to clinical outcomes demonstrates the value of epidemiology. Epidemiology is classically separated into either a descriptive or analytical part. Cross-sectional studies give background knowledge about a disease, where case control or cohort studies aim to give information about specific disease causes or factors (Eriksen et al., 2002). Eriksen et al. in 2002 said that criteria for proper epidemiological research should include: Measurable, mutually exclusive, validity, reproducible, and communicable. In the same study, they give the periapical index or PAI introduced by Orstavik in 1986 as an example of a system that fulfills these requirements (Eriksen et al., 2002; Orstavik et al., 1986). Recent studies have commonly used the PAI to assess radiographic presentation of root filled teeth (de Chevigny et al., 2008; Farzaneh et al., 2004a, 2004b; Marquis et al., 2006). For assessing survival, the

PAI is used to evaluate the presence or absence of apical periodontitis following treatment. The PAI has been suggested to be an accurate and reproducible method that minimizes variability and bias, and has been designed for and used in clinical trials and epidemiological surveys (Orstavik, Hörsted-Bindslev, 1993; Trope et al., 1999; Delano et al., 2001; Eriksen et al., 1988; Waltimo et al., 2001).

The Periapical Index System

The PAI is an ordinal scale ranging from 1(healthy) to 5 (severe apical periodontitis with exacerbating features) (Orstavik et al., 1986). The presence of apical periodontitis is considered absent or minimal if a low score (1-2) is given, while higher scores (3-5) are deemed to represent greater severity of apical periodontitis. Orstavik introduced the PAI in 1986 as a simplified version of Brynolf's method used in the classic 1967 study (Brynolf, 1967; Orstavik et al., 1986). Epidemiologic and clinical studies often use radiographic evidence of healing as a primary assessment of success in addition to clinical findings for obvious reasons including ease of data collection and processing. Brynolf's original method used a separate individual grading system that graded the each of the following radiographic features: shape and width of apical and lateral periodontal space, the shape and border of the lamina dura, the bone structure or trabeculation, the shape and width of the radiopacity at the lamina dura or bone border, and the presence or amount of excess root filling (Brynolf, 1967). In the PAI system, Orstavik combined the aforementioned features and reclassified them in 5 separate categories that encompassed all of Brynolf's features. The following reference radiographs defined the categories:

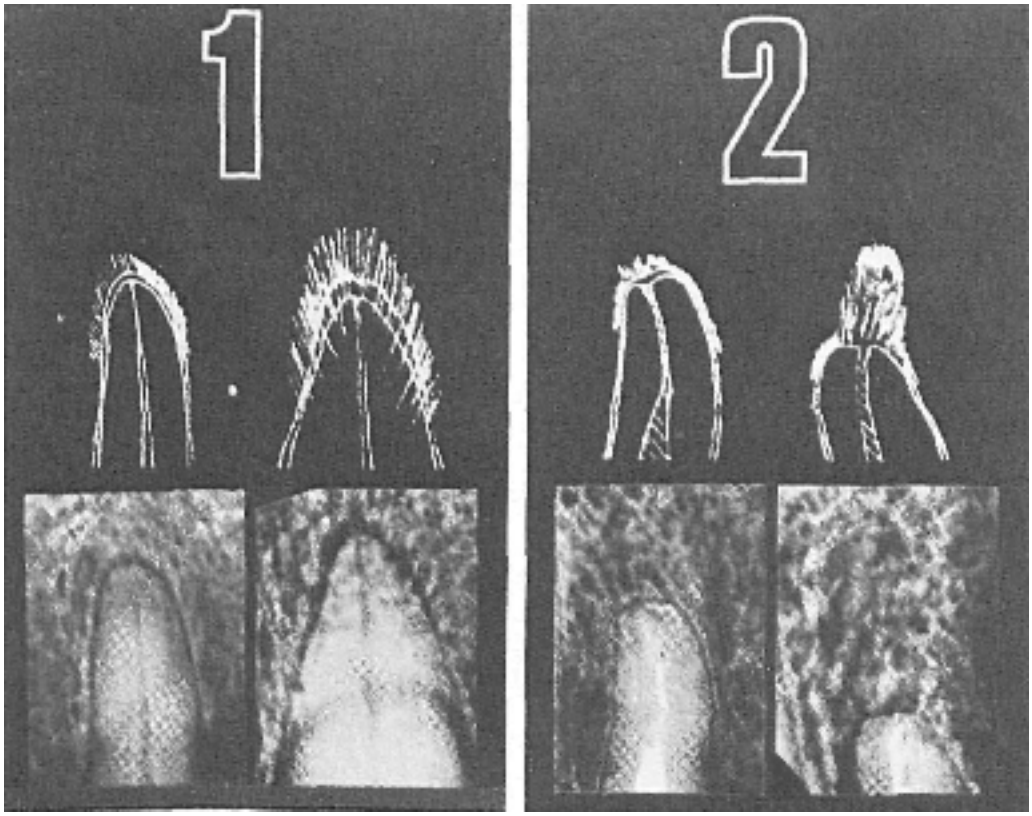

Figure 1: PAI reference classification 1 and 2 (From "The periapical index: a scoring system for radiographic assessment of apical periodontitis." Orstavik et al. 1986)

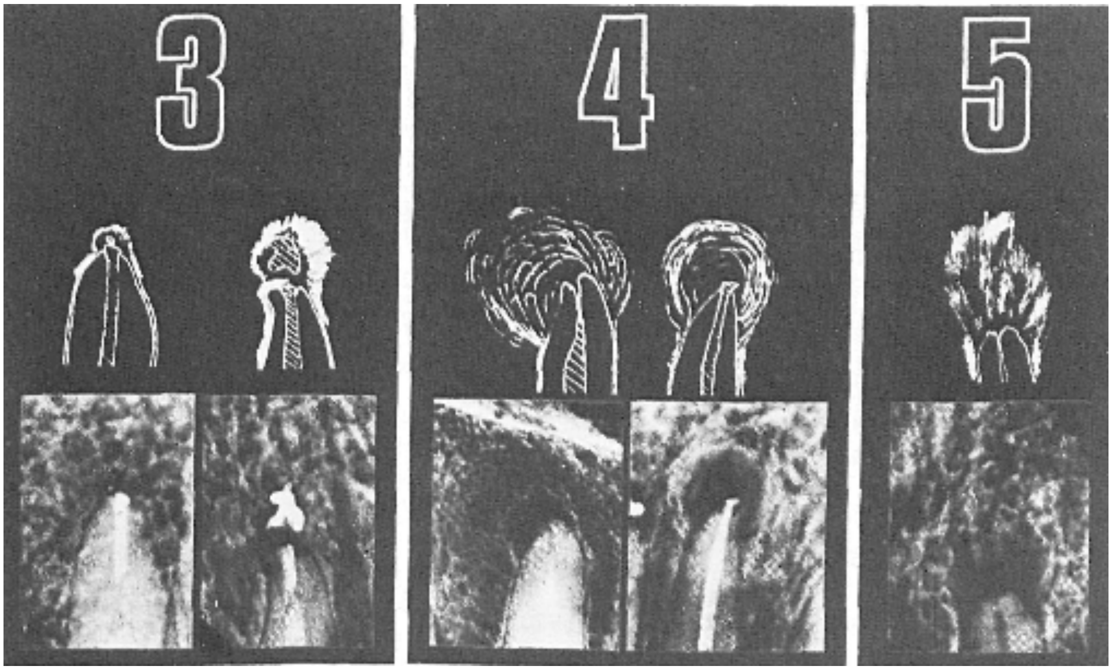

Figure 2: PAI reference classification 3, 4 and 5 (From "The periapical index: a scoring system for radiographic assessment of apical periodontitis." Orstavik et al. 1986)

Additionally, the following instructions were given:

1: Find the reference radiograph where the periapical area most closely resembles the periapical area you are studying. Assign the corresponding score to the observed root.

2: When in doubt, assign higher score.

3: For multirooted teeth, use the highest of the scores given for the individual roots.

4: All teeth must be given a score (Orstavik et al., 1986).

Output from the PAI was originally intended to fit in one of 3 categories: 1 = healthy, 2 and 3 = uncertain, 4 and 5 = diseased (Orstavik et al., 1986). Orstavik, as well as other studies have slightly modified this scale to make 1 and 2 = healed and 3 or greater non-healed (de Chevigny et al., 2008; Farzaneh et al., 2004a, 2004b; Marquis et al., 2006; Ng et al., 2007). Data recorded from the PAI is ordinal. This means data is forced into one of five categories and information cannot be derived about how the groups differ other than that one group is better or worse than another.

Radiographic Versus Histological Findings

Studies have conflicted on how radiographic appearance correlates to the histological findings. In a study by Brynolf in 1967, it was found that often periapical inflammation was found even when the radiographic appearance of the tooth in question was normal (Brynolf, 1967). The Brynolf et al. study in 1967 was refuted by Green et al in 1996 who found that there was an excellent correlation between radiographic findings and the amount of periapical inflammation (Green et al., 1997). Green et al. believed that the chloropercha technique used in Sweden, and diffusion or overextension of components into periapical tissues was partially to blame for the finding of inconsistent periapical inflammation even when radiographic appearances were normal (Green et al., 1997). Additionally, the 1967 study by Brynolf was solely done on maxillary anterior teeth, which have a slightly higher failure rate in one study (Jokinen et al., 1978). A study by Ricucci et al. in 2009 confirmed Green et al. finding that periapical inflammation rarely persisted in root filled teeth that were radiographically normal (Ricucci et al., 2009).

Methods to Evaluate Periapical Disease

Periapical Radiographs:

Our ability to visualize periapical pathology, while not our sole method of diagnosis, is nevertheless of utmost importance. Studies have conflicted on when periapical pathology can first be visualized on a periapical radiograph. In a classic two-part study by Bender et al, it was found that lesions were difficult to visualize on a periapical radiograph when confined to cancellous bone (Bender, Seltzer, 1961a, 1961b). A later study by the same author found that 7.1% mineral loss was required before radiographic visualization could be achieved (Bender, 1982). Lee et al. in 1986 refuted this claim finding that artificial lesions could be visualized when confined to cancellous bone (Lee, Messer, 1986). Barbat et al. backed up this claim with another cadaver study in 1998. They found that loss of only the lamina dura could result in visualization on traditional and digital images (Barbat, Messer, 1998). Kaffe and Gratt found that the most consistent feature when evaluating the radiographic appearance was the outline of the lamina dura and PDL space (Kaffe, Gratt, 1988). While Coolidge found that a PDL space could be widened by up to double thickness under heavy function, Andreason and Rud found that histologically, inflammation was likely present if the apical PDL space was thickened by double or more (Coolidge, 1937; Andreasen, Rud, 1972). The number of different radiographs used to evaluate a periapical lesion increases the ability of examiners to correctly visualize the presence of a radiographic lesion. Brynolf found that three radiographs increased the consistency of correctly identifying a periapical lesion compared to using only a single film (Brynolf, 1970).

Digital acquired images were equally effective at identifying artificially created periapical lesions when compared to conventional film based systems by Mistak et al. (Mistak et al., 1998). Original conventional films were shown to have greater diagnostic quality than digitized versions by Goga et al. In the same study, images digitized with digital cameras had higher quality than those digitized with a film scanner (Goga et al., 2004).

Potential challenges in interpreting radiographs:

Anatomic variations such as the mental foramen may masquerade as apical pathology in the mandibular premolar region (Phillips et al., 1990, 1992). The proximity of maxillary posterior teeth to the sinus floor may result in overlaying of apices on periapical films (Eberhardt et al., 1992). Superimposition of structures such as the zygomatic arch can further complicate interpretation (Lofthag-Hansen et al., 2007).

Different angulations of radiographs may hide or distort potential radiolucencies (Huumonen, Orstavik, 2002). Additionally, different radiographic techniques may present challenges for interpretation. Forsberg et al. found that lesions did not vary in size with bisecting angle or paralleling technique, but recommended the paralleling technique due to the reproducibility (Forsberg, Halse, 2003).

Observer reliability related to radiographs:

Inter-observer variation has been shown to be considerable. Studies by Goldman et al. have shown separate examiners agree only 47-73% of the time (Goldman et al., 1972). Other research has shown this number to be as low as 38% for complete agreement of periapical conditions (Lambrianidis, 1985). Intra-observer variation has been shown to be less variable. Goldman et al. showed that examiners agreed with their own readings from 73-88% of the time when radiographs were observed over 6-8 months apart (Goldman et al., 1974). Studies by Gelfand et al. are in agreement of this range at 78% reproducibility with the same observer (Gelfand et al., 1983). These findings highlight the need for using the same examiner when considering radiographic data in research requiring radiographic interpretation.

Ultrasound Techniques:

Ultrasound technology uses ultrasonic echoes to give information about contents of soft tissue lesions (Auer, 1990). A bony window is required for this technique to be employed, as the cortical plate causes complete reflection of the sound waves (Auer, 1990). Safety concerns have generally been associated with heat production from absorption of ultrasonic energy (Barnett, Maulik, 2001; Martin, 1984). Risk levels for complications are generally considered low, but guidelines still recommend employing ALARA or “as low as reasonably achievable” protocol (Barnett, Maulik, 2001). With the addition of Color Power Doppler, Cotti et al. showed ultrasound technique has some utility to decipher whether a lesion is a granuloma or a cyst by being able to visualize the presence or absence of vascularity (Cotti et al., 2003, 2002). The access, training and specialized applicability of this technique has limited its use in clinical endodontics.

Additionally, lesions that erode the cortical plate are generally well visualized on a radiograph (Bender, Seltzer, 1961a, 1961b).

Computed Tomography:

Computed tomography (CT) recently gained popularity for dentistry. Computed tomography techniques use multiple slices or planes of images and computer technology to reconstruct a 3 dimensional image of the subject. Hounsfield patented Medical CT in 1973. Medical images are generally either fan beam, or spiral (continuous) in nature. These images require multiple passes and/or sensors to acquire the images needed for the reconstruction. They require large and expensive equipment and are often reserved for hospital settings (Patel et al., 2007; Sukovic, 2003).

Cone beam computed tomography or CBCT uses a larger sensor and captures an image in a single sweep, rather than multiple passes or spiral sectioning. Independent Japanese and Italian groups developed this technology in the late 1990's (Mozzo et al., 1998; Arai et al., 1999). The technology gets its name from the cone shaped or oval shaped beam of the X-ray. The field of view of the scan is dependent on the sensor size and the beam size. CBCT images can capture fields as small as 40 X 40 mm (Veraviewepocs 3d J. Morita Corporation Osaka, Japan) or 37 X 50 mm (Kodak 9000 35, Kodak Digital Imaging, Atlanta, GA) or as large as 80 X 140 mm (Gendex GXCB 500HD Gendex Dental systems, Des Plaines, IL). Larger field units have seen success and acceptance in areas of maxillofacial trauma, facial reconstruction, orthognathic surgery, dental implants and complicated extractions (Enciso et al., 2005; Exadaktylos et al., 2005; Schwarz et al., 1987; Ziegler et al., 2002).

Smaller field units have been gaining popularity in areas such as endodontic diagnosis and treatment planning (Cotton et al., 2007; Patel et al., 2007). Detection of apical pathology has been shown to be more accurate with CBCT when compared to periapical images. Low et al. found that 34% of lesions detected with CBCT were missed with traditional periapical images in maxillary posterior teeth (Low et al., 2008). These findings are congruent with Estrella et al. who found that periapical radiography was only 55% accurate and panoramic radiography was only 28% accurate in identifying apical pathology identified with CBCT (Estrela et al., 2008). In addition to identifying apical pathology, CBCT has been shown to be superior to periapical (CCD and phosphor plate system) radiography for identifying root canal systems by endodontists (Matherne et al., 2007). Results of these studies are likely due to one of a few factors. The projection of a 3 dimensional object on a 2 dimensional surface results in superimposition of structures described as "anatomic noise." Additionally, geometric distortion and magnifications must be considered a greater factor in periapical radiography than with CBCT (Grondahl, Huumonen, 2004). These challenges are coupled with the proximity of root apices to other anatomic structures, such as the sinus floor, which can further complicate traditional radiographic interpretation (Eberhardt et al., 1992).

Challenges of CBCT:

While the advantages of CBCT have been stated above, shortcomings still exist. Uptake of this technology has been rapid in the craniofacial trauma/surgery specialties for obvious reasons (Patel et al., 2007). For routine non-surgical endodontic treatments and retreatments, CBCT may be experiencing a slower growth rate. Several factors may play a roll in this phenomenon. Current guidelines including ALARA protocols with respect to patient exposure to radiation are always at the front of our mind as clinicians. Larger field CBCT doses range 44.5 – 288.9 micro Sieverts (μSv) for their effective dose (Ludlow et al., 2006). This is considerably larger calculated dose than one would experience from a single periapical (5 μSv) or panoramic (6.3 μSv) radiograph (Ludlow et al., 2003; Ngan et al., 2003). Current limited field CBCT scans have reduced patient radiation effective doses to as low as 7.3 μSv at lower resolutions (Arai et al., 2001). This brings the effective dose of limited field to within the range of 2-3 periapical images depending on the resolution needed on the CBCT scan (Patel et al., 2007). All of these effective doses are considerably lower than maxillary or mandibular scans using conventional or medical CT (1320 – 1400 μSv) (Ngan et al., 2003). While current CBCT machines are impractical for intra-operative images, pre-operative, post operative, and recall scans may be a reality once these machines become ubiquitous. Challenges do not end with radiation dose. Cost of CBCT machines range from $115,000 to $260,000 per unit, and may translate into a significantly greater cost for patients who receive scans. When endodontic healing rates are commonly reported as being very high, considering the additional cost versus benefit to patients may be difficult to justify.

Digitally Aided Evaluation of Radiographic Healing:

Various methods have been used to aid in radiographic detection of periapical lesions. Digital imaging or digitizing traditional radiographs allows levels of image analysis unavailable to analogue film alone.

Fractal Analysis:

Fractals allow description of irregular objects that occur in nature. The classic example is the coastline of a continent. The coastline from city "A" to city "B" when measured as a line of sight is a certain length. Upon closer inspection, it is seen that the coastline is depressed toward the land in some "bay" areas, and protrudes into the ocean in other "peninsulas." When measuring the shoreline, the actual distance becomes much longer. Upon even further inspection, each bay or peninsula contains smaller bays and peninsulas. This continues to make the distance from city "A" to "B" longer. This smaller and smaller attention to detail results in a longer and longer distance each time the scope of observation changes. For these reasons, length is not an ideal measurement for this natural object. Fractal analysis enables these irregular objects to be described, measured and quantified (Mandelbrot, 1982). As an alternative to the scope of length, how much space or area each structure takes up in relation to its entirety is also measured. This refers to fractal dimension or a "filling factor." Fractal dimension is a number called "D" and can range in value from one to two. Objects that are open or linear are at or closer to D=1, while objects that are solid are at or closer to D=2 (UW Radiology, 2008). Using this method, fractals have been shown to describe the trabecular pattern of bone (Majumdar et al., 1993; Parkinson, Fazzalari, 2000). Applying this method for quantifying and describing trabecular bone is called fractal analysis. Fractal analysis often uses "box counting" to measure the complexity of the trabecular pattern. This simply places a grid over a section of interest and counts the number of pixels of trabecular borders present in each box. The greater the number of trabecular borders, the greater the complexity of bone (Chen et al., 2005). This method is difficult to use for quantifying an entire radiolucent lesion because it may only be used on a small fragment of that radiolucent area. Nearby anatomy such as sinus and proximity to adjacent structures such as root apices can contribute to noise and degrade useful information. With these limitations in mind, fractal analysis has been able to detect early changes in periapical trabecular pattern in a defined small region of interest on periapical radiographs (Chen et al., 2005; Yasar, Akgunlu, 2005).

Digital Subtraction:

Photographic subtraction was first described by Ziedses des Plantes. Subtraction uses the principal that variations in density or levels could be detected and magnified if the level from each image at each point could be negated or "subtracted." Digital subtraction uses pairs of digitized images to compare variation in density from one image to another. On a digital image, each pixel is assigned a "grey level" This grey level may be converted to a numeric value for each specific pixel. When two images taken at time 0 and time 1 are digitally overlaid, these two grey values may be numerically subtracted from one another. This "difference" is used to create a new image that allows better visualization of areas that show change from time 0 to time 1. Healing or progression of a lesion can then be accurately quantified (Gröndahl et al., 1983). Kasle and Klein were the first to demonstrate that induced periapical lesions in dogs could be detected 7-42 days earlier using subtraction technology (Kasle, Klein, 1976). A study by Rudolph et al. found that variations in cortical thickness as little as 0.12 mm could be visualized with digital methods (Rudolph et al., 1987). Digital subtraction is not without its challenges. Radiographic noise is defined as factors that affect the quality of the subtracted images

(Haiter-Neto, Wenzel, 2005). Small variations in exposure between the two images result in inaccurate subtraction of pixels, and degrade subtracted image quality (Chen, Hollender, 1993). Geometric variations due to the way three-dimensional images are projected on a two-dimensional film or sensor also contribute to this noise (Wenzel, Sewerin, 1991). Additionally, slight variations in alignment will hinder overlaying the images and result in non-uniformly subtracted images, although software is available to aid in this issue (Benn, 1990; Kozakiewicz et al., 2008). Rudolph et al. showed variations as little as 1 degree had a significant impact on the sensitivity of digital subtraction (Rudolph et al., 1987). For this reason, positioning devices such as custom vinyl poly-siloxane stints are generally fabricated for each patient studied. This may limit the usefulness of the technique and makes broad retrospective outcome studies impossible, as clinicians may not take the time to fabricate and catalogue these stints.

Lesion pixel analysis:

In a previous study, a method of radiographic evaluation was introduced by Bogle in 2009. This method entailed having examiners evaluate the perceived area that a radiographic lesion was contained within. It used images that were not standardized by a positioning stint. These images were digitized and digitally overlaid to approximate the apices of the images from time zero to time one. The lesion pixel analysis method was shown to have a moderate correlation with the PAI, while at the same time giving continuous data rather than ordinal data, and hence the ability to differentiate smaller changes between groups (Bogle, 2009). This method, however fails to account for image variation in angulations, magnification and projection as described by Webber et al. (Webber et al., 1984).

Dealing with the challenges of image angulation:

In a 2009 study by Bose et al. a method was introduced to overlay radiographic images and compensate for image angle variation and distortion. This method was used to evaluate small changes in dentinal wall thickness and root length in revascularization procedures. Image manipulation was done using NIH ImageJ and a free plug-in for the software called TurboReg. The software requires multiple identical points such as the cemento-enamel junction, adjacent root apices, alveolar crest, or cusp tips be identified on the two images to be corrected. TurboReg then manipulates one of the images to exactly overlay the other. Bose et al. showed that small variations in root thickness and length could be measured accurately using this method (Bose et al., 2009).

<u>Data attained from outcomes studies:</u>

Recent outcomes studies have placed the healing rate from 75% to 85% for non-surgical root canal treatments using strict criteria and 85% to 95% healing rates using loose criteria in pooled samples (de Chevigny et al., 2008; Farzaneh et al., 2004b; Marquis et al., 2006; Ng et al., 2007). Many of these and other outcome studies have used the PAI or close variations as their method for evaluating periapical healing (de Chevigny et al., 2008; Doyle et al., 2006; Farzaneh et al., 2004b; Marquis et al., 2006). As healing rates approach 100%, difficulties in differentiating small variations that exist between different treatment modalities becomes more challenging. As this band of data narrows, the type and quality of data may become more important. As noted above, the

PAI gives us ordinal data. This may not give us the type of data that we require to detect a change between two study groups. For example, a root could be placed in a category "3" of the PAI. This root could undergo a small amount of healing, and when evaluated on recall, an examiner may still place that root in category "3." This is not necessarily an error of the examiner as in his or her perception; the root may actually still be a category "3." Smaller changes like this must be detected with continuous data. Methods that produce quantitative data are superior in these cases. In our example above, the change from "3" to "3" on the PAI score results a net zero change interpreted as "no healing." A quantifiable method with a larger scale may be able to detect this smaller change. An example of a quantifiable method would be digital subtraction radiography. As mentioned previously, this method may have its challenges.

Objectives of this study:

In this study, the aim was to introduce a new quantitative method of evaluating periapical healing using a hybrid between the area methods described by Bogle and the image distortion compensation introduced by Bose et al. This method will be referred to as Lesion Area Analysis (LAA). We aim to compare this new method to the well-accepted PAI system of radiographic evaluation as a baseline realizing the data acquired from LAA may allow detection of smaller changes between study groups.

Hypothesis

LAA and PAI scores are comparable methods to radiographically evaluate periapical conditions.

Materials and Methods

Approval for this study was obtained from the University of Minnesota Institutional Review Board. Images were identified from a review of charts from endodontic recall patients from 7-26-04 through 9-24-09. Patient ages ranged from 15 to 96 years with a mean age of 63.6 years and a median age of 67 years. Inclusion criteria included cases selected with a minimum of 2mm by 2mm periapical radiolucencies on either initial or recall images. No attempt was made to select cases that only showed healing versus progression of the lesion. All images were non-standardized and captured without use of vinyl poly-siloxane positioning devices. Of the cases selected, attempts were made to select images that showed similar areas of interest. Exclusion criteria included missing or damaged films, gross radiographic distortions or errors, and the absence of radiographic rarefaction on initial of recall radiographs. Primary images were selected from pre-operative, intra-operative, or post-operative, films. Secondary images were from two months to 5.2-year recall appointments. Thirty-five cases were identified for inclusion in this study (distribution of teeth is detailed in table 1). Additionally, five untreated teeth with intact lamina dura and uniform periodontal ligament space were used as negative controls.

Table 1: Distribution of teeth for radiographic evaluation

Maxillary Anteriors	6
Maxillary Premolars	4
Maxillary Molars	3
Mandibular Anteriors	8
Mandibular Premolars	6
Mandibular Molars	8

Image processing:

Images were digitized and de-identified. All images were digitized with a Canon 10D SLR camera in full resolution in RAW format in a dark room with a lightbox at a standardized perpendicular angulation to the film. Image pairs were standardized for radiographic density (brightness and contrast) using the histogram in Adobe Photoshop CS3 on an Apple computer. Images were exported as TIFF images and aligned with ImageJ software in the following method:

1: Pairs of images to be aligned were opened.

2: The Plugin "TurboReg" was evoked.

3: "Affine" method was selected and "accurate" mode was used.

4: Three identical locations were identified on corresponding radiographs. Points such as the CEJ, adjacent apecies, restoration margins, or alveolar crest were used for reference points.

5: After identifying and selecting points, “Manual” mode was used to align images. Aligned image was saved as a new TIFF file.

6: Image one and the aligned image were combined in Adobe Photoshop CS3 and placed as separate layers in the same file. This method allows the two images to be viewed individually by selecting each layer one at a time in the same window with perfect alignment (Figures 3-5).

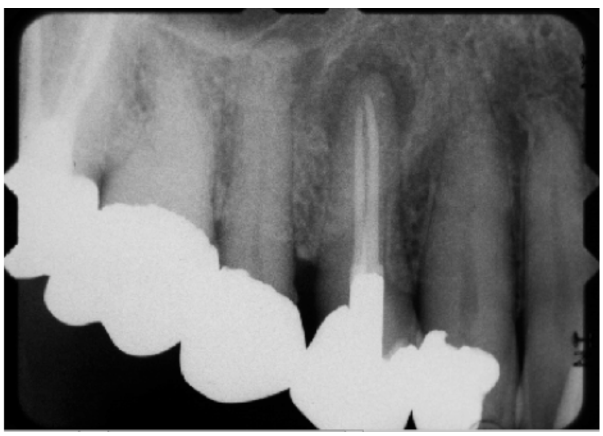

Figure 3: Unmodified Image from time 0

Figure 4: Unmodified Image from time 1

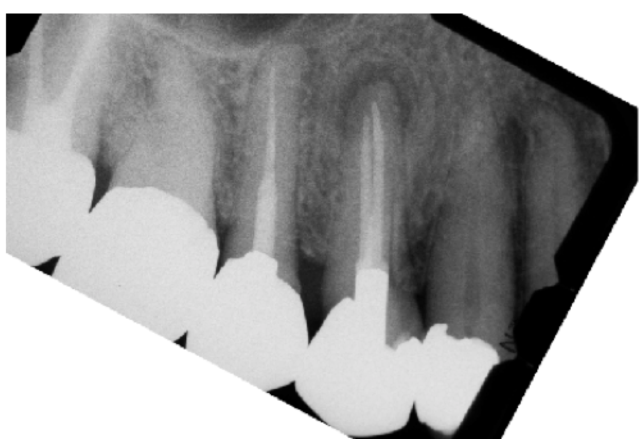

Figure 5: Image from time 1 modified with TurboReg to align with time 0

Image evaluation:

Radiographs were evaluated by three examiners, a board certified endodontist, and two second year endodontic residents. Each evaluator was individually calibrated with the instructions included in appendix A and guidelines in appendix B. Each image was uniformly displayed with an NEC LT380 (NEC Corporation Tokyo, Japan) projector on a 100-inch screen at 1024 X 768 pixel resolution in a light controlled 12 X 20 foot room.

Periapical index:

Evaluators were asked to assess the individual roots on each tooth with the PAI system adapted by Orstavik et al. (Orstavik et al., 1986). Reference radiographs (figures 1 and 2) of each PAI score were provided throughout the procedure. Additionally, the following descriptors and instructions were given:

PAI score	Verbal descriptors
1	Normal apical periodontium
2	Bone structural changes indicating, but not pathognomonic for apical periodontitis
3	Bone structural changes with some mineral loss characteristic of apical periodontitis
4	Well defined radiolucency
5	Radiolucency with radiating expansions of bone structural changes

1: Choose the score that most closely resembles both the visual and written description.

2: In multi-rooted teeth, each individual root receives a score.

3: When in doubt, choose a higher score

Lesion Area Analysis:

The examiners were then asked to use LAA to evaluate each radiograph. The following additional instructions were given:

Guidelines for Lesion Area Analysis:

1: Please use the mouse to outline your interpretation of the greatest extent of the lesion on the radiograph presented.

2: If the lesions/roots are present, multiple areas may be identified, and roots will be scored individually.

3: If a lesion is confluent with alveolar crest, a perpendicular line to the tooth at that point will be drawn approximating the average current height of the alveolar crest.

4: If no lesion is perceived, notify registrar and tooth / root will be assessed a "0."

The examiner was asked to circle each perceived lesion with the lasso tool in Adobe Photoshop CS3. When the examiner was content with the area identified, the registrar recorded the area in pixels that were encircled. Areas were acquired in one of two ways in multi-rooted teeth. If the examiner perceived the radiolucent lesions on different roots to be connecting, they were instructed to encircle the entire periphery of the image as a single radiolucency. If the examiner perceived the radiolucent lesions on different roots to be separate, the lesions were encircled individually, recorded and the areas were totaled.

This protocol was repeated for each root on each of the 35 cases and five controls for the time zero image and the time one image with separate private sessions for each examiner. Examiners repeated the evaluation 3-4 weeks from the first session. Identical instructions were given to the examiners at the second session.

Data were collected and processed as a function of change for both the PAI and a percentage of change for the LAA. If a lesion was graded a “4” on the PAI at time zero and graded a “1” at time one, then this difference would be three. Similarly, if an image were measured at 15,000 pixels at time zero and 2,000 pixels at time one, the difference would be 13,000 pixels. Dividing this by the original area and multiplying by 100 gives us a percentage change, or:

$$[(\text{ area time 0} - \text{area time 1 }) / \text{ area time 0 }] \text{ X } 100 = \text{Percent change}$$

In our example:

$$[(\ 15{,}000 - 2{,}000\ ) / 15{,}000\ ] \text{ X } 100 = 86.7\% \text{ change}$$

Positive numbers indicate lesion healing, negative numbers indicate progression of the disease process.

Statistical Analysis:

Means and standard deviations were calculated for each change measure within each examiner and exam. Pearson correlation coefficients were calculated to compare the change in PAI (ordinal data) to the change in LAA (continuous data) within each examiner and exam. Intra-class correlation coefficients were calculated to compare the three examiners for each method in each exam. Statistical significance was determined at $p \leq 0.05$. Statistical analysis was done with SAS software version 9.1.3 (SAS Institute Cary, NC).

Results

All 5 control teeth (radiographically normal) showed no change in PAI and 0% change with LAA from each examiner in each exam. Table 2 summarizes the mean and standard deviations for each exam and examiner. This summarizes the data and gives us information on variability of the raw data. Consistency of both mean and standard deviation indicates consistent data. Table 3 shows the Pearson's correlation coefficient comparing within-examiner change in PAI to the change in LAA. This data gives information on how well the PAI compared with LAA. Values are positive and at or greater than 0.5 indicating a strong positive correlation between the PAI and LAA (Cohen, 1988). This correlation was measured significantly different from 0 (no correlation) at p value ≤ 0.05 for all examiners and exams.

Correlations between exams one and two are detailed in Table 4. This gives information about how consistent each examiner was from their exam one to exam two for both the PAI and LAA. Both methods show a strong positive correlation greater than 0.5 indicating examiners largely agreed and were consistent with themselves when comparing the results of exam one to exam two for both methods. The strongest correlation between exam one and two was using the LAA method with examiner three at 0.91. The weakest correlation was measured with examiner one using the PAI system at

0.53. All correlations were significantly different from zero (no correlation) at p value ≤ 0.05.

Table 2: Summary of change in PAI and percent change in LAA

Measure	Examiner	Exam	Mean (SD)
Change in PAI	1	1	1.14 (1.12)
	1	2	1.11 (0.87)
	2	1	1.03 (0.89)
	2	2	1.17 (0.86)
	3	1	1.31 (1.35)
	3	2	1.37 (1.40)
% Change in LAA	1	1	52.68 (46.89)
	1	2	59.44 (37.99)
	2	1	38.93 (79.81)
	2	2	55.24 (47.60)
	3	1	65.53 (48.20)
	3	2	55.24 (59.91)

Table 3: Within-examiner change in PAI/change in LAA Pearson's Correlations

Examiner	Exam 1	Exam 2
1 (2nd Year Endodontic Resident)	0.70 ($p < 0.0001$)	0.49 ($p=0.0027$)
2 (Board Certified Endodontist)	0.51 ($p=0.0019$)	0.52 ($p=0.0013$)
3 (2nd Year Endodontic Resident)	0.72 ($p < 0.0001$)	0.68 ($p < 0.0001$)

All correlations are statistically significantly greater than 0 ($p < 0.05$).

Table 4: Pearson's Correlations between exams 1 and 2 for each examiner

Examiner	Change in PAI	Change in LAA
1: (2nd Year Endodontic Resident)	0.53 ($p=0.0010$)	0.57 ($p=0.0003$)
2: (Board Certified Endodontist)	0.69 ($p < 0.0001$)	0.54 ($p=0.0007$)
3: (2nd Year Endodontic Resident)	0.78 ($p < 0.0001$)	0.91 ($p < 0.0001$)

All correlations are statistically significantly greater than 0 ($p < 0.05$).

Table 5: Intra-class correlation coefficients (ICC) between all 3 examiners

Exam	Change in PAI	Change in LAA
1	0.47	0.29
2	0.46	0.43

Figure 6, 7 and 8 show the change in PAI plotted against change in LAA. Trend lines are calculated for exam 1 and exam 2 for a graphical visualization of consistency for each individual examiner.

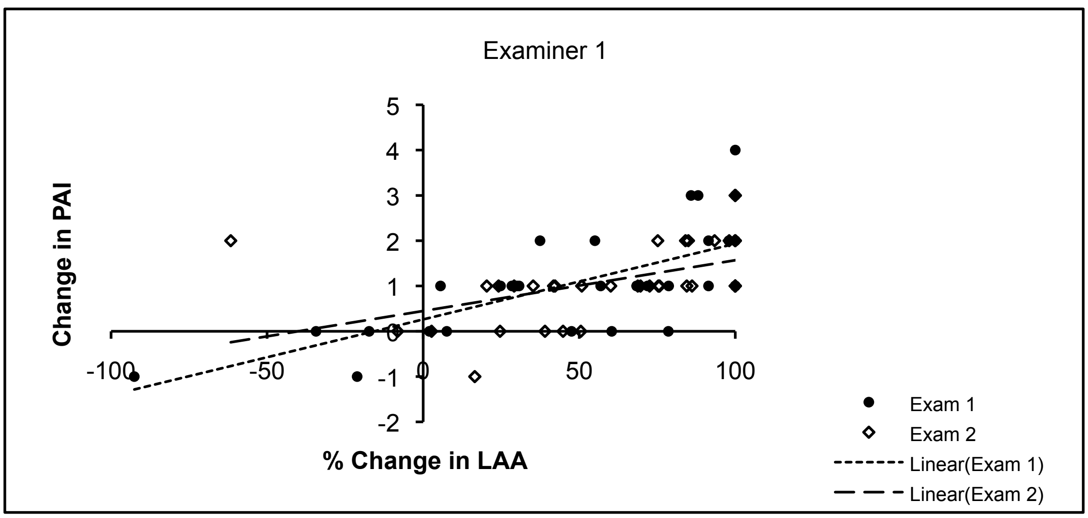

Figure 6: Change in PAI versus change in LAA for Examiner 1

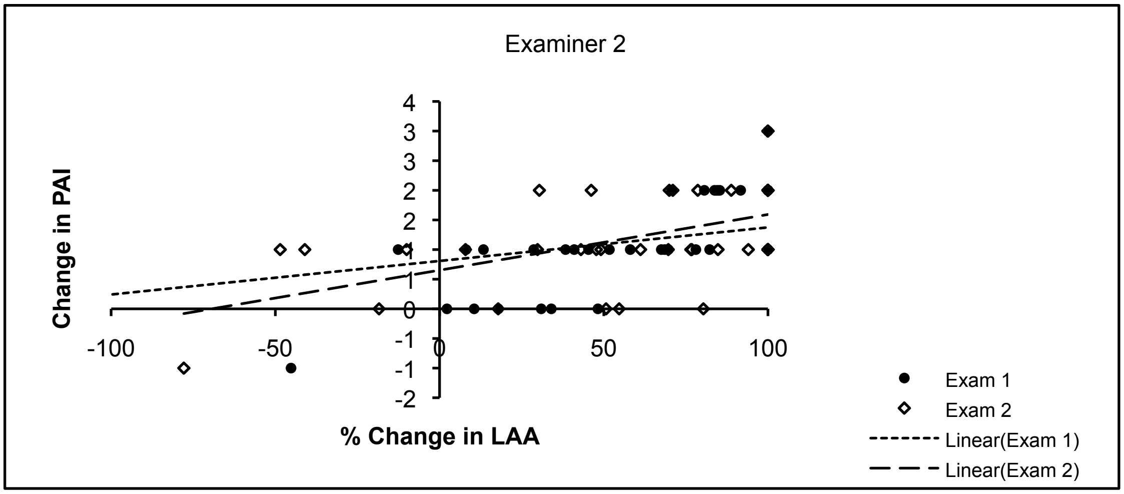

Figure 7: Change in PAI versus change in LAA for Examiner 2

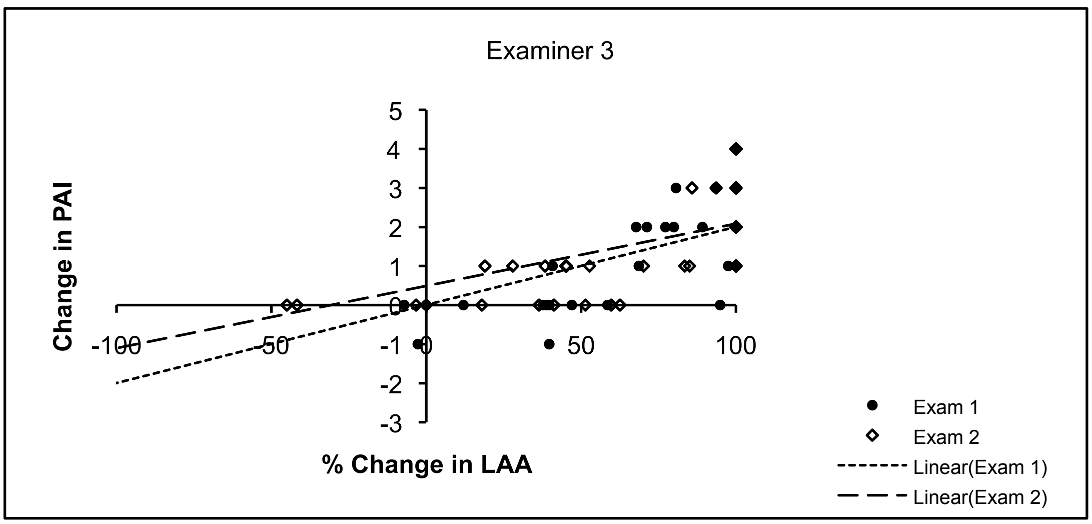

Figure 8: Change in PAI versus change in LAA for Examiner 3

Intra-class correlations between all three examiners are shown in Table 5. This data gives information on how well the examiners agreed with one another for each test with each exam. Data shows a medium correlation for both the PAI and LAA when compared across all three examiners (Cohen, 1988). Correlations ranged from 0.46 to 0.47 for the PAI exams, and 0.29 to 0.43 for the LAA exams.

Discussion

The purpose of this study was to introduce a quantitative method of measuring radiographic periapical changes using hybridizing techniques (designed by Bogle and Bose et al.), and to compare this method with the PAI system introduced by Orstavik et al. Our results show that a strong correlation exists between the PAI and LAA with a range of 0.5 to 0.7 within the category of a strong correlation (Table 3). Additionally, this method is shown to be reproducible as strong correlations between exam one and exam two are evident with a range from 0.5 to 0.9 for both the PAI and LAA (Table 4). This argument is graphically presented in figures 6, 7, and 8. At first review, the data from the inter-rater correlations between all three examiners are somewhat concerning. Table 5 shows that the correlations are in the moderate range for both the PAI and LAA. Additionally, these results show the change in LAA to be lower than the PAI. This is likely a result of the nature of the data. With the ordinal data that the PAI provides, teeth are placed in one of five groups. The data that the LAA provides is continuous and there are an infinite number of groups in which a tooth could be placed. This greater variability of categories with LAA when compared to the only five possibilities available with the PAI could account for the lower intra-class correlation coefficient for LAA. When considering examiner reliability, these findings are in agreement with previous studies that found inter-rater consistency to be lower than intra-rater consistency (Goldman et al., 1974).

A 1999 study by Trope et al. looked at treatment outcomes at 52 weeks comparing one-visit versus two-visit endodontics with the PAI system. They found no significant difference between one-visit and two-visit treatments when using the PAI. Furthermore, power analysis was used to estimate the required *n* (354 and 571 patients) to see a significant difference between the groups (Trope et al., 1999). Large study groups such as this may be difficult to manage. With a quantitative method to evaluate healing, it is possible that these large study groups may not be required. Further research is required to validate these claims.

The nature of the data collected from LAA is continuous rather than ordinal as in the PAI. This continuous data allows more detailed and quantitative values to be derived. Smaller changes in study groups may be able to be detected. Further research is required to determine if these smaller changes are clinically significant. The method for LAA yields a percentage of healing or progression. The advantage to converting to a percentage rather than an absolute area or value is that we can compare groups of images that vary in resolution or size very easily. In the present study, images varied slightly from image to image. TurboReg handles standardizing pairs of images for variations in resolution and size. This means that each pair is effectively changed to the identical resolution when processed. It is particularly helpful if one image comes from a digital system, and one image comes from a scanned or photographed traditional film. The conversion to percentage is helpful if pairs of images are of slightly different resolutions. Even though TurboReg standardizes the image pairs, it fails to standardize the grouped pairs to one another, which means that one pair of images could have double the resolution of another. Assume we have identical anatomic size of a lesion and identical healing of two separate cases, the case with the larger resolution would show more area for its lesion when calculated for the area of pixels at time "0" and time "1" and would be detectable even though the actual anatomic size and healing is the same. Converting to a percentage of healing would yield a number that should identically correlate. This challenge could also be remedied by a custom software solution designed specifically for LAA with built-in resolution compensation.

Traditional two-dimensional radiography suffers from several shortcomings. First, images may overlap anatomic structures making interpretation difficult (Eberhardt et al., 1992). Second, radiolucencies may exist in any combination of shapes. Capturing a three-dimensional structure on a two-dimensional medium could result in inaccurate information about the true geometric shape or volume of the lesion (Huumonen, Orstavik, 2002). Third, images that appear to be similarly angled may have distortions that are not detectable until the two different images are directly overlaid. Webber et al. have characterized various types of distortion in 1984. Digital compensation of some of these distortions is easier than others. As distortions become more complex, more complex digital manipulation is required (Webber et al., 1984). In the present study, “affine” correction was used. This method is most useful for small variations in film placement. It requires only three corresponding points to be selected on each radiograph. More complex multi-dimensional distortions or “warping” distortions require more corresponding points to be selected. These methods have been shown to be acceptable for digital correction of these warping distortions (Webber et al., 1984). Affine, or three-point correction was selected in this study for correcting smaller changes in angulation as well as for efficiency lending respect to the possibility of using the method in larger scale clinical studies. Advantages to LAA include the ability to correct for small variations in angulation. This has been shown to work for small variations in angulation for measuring root length and thickness as previously studied (Bose et al., 2009).

As presented in this study, LAA is not without its own set of challenges. Currently, image manipulation is tedious. In the present study, two different software programs are required for LAA. In the future, an integrated solution involving a single software solution could be designed to allow the same image manipulation, alignment, and apical measurements used in this study that would decrease the time required for image processing, and measurement. In comparison, the PAI requires little or no image manipulation, but does require some examiner calibration. Thus, the PAI may demonstrate a faster image evaluation time. Integrated computer software with a user-friendly interface would likely be required to get processing and evaluation times near those of the PAI.

One of the more challenging steps in LAA is standardizing the images for grey value and contrast. In Adobe Photoshop, a histogram is available to aid in standardizing levels. The histogram's usefulness is somewhat limited by the two images to be manipulated. For grayscale images, histograms give information on the quantity of each pixel at each grey value in a given image. This information may be very useful if two images are identical size and have the same information on them i.e. 2 radiographs shot from identical angles of the same tooth. As these images start to vary from one another, the data available from the overall histogram may become less useful. In the present study, this was the case as non-standardized radiographs were purposely selected. Therefore, corresponding known areas that were present and visible on both images were sampled and the entire image was modified accordingly. This challenge may be overcome by some of the techniques used in fractal analysis and box counting.

Fractal analysis and box counting have been shown to detect early changes in the trabecular pattern of bone using a limited region of interest (Chen et al., 2005; Yasar, Akgunlu, 2005). The image processing for fractal analysis involves "forcing" the computer to decide if the portion of the image viewed is bone or if it is marrow space. This is accomplished by applying a "Gaussian blur" to an 8-bit grayscale image. The Gaussian blur, or Gaussian average is a mathematical equation that applies a weighted average to a pixel based on the level of neighboring pixels in concentric circles around that original pixel. This gives surrounding pixels further away from the original a lower weighted average and the original pixel a higher average. In this way, edges and features are preserved rather than softened or lost (Nixon, Aguado, 2008). Then, the original 8-bit grayscale image is taken and this new blurred image (figure 9b) is subtracted from it in a similar method to digital subtraction. At this time, only information in the image that is the "difference" between the blurred image and the original (figure 9c) exists. Universally adding value to all pixels to 128 or middle grey allows visualization of this image (figure 9d). A "Threshold" command is run on the image to cut any data or noise below a certain level essentially forcing the program to decide to show white where assumed bone is detected (radiopaque), and black where assumed marrow space is detected (radiolucent; figure 9e). Further processing is done to refine the edges and "skeletonize" the trabeculae (figure 9f and g). The example here has been processed from a radiograph of a segment of bone from one of the test images from the present study.

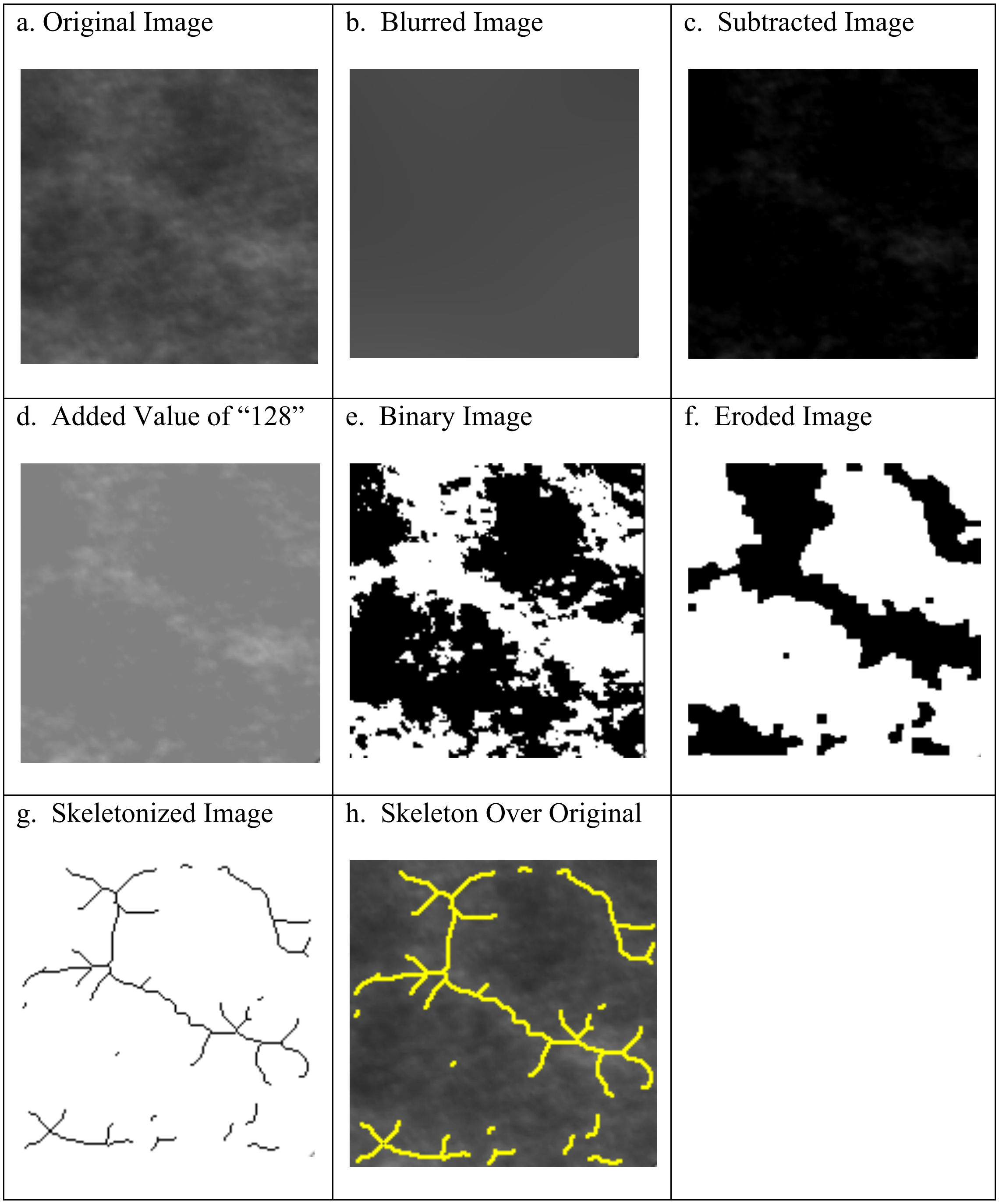

Figure 9: Steps in fractal analysis: a: Original image, b: Gaussian blur applied to original image, c: Blurred image subtracted from original image, d: Value of 128 added to bring image to visible range, e: Threshold command run to cut data below 128 and converted to binary, f: Eroded and dilated image to further define, g: Skeletonized image used to initiate box counting, h: Demonstration of skeletonized image overlaid over original for comparison purposes.

From this point, box counting can be applied to the skeletonized image. Overlaying grids of different sizes, and counting the number of pixels present in each box at each size gives a table of data that can be plotted on a log-log plot. This plot yields a straight line. The slope of this line gives the fractal dimension or "D" value between one and two (UW Radiology, 2008). Fractal dimensions closer to two indicate more complex trabecular pattern while numbers closer to one indicate a less complex pattern (Chen et al., 2005).

Portions of this method have several applications. The first is the edge detection that fractal analysis requires. The second advantage is "normalizing" or "standardizing" the image for radiographic density. By subtracting the image from itself, small variations in exposure are minimized and the computer is "forced" to decide if an area has greater or lesser bone density. This could possibly lead to a technique that allows a computer program to automatically detect a radiographic lesion and calculate its area with very little input from a provider. A method employing this technique could eliminate both the challenges of various densities, angulation and some aspects of interpretation. When applied (steps "a" through "f" of figure 9) to an entire radiograph the results of this "forced lesion detection" can be seen in figure 10.

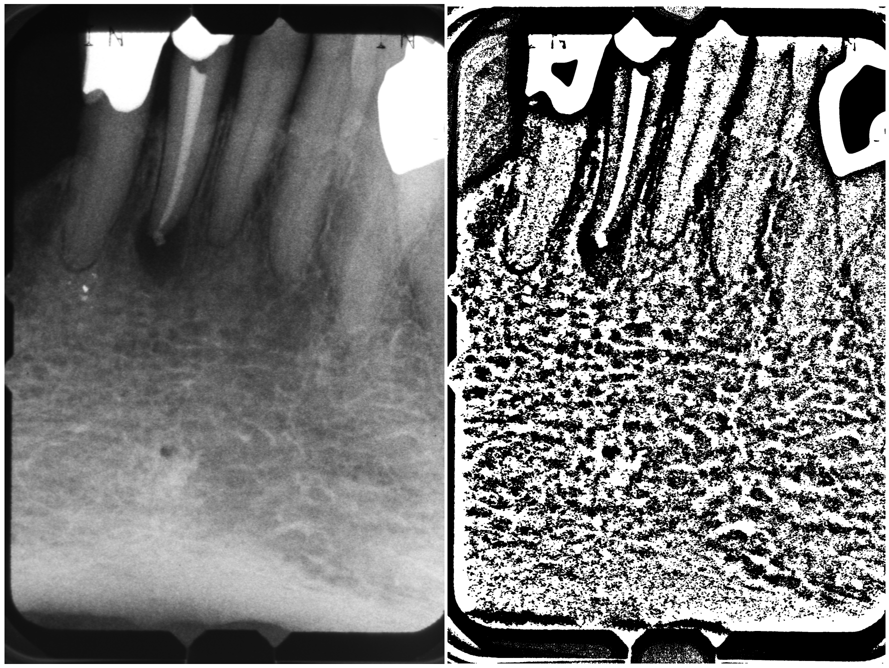

Figure 10: Mandibular anterior forced lesion detection

Edge detection for figure 10 shows a fairly well defined radiolucency around tooth number 26. This radiograph presents a best-case scenario for radiographic detection. As currently demonstrated, the technique becomes less useful in situations where anatomic variations and soft tissue shadowing are more prominent (figure 11).

Figure 11: Maxillary anterior forced lesion detection

As the anatomy becomes more complex, such as in the case of maxillary posterior teeth, the technique encounters more difficulty (figure 12).

Figure 12: Maxillary posterior forced lesion detection

As presented, this “forced lesion detection” has some challenges. This probably stems from the result of applying a Gaussian Blur to an entire image, and having normal anatomy and root density variation influence blurred pixel density thereby inducing noise into the subtracted image. This reason is why other studies have used such a limited region of interest (Chen et al., 2005; Yasar, Akgunlu, 2005). While forced lesion detection does not seem to yield perfect visualization of any lesion, further research is required to determine if it has clinical utility.

Conclusions

The results of this study validate LAA as a method of radiographic evaluation that is as effective as the PAI. An advantage to LAA is that the examiner is not forced to place a tooth in only one of five groups. Furthermore, LAA allows for continuous data, rather than ordinal data to be collected. This equates in a quantitative method of analysis rather than a categorical one such as with the PAI. In this way, the data recorded from LAA may allow the ability to differentiate smaller changes in study groups. An accurate method of evaluating radiographs becomes even more important when using a biological approach to assess our outcomes. Our ability to detect minute changes may be the difference between placing a tooth in Friedman’s “healing” or “persistent disease” categories (Friedman, 2002). While further research is required to determine if these smaller changes are clinically significant, this ability to detect smaller differences between study groups could open the door to more critical, precise, and biologic assessment of endodontic outcomes.

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Appendix A:

Instructions for visualizing radiographs.

Thank you for participating in the present study, "Quantitative digital assessment of periradicular healing." Your assistance will help advance the science of endodontics.

You will be asked to complete a series of radiographic evaluations which require use of a computer imaging software program. This process will require use of a computer and a mouse. You will also be asked to become standardized with a radiographic evaluation process referred to as the Periapical Index or PAI with the help of a powerpoint presentation and printed images as examples. If you require clarification of the various images, please inform the registrar and he will be happy to assist you. Please feel free to ask questions if clarification is needed.

PAI evaluation:

Here are a series of radiographs and images that correspond with a numerical value or score. Please focus on the root end or periapical area to discriminate between the various images and radiographs. Try to make a mental picture of what each image represents. If you require the registrar to return to any of these slides throughout the procedure please let him know. You will be provided printed examples of these images as well. The goal of this portion is to evaluate the change in PAI score if observed.

LAA evaluation:

Now we will begin the process of evaluating the size of the periapical area with the computer mouse. For each radiograph please note that one measurement and one PAI score are needed for each root on the tooth described by the registrar. If you wish to change a measurement, please inform the registrar as soon as possible. The registrar will now demonstrate how the measurement will be made. The goal of our study is to evaluate the change in size in the lesion or periradiuclar radiolucency from the initial visits to a recall period if observed. Please attempt to outline the greatest extent of the lesion that you interpret.

Appendix B:

Thank you for your contribution to the field of endodontics. You will be requested to complete another evaluation in approximately 3 weeks. If you have any questions, please inform the registrar now and we will begin.

Guidelines for area analysis:

1: Please use the mouse to outline your interpretation of the greatest extent of the lesion on the radiograph presented.

2: If the lesions/roots are present, multiple areas may be identified, and roots will be scored individually.

3: If a lesion is confluent with alveolar crest, a perpendicular line to the tooth at that point will be drawn approximating the average current height of the alveolar crest.

4: If no lesion is perceived, notify registrar and tooth/root will be assessed "0"

Guidelines for PAI:

PAI score	Verbal descriptors
6	Normal apical periodontium
7	Bone structural changes indicating, but not pathognomonic for apical periodontitis
8	Bone structural changes with some mineral loss characteristic of apical periodontitis
9	Well defined radiolucency
10	Radiolucency with radiating expansions of bone structural changes

1: Choose the score that most closely resembles both the visual and written description.

2: In multi-rooted teeth, each individual root receives a score.

3: When in doubt, choose a higher score