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REVIEW ARTICLE

Efficacy of imaging techniques for the diagnosis of apical periodontitis: A systematic review

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Abstract

Background: Apical periodontitis (AP) is a chronic inflammatory response of microbial aetiology. Pathological changes associated with AP may not be visible on radiographic images and may linger without causing any symptoms. Clinicians rely mostly on clinical examination and imaging techniques to establish a diagnosis.

Objectives: The aim of this review was to answer the following question using the PICO format: In the adult human permanent dentition (P), what is the efficacy of diagnostic imaging of the periapical tissues (I) using histopathology as a reference standard (C) in the diagnosis of apical periodontitis, in terms of diagnostic accuracy (O).

Methods: MEDLINE, EMBASE, Scopus and Cochrane Library were searched for English articles published through October 2021. At least two independent reviewers evaluated the study design, imaging modality used, histopathological assessment, outcome measures, results and conclusions for each article. The risk of bias was assessed using the Quality Assessment Tool for Diagnostic Accuracy Studies-2.

Results: The initial search strategy identified 544 articles. Seven articles were included for analysis in the final review, all of which involved tissue samples obtained from cadavers. No clinical studies were identified that met the eligibility criteria. A consistently low sensitivity score and negative predictive value were reported for periapical radiography, especially in comparison to CBCT, which scored highly. Both modalities achieved high scores for specificity and positive predictive value. Diagnostic accuracy of CBCT was lower for root-filled teeth in comparison to non-root-filled teeth.

Discussion: Assessment of the periapical tissues using periapical radiographs was shown to have a low to moderate agreement with the histopathological assessment. CBCT was reported to be more accurate than PR and demonstrated a good agreement with histopathology, especially for non-root-filled teeth.

Conclusions: This review identified a need for greater standardization in methodology and reporting, and as the findings are based on cadaver studies, their clinical relevance must be interpreted with caution.

Registration: PROSPERO (CRD42021272147).

KEYWORDS

apical periodontitis, diagnosis, systematic review

INTRODUCTION

Apical periodontitis (AP) is a highly prevalent disease globally (Tibúrcio-Machado et al., 2021) and represents an important transition where the consequences of intraradicular pathology are no longer contained within the tooth, and pose a risk to the oral and systemic health and well-being of the patient (Segura-Egea et al., 2015).

Apical periodontitis is the inflammation and destruction of periradicular tissues caused by aetiological agents of endodontic origin (Nair, 2004, 2008). It is essentially an immune response with the primary purpose of limiting the spread of infection arising from the pulp space. The pathogenesis is complex and involves the reaction to microbes, irritants, toxins, and/or molecular mediators derived from the pulp and root canal system (Fouad & Khan, 2020; Kakehashi et al., 1965; Möller et al., 1981; Ricucci et al., 2019; Stashenko et al., 1998; Torabinejad, 1994). AP is characterized by the triad of endodontic pathology, a localized inflammatory infiltrate, and periradicular bone loss (Nair, 1997), and arriving at a definitive diagnosis of AP requires confirmation of these three criteria. However, the means to achieve this are typically not available to the clinician, especially as AP typically presents asymptomatically (Abbott, 2004).

The selection and interpretation of diagnostic investigations are further complicated by the spectrum of endodontic presentations that can be associated with AP, from untreated teeth to root-filled teeth or surgically-treated teeth with complex restorations. In any case, AP by definition occurs as a continuum of the preceding endodontic pathology (Nair, 2004). Where initially there is vital pulp tissue, the first signs of periapical bone loss and inflammation can occur in the early stages of the disease process prior to necrosis of the radicular pulp (Fouad & Khan, 2020; Kawashima et al., 1996; Langeland, 1987; Lin et al., 1984; Yamasaki et al., 1994), meaning AP may be present, or absent, in combination with a broad spectrum of possible pulpal signs and symptoms (Abbott, 2004; Ricucci et al., 2019). Similarly, the diagnosis of root-filled teeth is complicated by the current inability for a precise microbiological assessment of the root canal system clinically (Siqueira Jr & Rôças, 2014), pre-existing iatrogenic factors, and a limited understanding of the lesion dynamics over time. Therefore, it is usually necessary to rely on surrogate measures of both endodontic pathology and apical inflammation, as identified through clinical investigations and diagnostic imaging.

However, it is well established that clinical investigations are experienced subjectively by the patient, and are conducted and interpreted subjectively by the clinician (Khan et al., 2007; Mejàre et al., 2012; Rotstein & Simon, 2006). In the absence of routine histological and/or microbiological examination of the endodontic and periapical tissues, a diagnosis of AP is reached by confirming the presence of periradicular bone loss associated with putative endodontic pathology. The clinician is reliant on confirmatory radiographic imaging, usually by periapical radiography (PR), where AP typically presents as a periapical radiolucency and its presence is considered an objective measure on which to base clinical decisions (Brynolf, 1967; Orstavik et al., 1986; Rechenberg et al., 2021).

Despite its ubiquity, PR has well-documented limitations such as the inability to detect small changes in bone density confined to the trabecular bone (anatomical noise), geometrical distortion, and the lack of three-dimensional assessment (Bender & Seltzer, 1961; Patel, Dawood, Mannocci, et al., 2009; Patel, Dawood, Whaites, & Pitt Ford, 2009; Shoha et al., 1974). Three-dimensional imaging techniques such as cone beam computed tomography (CBCT), magnetic resonance imaging (MRI), ultrasonography (US) and tuned-aperture computed tomography (TACT), have been suggested as alternative or supplementary forms of imaging that may overcome some of these limitations (Patel, Dawood, Mannocci, et al., 2009; Patel, Dawood, Whaites, & Pitt Ford, 2009).

Cone beam computed tomography allows the visualization and manipulation of a reconstructed three-dimensional image of the maxillo-facial structures, however, this is offset by a lower resolution image and a higher radiation dose compared to PR (Patel et al., 2019). Alternatively, MRI and US avoid patient exposure to ionizing radiation and may possess a number of potential advantages for the diagnosis of AP. For example, unlike CBCT, these techniques are able to differentiate soft tissues and fluid-filled cavities (Di Nardo et al., 2018; Plotino et al., 2007), and artefacts associated with solid or metallic objects are localized and do not appear to affect the diagnostic value of the surrounding image (Bohner et al., 2020; Jungmann et al., 2017; Reusz et al., 2014). As AP is essentially a soft tissue lesion, commonly found in the region of restorative or prosthodontic to materials, these features present unique potential benefits over radiographic techniques (Juerchott et al., 2018). However, as these techniques involve the interaction of transmitted energy with bodily tissues, there are also potential exposure-related risks. For example, the intensity-dependent risks of thermal bio-effects produced with ultrasound are well-established and may be of greater significance in modern machines that can involve substantially greater acoustic outputs (Church & Barnett, 2012). Similarly, MRI can induce heating and subsequent tissue damage, which may be intensified in the presence of conductive metallic objects (Panych & Madore, 2018). Although these risks are largely theoretical at the levels used for diagnostic purposes, they

highlight the universal application of ALARA and appropriate risk assessment.

Determining the usefulness and value of a diagnostic imaging technique involves assessment of its efficacy, effectiveness and efficiency (Stengel & Porzsolt, 2006), which refers to the test's accuracy under ideal conditions, under clinical conditions, and with consideration to the relative benefits to patient and society, respectively. The corresponding level of supporting evidence is commonly classified and evaluated using the hierarchical model of diagnostic efficacy proposed by Fryback and Thornbury (1991). This model comprises six levels of efficacy of increasing impact; technical efficacy, diagnostic accuracy, diagnostic thinking, therapeutic decision-making, patient-related outcomes, and efficacy at the societal level. The classification of evidence in this regard is essential to inform the clinician on the most appropriate use of currently available techniques, identify the needs of the dental workforce, and offer direction for future research and development.

Obtaining evidence requires the identification, evaluation, integration and analysis of available relevant data, in a comprehensive and reliable manner (Muka et al., 2020). This is best achieved through a process of systematic review, where standardized and transparent protocols for searching the literature and assessing methodological quality ensure the process and conclusions are valid, reproducible, and can be independently evaluated.

The aim of this systematic review was to evaluate the diagnostic efficacy of imaging techniques for the diagnosis of apical periodontitis, by answering the following clinical question: In the diagnosis of apical periodontitis, using histopathology as a reference standard, what is the diagnostic accuracy of different imaging techniques of the periapical tissues?

METHOD AND MATERIALS

Eligibility criteria and literature search

This systematic review is reported in accordance with PRISMA and PRISMA-DTA guidelines (McInnes Moher et al., 2018; Page et al., 2021) and is registered on PROSPERO (CRD42021272147). The aim of this review was to answer the following question using the PICO format: In the adult human permanent dentition (P), what is the efficacy of diagnostic imaging of the periapical tissues (I) using histopathology as a reference standard (C) in the diagnosis of apical periodontitis, in terms of diagnostic accuracy (O). Eligible studies must have a primary objective to evaluate the accuracy of a diagnostic imaging technique to detect signs of apical periodontitis and a histopathological reference standard.

Search strategy

Electronic searches were conducted using a number of relevant keywords and MeSH search terms that were combined using Boolean operators (AND, OR). The search strategy was conducted in the MEDLINE database (PubMed) and was adapted to be used in Embase, Scopus, and the Cochrane Library. The most recent search was conducted in November 2021 and searches were limited to the English language. A detailed explanation of the search strategy is described in Table S1. Further manual searches were conducted of the references of the included articles. Articles identified in the searches were screened for eligibility by at least 2 independent assessors by inspection of the title and abstract, or full text if further clarification was necessary. Disagreements on eligibility were resolved by discussion and consensus. Full texts were obtained for all studies meeting the eligibility and inclusion criteria. The inclusion criteria are detailed in Table 1. EndNote 20 was used to remove duplicate records.

Quality assessment and risk of bias

Quality assessment was conducted by at least 2 assessors (SP, JG, KM, and/or AH). The risk of bias was evaluated using the Quality Assessment Tool for Diagnostic Accuracy Studies-2 (QUADAS-2) by Whiting (Whiting Rutjes et al., 2011). It was adapted and piloted for use in this context by including additional signalling questions, which were informed by the Downs and Black quality assessment checklist (Downs & Black, 1998), Newcastle-Ottawa scale (Wells et al., 1999), Oxford Centre for Evidence-Based Medicine (CEBM, 2021), and The Cochrane Collaboration (Higgins et al., 2011). Responses to the signalling questions were answered with either 'yes', 'no', or 'unclear', with the risk of bias categorized as either 'low', 'high' or 'concern', in accordance with the QUADAS-2 guidelines. The presence or absence of a conflict of interest statement in the included studies was considered in the context of the publication, and whether it can be ascertained that a

TABLE 1 Inclusion criteria.

Criteria	Required standard
Sample	Human teeth
	Sample including teeth with apical periodontitis
	Reference teeth
Radiographic assessment	Details of radiographic presentation of periapical region
Histopathological assessment	Details of histopathological assessment of periapical tissues

conflict of interest disclosure has already been presented to the journal's editorial board prior to publication and in an appropriate manner (Nagendrababu et al., 2021).

Data extraction and statistical analysis

Data were extracted from included articles using a custom-designed and piloted data extraction form. Extracted data included study authors, date of publication, date of study completion, type of study, geographic location, sample size, sample characteristics, tooth types, outcome measures, clinical details, imaging protocols, histological techniques, radiological assessment details and examiner reliability assessment. Quantitative data were pooled where possible, and statistical analysis was conducted when appropriate (JMP 10.0.0, SAS Institute).

RESULTS

> In the diagnosis of apical periodontitis, using histopathology as a reference standard, what is the diagnostic accuracy of different imaging techniques of the periapical tissues?

The search strategy is illustrated in the PRISMA flow chart (Figure 1). The initial search strategy identified 544 articles, and after the removal of duplicates and abstract screening, 25 articles were remaining for full-text evaluation. Six articles satisfied the inclusion criteria and were included for analysis in the final review. The details of the excluded articles and the reason(s) for exclusion are outlined in the (Table S2). Many of these studies are important in the field of endodontics, as these are the few studies that examined periapical lesions using methods such as histology and a combination of imaging techniques; however, they did not fulfil the eligibility criteria as determined by the clinical question of this review they could not be included in the final analysis. Due to methodological heterogeneity between studies, such as imaging protocols, test and reference teeth, and histological assessment, a meta-analysis of their outcome was not performed (Sterne et al., 2011).

The included studies used human cadavers of varying post-mortem storage times and methods. Two studies utilized jaw specimens from deceased donors that were fixated within 24 h (Brynolf, 1967; Kruse et al., 2019) and two using unpreserved samples within 14 days of death (Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017). The remaining two studies did not report the time of death, and only one of these studies described the storage medium (Barthel et al., 2004). A mixture of anterior and posterior teeth from the maxilla and mandible were included in most studies (Tables 3 and 4). One study (Brynolf, 1967) used maxillary incisor teeth only, and one study did not provide details of the tooth types included (Barthel et al., 2004).

The included studies employed the use of two imaging modalities: PR (film or digital) and/or CBCT (Table 2).

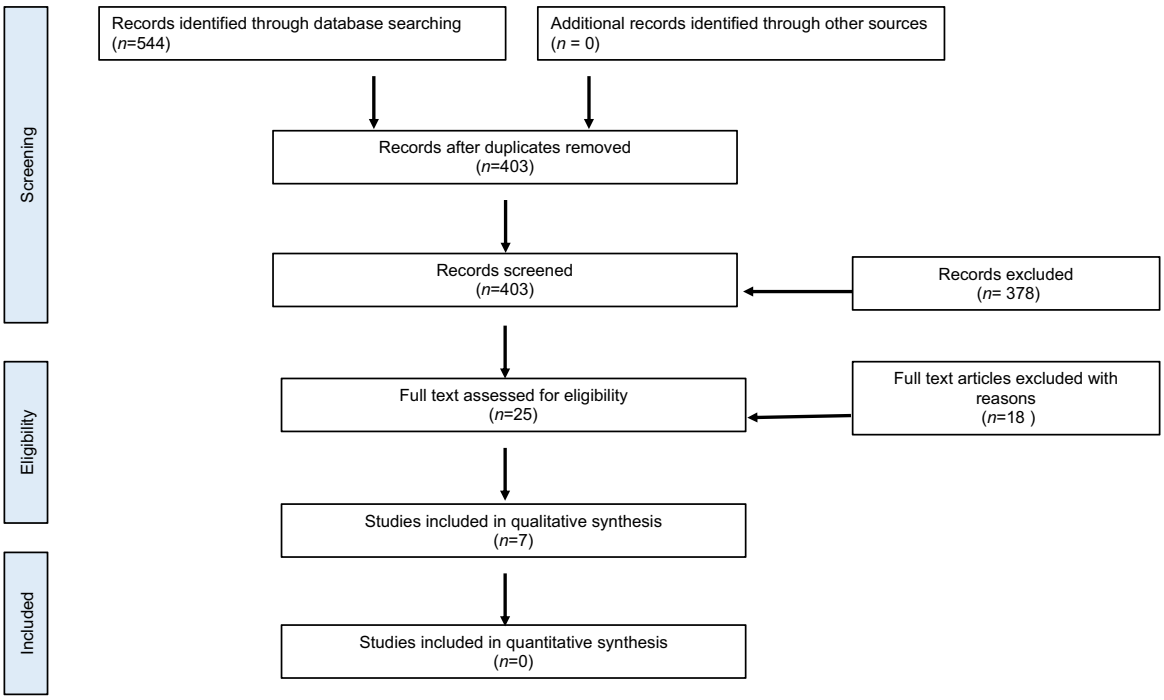

FIGURE 1 PRISMA flow diagram.

TABLE 2 Details of included studies.

Study	*n*	Imaging modality	Set-up details	kV	mA	Time (s)	Distance (cm)	Beam angle	Specimen set up	Assessment
Brynolf, 1967	217	FPR	NR	NR	NR	NR	NR	NR	NR	Detailed
Green, 1997	29	PR	NR	NR	NR	NR	NR	NR	Jaw only	Unclear
Barthel, 2004	53	FPR	D speed	70	NR	0.16	10	NR	Jaw only	Detailed
Kanagasingam, 2017	86	FPR	F speed	70	4	0.50	10	Centred, +/− 10′ M-D shift	Ribbon wax	Detailed
		DPR	Visualix eHD sensor	70	4	0.25	10			
Kanagasingam, 2017[a]	86	CBCT (9000 3D Carestream)	FOV 50 × 37 mm	60	2	10.8	—	180′ rotation	Ribbon wax	Detailed
		DPR	Visualix eHD sensor	70	4	0.25	10	Centred, +/− 10′ M-D shift		
Kruse, 2019	335	CBCT (Cranex® 3Dx)	FOV 50 × 50 mm	90	6.3	8.7	—	NR	Immersed in ethanol, stabilized using wax	Detailed

Abbreviations: CBCT, cone beam computed tomography; DPR, digital periapical radiography; FPR, Film periapical radiography; NR, not reported.

[a]Details of DPR used in this study same as Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017.

Four studies employed PR only (Barthel et al., 2004; Brynolf, 1967; Green et al., 1997; Kanagasingam, Hussaini, et al., 2017), one study involved CBCT only (Kruse et al., 2019), and one study involved both PR (digital and film) and CBCT (Kanagasingam, Lim, et al., 2017).

There were variations in the radiographic protocols for both PR and CBCT between the included studies (Table 2), in particular the exposure settings, object-tube distance, and beam angulations. Both bisecting and paralleling techniques were used, with two studies including additional parallax views (Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017).

Methods of radiological evaluation included dichotomous classification of absence/presence of a radiolucency (Green et al., 1997; Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017), or using an ordinal scale or index (Barthel et al., 2004; Brynolf, 1967; Kruse et al., 2019). The ability of the examiners to manipulate the radiographic images was possible in some studies (Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017; Kruse et al., 2019), however, it was not clear whether this was carried out; if so to what extent and whether it affected the findings. Inter-examiner agreement with blinding was described in three of the six studies (Barthel et al., 2004; Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017) but one or both were not mentioned in the remaining studies.

Regarding the histological processing of the samples, formalin fixing, paraffin embedding and longitudinal sectioning were the most common techniques employed. Characterization of histological slides varied between studies. Four studies employed a nominal dichotomous classification based on the presence or absence of a cellular inflammatory infiltrate (Barthel et al., 2004; Green et al., 1997; Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017), and two studies used an ordinal classification (normal tissues to severe AP) (Brynolf, 1967; Kruse et al., 2019). Calibrating and blinding the examiners to the radiological presentation of the teeth was only described in two of the six studies (Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017). As described, the histological evaluation of the PA tissues was carried out by a single examiner (Barthel et al., 2004; Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017; Kruse et al., 2019). Results of the histological examination of the reference teeth were stated in the majority of the studies (Brynolf, 1967; Green et al., 1997; Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017; Kruse et al., 2019).

The results of the included studies are presented in Tables 3 and 4. Regarding PR, although a general finding was the low sensitivity and NPV scores, wide ranges in sensitivity and NPV scores were reported, ranging from

TABLE 3 Characteristics and results of included studies for non-root-filled roots.

Study	*n* per group	Tooth type	Parallax views (Yes/No)	Imaging	*n* per group of imaging data (T/R)	*n* per group of histology data (T/R)	SE/SP	OR/PPV/NPV	AUC
Brynolf, 1967	*n* = 144 (roots)	AT	No	FPR	56/88	39/105	SE 0.90 SP 0.80	PPV 0.63 NPV 0.95	—
Kanagasingam, 2017	*n* = 86 (roots)	MT	Yes	FPR	9/77	58/28	SE 0.16 SP 1.00	PPV 1.00 NPV 0.36	
				PFPR	21/65	58/28	SE 0.37 SP 1.00	PPV 1.00 NPV 0.43	
				DPR	17/69	58/28	SE 0.27 SP 0.99	PPV 0.99 NPV 0.39	0.63
				PDPR	23/63	58/28	SE 0.38 SP 0.99	PPV 0.99 NPV 0.44	0.69
Kanagasingam, 2017	*n* = 86 (roots)	MT	Yes	CBCT	52/34	58/28	SE 0.89 SP 1.00	PPV 1.00 NPV 0.81	0.94
				DPR	17/69	58/28	SE 0.27 SP 0.99	PPV 0.99 NPV 0.39	0.63
				PDPR	23/63	58/28	SE 0.38 SP 0.99	PPV 0.99 NPV 0.44	0.69
Kruse, 2019[c]	*n* = 220 (roots)	MT	N/A	CBCT	53/167[a]	34/186[b]	SE 1.00 SP 0.87	PPV 0.64 NPV 1.00	—

Abbreviations: AT, anterior teeth; AUC, area under curve; DPR, digital periapical radiography; FPR, film periapical radiography; MT, mixed anterior and posterior teeth; NPV, negative predictive value; NR, not reported; PDPR, parallax-views digital periapical radiography; PFPR, parallax-views film periapical radiography; PPV, positive predictive value; Reference, roots deemed to have no AP; Target, roots with suspected apical periodontitis (AP).

[a]'Unsure' included as 'no lucency'.

[b]'Mild AP' counted as 'no AP'.

[c]CBCT only.

TABLE 4 Characteristics and results of included studies for root-filled roots.

Study	*N*	Tooth type	Parallax radiographs (Yes/No)	Imaging	*n* per group of imaging data (T/R)	*n* per group of histology data (T/R)	Sensitivity (SE) / Specificity (SP)	OR/PPV/NPV	AUC
Brynolf, 1967	*n* = 73 (roots)	AT	No	FPR	54/19	67/6	SE 0.79 SP 0.83	PPV 0.98 NPV 0.26	—
Green, 1997	*n* = 29 (teeth)	MT	—	PR	10/19	15/14	SE 0.67 SP 1.0	PPV 1.0 NPV 0.74	—
Barthel, 2004	*n* = 53 (roots)	—	No	FPR	16/37[a]	27/26	SE 0.48 SP 0.88	OR 9.2 PPV 0.81 NPV 0.67	—
Kruse, 2019[d]	*n* = 115 (roots)	MT	N/A	CBCT	40/75[b]	21/94[c]	SE 0.91 SP 0.68	PPV 0.48 NPV 0.99	—

Abbreviations: AT, anterior teeth; AUC, area under curve; DPR, digital periapical radiography; FPR, film periapical radiography; MT, mixed anterior and posterior teeth; NPV, negative predictive value; NR, not reported; OR, odds ratio; PPV, positive predictive value; PR, periapical radiography (unknown type); R, 'Reference' roots deemed to have no AP; T, 'Target' roots with suspected apical periodontitis (AP).

[a]'Widened PDL' included as 'no lucency'.

[b]'Unsure' included as 'no lucency'.

[c]'Mild AP' counted as 'no AP'.

[d]CBCT only.

0.16 to 0.90 and 0.26 to 0.95, respectively. Additional parallax views resulted in greater sensitivity and NPV of both digital and film PR (Kanagasingam, Hussaini, et al., 2017). CBCT consistently scored the highest sensitivity and NPV values. Both modalities achieved high scores for specificity and PPV. In one study (Kruse et al., 2019), the diagnostic accuracy parameters were lower with root-filled teeth compared to non-root-filled teeth. This variable was not examined in the other included studies.

The QUADAS-2 ratings of the included studies are presented in Table 5. There were some concerns in the studies, most notably in observer blinding and calibration and in histological grading of tissues, which were unclear or inconsistent with previously proposed methods (Table S3; Eaton et al., 2007; Geboes et al., 2000).

DISCUSSION

The aim of endodontic treatment is the prevention or healing of AP (ESE, 2006). Determining the presence or absence of AP is complex and depends on the ability to accurately assess the periapical tissues in the context of a putative endodontic aetiology. It was the aim of this review to appraise the best available evidence for the use of imaging techniques in the diagnosis of AP.

The radiographic presentation of AP is influenced by a myriad of patient, clinician or technology-driven factors (Fava & Dummer, 1997). PR is the current standard imaging technique for periapical assessment (ESE, 2006). However, for a PA lesion to be detected using PR, it has been reported that a minimum of 6.6% and 12.5% mineral and cortical bone loss, respectively, must have occurred (Bender, 1982). As a result, PR may not be accurate in detecting the presence or size of PA lesions, especially regarding posterior teeth where the presence of thicker cortical plates may reduce the diagnostic accuracy

TABLE 5 Quality assessment of the included studies.

compared to anterior teeth (Low et al., 2008). The interpretation and comparison of studies are thus complicated by differences or lack of details regarding the sample teeth examined. Of the five included studies investigating PR, three combined anterior and posterior teeth (Green et al., 1997; Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017), one included only anterior teeth (Brynolf, 1967), and one did not provide details of the tooth types (Barthel et al., 2004).

These limitations may be mitigated by manipulating radiographic and/or exposure settings, or obtaining additional parallax views, and may result in a subtle lesion being manifested on a radiograph. The inclusion of parallax views was performed in two of the included studies (Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017) and was shown to significantly increase the diagnostic accuracy of PR. However, the potential benefits of any additional patient exposures must be justified in light of the increased patient radiation dose (Brynolf, 1970; Kanagasingam, Hussaini, et al., 2017; LeQuire et al., 1977). Similarly, depending on the lesion size and various other factors, the use of digital radiography and different film speeds has been shown to either equivocally or positively influence the detection of artificial lesions or AP (Farman et al., 1998; Kanagasingam, Hussaini, et al., 2017; Mistak et al., 1998; Tirrell et al., 1996; Wallace et al., 2001). Although, differences in radiographic interpretation between and within observers cannot be ruled out (Goldman et al., 1972), the findings of this review appear to support the use of digital PR over the conventional film, and the inclusion of additional parallax views where there is clinical justification.

PR alone was evaluated in four of the six included studies in this review (Barthel et al., 2004; Brynolf, 1967; Green et al., 1997; Kanagasingam, Hussaini, et al., 2017), and combined CBCT/PR or CBCT alone were tested in two studies (Kanagasingam, Lim, et al., 2017; Kruse et al., 2019). Overall, the diagnostic accuracy was reported to be significantly higher with the use of CBCT compared to PR. However, where root-filled and non-root-filled roots are analysed separately, diagnostic accuracy differed for both PR and CBCT (Tables 3 and 4). Three of the included studies, two of which included the same sample, investigated the accuracy of PR for non-root-filled roots (Brynolf, 1967; Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017) and reported markedly different results, with sensitivity values ranging from 0.16 to 0.90 (Table 3). The reasons for this are not clear, and possibly attributable to differences in methodology and sample characteristics. Although only incisor teeth were included in Brynolf (1967), 66% of the sample used in the studies by Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017 were anterior teeth and this factor alone may not explain the differing findings. Conversely, the two included studies employing CBCT to image non-root-filled roots were in agreement on the high diagnostic accuracy of CBCT in this context (Kanagasingam, Lim, et al., 2017; Kruse et al., 2019).

Regarding root-filled roots, there was considerable variation in the reported diagnostic accuracy parameters between studies utilizing PR (Table 4), and meaningful comparison between these studies and with those of non-root-filled teeth was not possible. More notably, the diagnostic accuracy of CBCT for root-filled roots was investigated by a single study (Kruse et al., 2019), which reported a lower accuracy compared to non-root-filled teeth. As noted by the authors, this discrepancy between root-filled and non-root-filled roots only concerned cases where histopathological examination revealed mild inflammation, and the consequences thereof on diagnostic accuracy parameters were dependent on whether 'mild AP' was classified as 'AP' or 'no AP'. This relates to more fundamental questions of how AP should be categorized histologically and what constitutes disease, which are currently unresolved in the literature. In three of the included studies 'health' was defined as the absence of an inflammatory cell infiltration (Barthel et al., 2004; Brynolf, 1967; Green et al., 1997), whereas two studies categorized 'disease' as a moderate to intense inflammatory infiltrate (Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017). From the perspective that mild AP does not represent a condition that definitively or reliably indicates endodontic infection (Kruse et al., 2019), particularly for root-filled roots (Orstavik et al., 1986), no statistically significant differences were identified between non-root-filled and root-filled roots except for specificity which reduced from 0.87 to 0.68, respectively (Kruse et al., 2019). Importantly however, whether mild AP is classified as health or disease when utilizing CBCT for diagnosis of AP, consideration should be afforded to the greater risk of missed apical lesions or an incorrect diagnosis of AP for root-filled teeth compared to non-root-filled teeth. This is of particular pertinence as the array of clinical tests available to assess the apical tissues associated with root-filled teeth is limited in number and reliability.

Based on the limited available evidence, the findings of this review support the current position that the supplementary use of CBCT should be considered where a diagnosis cannot confidently be formulated based on conventional means involving a detailed patient history, thorough clinical examination, and PR (AAE, 2016; Patel et al., 2019).

Although considered as the gold standard in diagnosis, histological examination presents several challenges in preparation, standardization and interpretation of samples. For example, differences in tissue sectioning and

the choice of section to assess can affect the diagnosis (Ramachandran Nair et al., 1996). Similarly, the interpretation of a tissue slide by an examiner involves a complex set of intuitive judgements, and the classification of disease (which presents as a continuous spectrum) into arbitrarily defined boundaries, and which can introduce bias and heterogeneity between studies (Cross et al., 2011). As with most studies involving human tissues and patients, one of the most significant sources of bias is the sample, which should be representative of the target population. However, it would not be possible to obtain consecutive or randomized PA samples of normal reference teeth—the key component of diagnostic testing- from live human subjects. The best available technique was procuring cadavers for the purpose of confirming the histological status of the PA tissues in both the test and reference teeth with their radiographic presentation. For the quality of the post-mortem tissues to remain intact and reflective of their pre-mortem state, it is necessary for the cadavers to be dissected as soon as possible after the time of death (Bauer et al., 2018). Adequate samples can be obtained either by immediate preparation of fresh tissue, or immediate preservation to allow tissues to be stored and prepared at a later date. Immediate fixation within 24 h was reported in two studies (Brynolf, 1967; Kruse et al., 2019), however, the post-mortem storage duration was not described. Similarly, two studies reported preparation of fresh tissue within 14 days (Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017), but did not describe the post-mortem conditions or period prior to cold storage. The remaining studies provided little or no detail regarding the post-mortem duration or storage or dissected the cadavers up to 14 days after death when tissue deterioration might have skewed the histological evaluation even in the presence of a preserving agent (Bauer et al., 2018). In addition, blinding to the radiographic data by the histological evaluators was not indicated in most of the studies.

Intra- and inter-observer agreement with blinding to diagnoses or histopathological data is crucial in avoiding bias when investigating the accuracy of diagnostic tools such as radiographs (Viera & Garrett, 2005). Scoring indices specific for radiographic evaluation of the periapices of teeth have been proposed (Estrela et al., 2008; Orstavik et al., 1986) and used in several studies (de Chevigny et al., 2008a, 2008b; Rechenberg et al., 2021) to report observer reliability and weighted kappa values. None of the included studies utilized these methods although blinding with a thorough description of the observer reliability testing was detailed in two studies (Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017).

Where ordinal categorical methods were used to measure inflammation, kappa statistics are a relevant tool in assessing reproducibility (Cross, 1996). Of the six evaluated studies, four had a single histological examiner (Barthel et al., 2004; Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017; Kruse et al., 2019) whilst the rest did not specify the number of examiners, or the relevant method was quite unclear. A robust intra-observer kappa value of over 0.90 was obtained in two studies but the inter-observer agreement cannot be calculated with a single examiner (Kanagasingam, Hussaini, et al., 2017; Kruse et al., 2019). Employing a single examiner to identify and correct bias would need to be clarified as ideally, inter- and intra- observer agreement go hand-in-hand where two or more observers are tested for objectivity (Viera & Garrett, 2005). In terms of the histological scoring itself, the methods described in the studies did not specify an objective, quantifiable and reproducible system (i.e. numbers or percentages), especially where ordinal scoring (normal to severe AP) is used. Reproducible scoring methods in quantifying histological sections of inflamed tissues have been proposed as a tool to quantify the percentage of microscopic fields in which lesions are present, rather than on subjective estimates of lesion presence or severity (Eaton et al., 2007; Geboes et al., 2000).

To comprehensively address the clinical question proposed in this review would entail the identification of studies that involve a clinical examination, diagnostic imaging, a histological reference standard, and measurable outcomes in terms of diagnostic accuracy. However, studies fulfilling these criteria with a large and representative sample size were not identified in the current review, and the included studies utilized imaging and histological assessment of samples obtained from cadavers. Given the ethical implications of obtaining histological samples from healthy patients, obtaining samples from cadavers remains the best available alternative. Cadaver studies allow for methodological standardization and consistency, but the findings may not be reliably translated to the clinical context. This level of evidence corresponds to diagnostic accuracy efficacy and level 2 in the Fryback and Thornbury model (Fryback & Thornbury, 1991). As this is a hierarchical model, only once efficacy is established at this level can consideration be given to higher levels of efficacy that relate to clinical decision-making and patient outcomes. Whilst efficacy at higher levels necessitates efficacy at lower levels, the reverse is not the case. Notwithstanding the limited generalisability of *ex vivo* histopathological studies, this model highlights their important role in the development of evidence to inform the use of diagnostic imaging and emphasizes that these studies represent one level in a continuum. Improvements in diagnostic accuracy under 'ideal' conditions (efficacy) do not equate to improvements in a 'real' clinical setting (effectiveness) and similarly do not guarantee commensurate

improvement in clinical decision-making and patient outcomes (Fryback & Thornbury, 1991). This review has identified some evidence for diagnostic accuracy efficacy, and it is the hope that this can provide a foothold from which future research can aim to address questions of efficacy at higher levels.

A patient history and results of clinical investigations are typically not possible in studies involving cadavers, and the included studies provided little detail regarding the histological or microbiological assessment of the pulp or root canal contents (Kanagasingam, Lim, et al., 2017; Kruse et al., 2019). Furthermore, the histological difference between 'reparative' and 'destructive' inflammatory tissue (Atri et al., 2018; Shapouri-Moghaddam et al., 2018) was not described in the included studies, and such lesions are indistinguishable radiographically (Kruse et al., 2019; Molven et al., 1996; Tibúrcio-Machado et al., 2021). This places great emphasis on observing changes in the radiographic appearance of a lesion over time in order to gain some insight into the lesion dynamics.

The major limitation of this systematic review is the methodological heterogeneity of the included studies with regard to post-mortem biopsy time, tooth location, imaging techniques (modality, angulation, image manipulation), radiographic and histological evaluation, blinding and calibration of evaluators. Moreover, only three studies were specifically designed to evaluate the diagnostic efficacy where sensitivity, specificity, odds ratio, positive and negative predictive values were reported (Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017; Kruse et al., 2019). Two of these studies were from the same authors and presumably from the same source of materials (Kanagasingam, Hussaini, et al., 2017; Kanagasingam, Lim, et al., 2017). It is clear that there is very limited available high-quality evidence to inform diagnostic thinking regarding AP, arguably one of the most ubiquitous and fundamental of clinical decision-making in endodontics. This has further implications for addressing heterogeneity in endodontic practices and research, and the formation of S3-level guidelines, which relies on an adequate body of good-quality primary research (Duncan et al., 2021). Conducting studies of this type on human tissues is a formidable task, involving considerable resources and the coordinated expertise in histopathology, diagnostic imaging and endodontology. The possibility and impact of future diagnostic accuracy studies may depend on the creation of further opportunities for increased academic collaboration and standardization of research practices.

Employing strict eligibility criteria resulted in the exclusion of a number of studies. Diagnostic studies evaluating radiographic imaging involve significant potential harm to a large number of patients; as a direct consequence of the patient exposures during the study, and indirectly following dissemination of the findings. The justification of these risks is dependent on the findings of studies being accurate, reliable, and generalisable, which is determined largely by study methodology and reporting. Similarly, despite their potential relevance, this review did not include animal and simulated *ex-vivo* studies as it has not been established that these models are valid representations of the clinical condition (Aerssens et al., 1998; Kruse et al., 2015). Additionally, in consideration of the clinical, imaging, and laboratory demands on diagnostic accuracy studies, inclusion of unpublished or technical reports was not considered appropriate in this context. Non-English studies were not included, which was acknowledged as a potential source of publication bias (Sterne et al., 2011) but was unavoidable in the current review. It may be a consideration for future systematic reviews to include authors fluent in more than one language.

The included studies were quality assessed using the QUADAS-2 tool (Whiting Rutjes et al., 2011), which is specifically designed for diagnostic studies, and developed through multiple phases of peer review (Yang Mallett et al., 2021). As recommended in the QUADAS protocol, additional context-specific questions were included with the aim of reducing the sources of potential bias not captured by a single universal tool. A potential source of bias in the included studies relates to sample selection. Spectrum bias, which can arise as a result of differences in sample characteristics, can detract from the generalizability of the findings by causing a significant disparity in disease prevalence between the sample and general populations (Ransohoff & Feinstein, 1978). For example, where sample selection occurred based on the suspected presence of endodontic disease in a hospital or specialist practice setting, a higher frequency or severity of disease in the sample may exaggerate a test's clinical significance. Similarly, sample characteristics such as geographic location, age, medical conditions, restorative status and location of the teeth, may affect the relevance and significance of the findings (Kirkevang & Vaeth, 2019; Tibúrcio-Machado et al., 2021).

As with all systematic reviews, the accuracy and reliability of the conclusions are determined by the number and quality of the included studies, and the conclusions of this review must be considered with some caution. Obtaining study data was challenging owing to the differences in classifications, reporting and presentation of study data. This highlights a need for improved standardization in order to maximize the benefit obtained through patient exposures, and the need for greater methodological standardization in future studies (Rutjes et al., 2006) to allow better interpretation, comparison and pooling of data (Lang et al., 2012; Pigg et al., 2021).

CONCLUSIONS

This review identified six studies that investigated the efficacy of PR and/or CBCT for the diagnosis of AP in human cadavers, which corresponds to level 2 in the Fryback and Thornbury (1991). Overall, the assessment of the periapical tissues using PR was shown to have a low to moderate agreement with histopathological assessment. Although specificity was consistently reported as high (0.80–1.00), there was marked variation in sensitivity scores. This was particularly apparent in the two studies that assessed non-root-filled roots, where sensitivity ranged from 0.16 to 0.90. Conversely, the use of CBCT for the assessment of non-root-filled roots was consistently reported to demonstrate a good agreement with histopathology and was generally of greater diagnostic accuracy than PR. A single study employed CBCT for the assessment of root-filled roots and found diagnostic accuracy scores were lower than those for non-root-filled roots. This suggests there is a greater risk of missed lesions or incorrect diagnosis of AP with the use of CBCT for assessing root-filled roots compared to non-root-filled roots.

The findings of this review suggest that CBCT has diagnostic accuracy superior to that of PR, particularly for non-root-filled teeth. However, this review included a limited number of studies with substantial heterogeneity, and as a result, the findings should be taken with caution. It is recommended that the use of CBCT for diagnosis of AP should only be considered following a detailed patient history, clinical examination and PR. There is a clear need for further research investigating the diagnosis of AP, with a view to establishing diagnostic efficacy in relation to clinical decision-making and patient outcomes, and a greater emphasis on increased standardization of methodology and reporting.

AUTHOR CONTRIBUTIONS

JCG and KM—Conceptualized the study, searched, reviewed and assessed the articles and wrote the manuscript. AH and SP—Conceptualized the study and contributed to the writing of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ETHICS STATEMENT

This paper did not involve human or animal subjects.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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