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Outcome of non-surgical retreatment

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Abstract

The purpose of this review was to find and critically analyse the relevant literature to synthesise an overview on the clinical outcomes (radiographically judged periapical healing and tooth survival) following root canal retreatment and the factors influencing them. A further aim was to explain the findings as far as possible.

The relevant literature was found and critiqued using the principles of a systematic review. The data were classified into a coherent structure for analyses and presentation but are not presented as a systematic review; rather the authors have chosen a narrative style to enable integration of the clinical outcomes with relevant findings from laboratory and animal studies.

Overall, the outcomes were similar to those for teeth undergoing primary treatment with common factors influencing the outcomes. The major differences between the outcomes of primary and secondary root canal (re)treatment reside only in the ability to predictably access and negotiate the root canal system to the (residual) apical infection. The data offer very favourable prognosis for non-surgical root canal retreatment performed to guideline standards.

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Introduction

The Endodontic literature is replete with evidence of the earnest work of many investigators into the problem of management of root canal infection and periapical disease. There is however, no optimal, standardized, universally accepted protocol for root canal treatment. Clinicians are left to decide on their own particular approach through a combination of the wealth of published information, their training and subsequent experience. The call for standardization of root canal treatment procedures was first raised at the beginning of the last century (1, 2). Biological and clinical evidence, tempered by practice experience has been used to generate guidelines on the quality of root canal treatment by societies of Endodontology in UK (3), Europe (4, 5), and Canada (6). They have collectively highlighted the importance of a number of steps, including: 1) the use rubber dam tooth isolation to facilitate an aseptic technique; 2) the proximity of the canal preparation to the canal system terminus (5, 6); 3) the sufficiency of the taper given to the canal preparation; 4) the adequacy of irrigation of the canal system using a solution with disinfectant and tissue-dissolving properties; 5) the adequacy of the antiseptic dressing of the canal system between visits; 6) the adequacy of a biologically acceptable seal of the canal system when the infection is judged to have been controlled; 7) the extension of a homogenous canal filling to the terminus of the canal system without extrusion; and 8) the adequacy of the final restoration to prevent bacterial recontamination of the canal system or fracture of the tooth. All three societies recommend clinical and radiographic assessment of treatment outcome for quality assurance purposes. The above guidelines apply to root canal treatment regardless of whether it is primary or secondary (retreatment) in nature.

Over one hundred articles have been written on the clinical outcome of primary root canal treatment and retreatment since 1921 (7). However, substantially more studies on primary treatment (8) have been published than on retreatment (9).

Overview of methodological characteristics of published studies

The level of evidence for the outcome of root canal retreatment was found to be sub-optimal in a systematic review (10). There exist three low-level randomised controlled trials comparing the outcome of non-surgical versus surgical retreatment (11-13). *No randomized controlled trial has thus far investigated any aspect of retreatment procedures*.

The effect of pre-operative prognostic factors has been investigated using a prospective cohort study design by only a small proportion of previous studies (14–22); the majority of the rest have used a retrospective design. Given the difference in the nature of infection between previously untreated and root-filled teeth (23), it is not inconceivable that the outcome of primary treatment and retreatment and their related prognostic factors may be different. It may therefore be argued that analysis of the outcome data for the two types of treatment should be performed separately. Unfortunately, most of the data on retreatment has in fact been presented and analysed together with the data on primary treatment (14, 15, 17, 24–32) or surgical retreatment (33). In most of these studies, retreatment represented a small proportion of their total sample (14, 15, 17, 24, 28, 29, 34). Only a few studies (11, 16, 18–20, 35–37) have been specifically designed to investigate re-treatment. A recent study (21, 22) compared the direction and magnitude of the effect of potential prognostic factors on primary treatment and retreatment by including similar numbers of cases from the two types of treatment.

Outcome measures and criteria for successful treatment

The outcome of root canal treatment has been assessed using different measures depending on the perceived outcome of importance from the perspective of the researcher, dentist or patient. Academic clinicians interested in identifying prognostic factors, have tended to opt for a combination of radiographic and clinical signs of resolution of periapical disease (38). The patient's perspective has been measured by resolution of symptoms (39, 40), functionality of the tooth (41) and the quality of life index (42). The health planning professional or dental insurance company may be more interested in the survival of the root canal fillings or treatment (43–47) and tooth retention or survival (22, 48, 49). More recently, the use of patient reported outcomes has become a requirement for measuring the quality of care by the National Health Care System in the UK (50) (Department of Health 2008 www.dh.gov.uk/publication) and by other bodies in other countries but none of the published studies has yet included this outcome measure.

The traditional two-dimensional radiographic image has been a well accepted method for assessing periapical status of root treated teeth. However, the development of digital imaging technology (51) brought the possibility of image manipulation, including digital subtraction (52–55), densitometric analysis (56), and correction of gray values (57) or brightness & contrast (58). The use and limitations of the two-dimensional radiographic image for assessing treatment outcome has been reviewed thoroughly before (59).

Recently, cone-beam computed tomography (CBCT), a new three-dimensional imaging technique requiring only 8% of the effective dose of conventional computed tomography (60), has been proposed as a means of overcoming the problem of superimposition. It rapidly gained popularity amongst Endodontists (61–63), even before the data on sensitivity or specificity was available. It has been suggested that 34% of lesions associated with posterior teeth failing to be detected by conventional periapical radiography, could be detected by cone beam tomography (64). Recently, the diagnostic values of periapical radiography and cone beam tomography were compared on dogs' teeth using a histological gold standard to detect apical periodontitis 180 days after root canal treatment (65); the latter was found to be significantly more accurate. Curiously however, stratifying the analyses by the experimental groups only revealed a significant difference amongst teeth with apical periodontitis undergoing the two-visit treatment (66). The validity of clinical outcome studies using conventional radiographic technique has been questioned (67) and the routine use of CBCT has not been recommended by the Health Protection agency (68) owing to its higher radiation dosage (×2-3) (68, 69).

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Many studies consider the threshold of treatment success to be passed only when both radiographic and clinical criteria are satisfied (41). A small proportion of cases present with persistent symptoms despite complete radiographic resolution of the periapical lesion (70). Comparison of success rates estimated with or without clinical examination revealed no (17) or only a very small difference (1%) (21). Interestingly, presentation of pain has only been used as an outcome measure in studies following-up cases for 1 month (71–74).

The definition for success/failure by Strindberg (1956) (75) embracing both radiographic and clinical findings have been widely adopted or adapted in many studies (14, 21, 24, 29, 31, 76) (Table 2). Friedman & Mor (2004) (41), sceptical about the terms "success/failure" because of their potential to confuse patients, instead adopted the labels, "healed", "healing" and "diseased". In table 2, the "healed" category corresponds to "success" as defined by Strindberg (1956) (75), whilst "healing" corresponds to "success" as defined by Bender *et al.* (1966a&b) (39, 40).

Criteria setting the threshold for success at complete resolution of the periapical radiolucency have been described as "strict" (8) or "stringent" (41). Whilst choosing a mere reduction in size of periapical radiolucency (39, 40) has been described as setting a "loose" (8) or "lenient" (41) threshold. The frequency of adoption of these two thresholds in previous studies has been similar; the expected success rates using "strict" criteria would be lower than those based on "loose" criteria. The literature finds the difference to vary from 4% to 48% (9, 38).

When using the periapical index (PAI), earlier studies (77, 78) only reported the increase or decrease in mean scores for the factors under investigation, with reporting of the proportion of cases successful. In other studies, the PAI scores were dichotomized into "healthy" (PAI 1 or 2) or "diseased" (PAI 3–5) categories (79, 80), allowing the data to be compared directly with more traditionally used binary outcomes of success or failure. In this system of designation, given that the periodontal ligament space is slightly widened in score PAI 2, it effectively signals the adoption of the "loose" threshold. The longitudinal analyses (81) of 14 cases presenting with widened apical periodontal ligament space (PAI score at 2) after 10 years post-operatively, revealed unfavourable future healing in a proportion (28%, 4/14).

Recently, the outcome measure, "functional retention" has been introduced (41) to aid comparison between the outcomes of endodontic treatment and tooth extraction followed by implant replacement. A tooth was judged "functional" in the absence of clinical signs and symptoms, regardless of the presence or absence of periradicular radiolucency (18, 82). The prognostic factors influencing this outcome measure have never been reported.

"Survival of teeth after root canal treatment" is a similar but more lenient outcome measure than "functional retention", as it ignores the clinical condition of teeth at recall. The perceived "threat" to endodontic treatment from the competing treatment option (extraction & implant supported prosthesis) has popularized the study of "tooth survival" (21, 45, 48, 49, 83–93). Only the latter two studies (21, 93), however, offered survival data specifically for root canal retreatment. Apart from tooth extraction, other competing outcomes such as the tooth undergoing further non-surgical or surgical treatment may also be considered failure events (45–47).

More rarely used dimensions of root canal treatment outcome are "quality of life" and "patient satisfaction" (42). It has been found that the quality of life of patients was found to improve significantly after endodontic treatment as a result of pain relief and allowed return to normal sleep patterns. No published study has specifically used this measure for assessing the outcome of root canal retreatment.

Unit of outcome assessment

Both tooth or root, independently or in combination have been used as the unit of assessment (9). "Patient" has only been used as a unit for assessing "quality of life" and "patient satisfaction" (42). Given that it is considered clinically appropriate to either extract or repeat the root canal treatment of the entire tooth when disease persists, it has often been considered more appropriate to use "tooth" as the unit of measure. In reality, multi-rooted teeth may be selectively treated by root-end surgery, root-resection or hemi-section to manage individual root(s) with persistent problems.

Conceptually, when determining the root-level prognostic factors for resolution of apical periodontitis, use of “tooth” as the unit of assessment would confound the analyses. On the other hand, using “root” as the unit of assessment would over-estimate success when multi-rooted teeth are analysed (38). Two studies (17, 21) providing simultaneous outcomes for both units of assessment did not support this conceptual prediction (Table 1)

Duration after treatment and recall rate

The duration after which treatment is reviewed in studies is subject to considerable variation, ranging from 6 months (15, 33) to 27 years (94). The European Society of Endodontology’s Quality Guidelines (2006) (5), recommend clinical and radiographic follow-up at least one year after treatment with subsequent annual recall for up to four years before a case is judged to have failed. The American Association of Endodontists concurs with a suggestion of clinical and radiographic evaluation for up to five years. The origin of the “four year” standard is probably based on the work of Strindberg (1956) (75) who reported that stabilisation of periapical healing was not observed until 3 years after the treatment. Forty years later, Ørstavik (1996) (78) reported the peak incidence of healing to be at 1 year whilst ten years earlier, Byström *et al.* (1987) (95) reporting on healing dynamics had noted that completely healed lesions decreased to about 2 mm within 2 years, regardless of their initial size. Recently, a prospective study (21) reported that the majority (96%) of the lesions associated with retreatment healed completely within 2 years post-operatively. They also found that the duration after treatment (2–4 years) did not have a significant influence on the proportion of teeth with complete periapical healing. On the other hand, it has been reported that late periapical changes, with more successful cases, were recorded when a 10-17-year follow-up after root canal retreatment was extended for another ten years (94)

The research problem is that the longer the duration of follow-up after treatment, the lower the recall rate; the literature reveals this to range from 20% (26) to 100% (11) for retreatment. It has been reported that patients who were female, in the older age group, or had teeth with pulp necrosis or previous root fillings, were more likely to attend follow-up appointments (96). Although there is no specific threshold of loss to follow-up at which attrition-related bias becomes problematic (97), the possibility of bias in a randomized controlled trial is a concern when the loss is more than 20% (98). This is particularly so when there is a significant difference in the drop-out rate between the two arms of a trial (97). There is however, no equivalent threshold related to longitudinal observational studies.

Statistical methods for investigation of prognostic factors

One of the most common design problems in medical research is that the sample size is too small with inadequate power to detect an important effect, if one exists (99). Unless the true treatment effect is large, small trials can yield a statistically significant result only by chance or if the observed difference in the sample is much larger than the real difference (100). Amongst the clinical outcome studies on retreatment, the use of power calculation for determination of sample size has only been reported occasionally (18, 20). The sizes of sample populations have varied substantially from 18 to 452 teeth amongst the studies included in a systematic review (9). At the time of writing this review, the largest clinical outcome study on retreatment using periapical healing as the outcome measure was based in an Endodontic specialist training centre in UK with a sample size of 750 teeth (21, 22). In contrast, a study (93) on tooth survival following retreatment performed by endodontists participating in an insurance service was able to include 4744 teeth with a 5-year follow-up.

When analysing the association between potential influencing factors and treatment outcome, the occurrence of confounding can produce spurious effects such as hiding, reducing the true effects of a genuine prognostic factor or magnifying the effect of a dubious factor (101). For confounding to occur, the variable of interest must be associated with the confounder which must in turn be associated with the outcome. However, most studies on retreatment outcome have not used a multi-variable regression model (101) to account for the effects of potential confounders but have instead used the uni-variable chi-squared test (9). In addition, the hierarchical structure of the Endodontic dataset is mostly ignored. By this is meant that the fact that multiple roots are nested within the same tooth, and multiple teeth are nested within the same patients, is ignored. The units within each cluster cannot be considered to be independent to each other and this must be accounted for in the analytical method. In addition, the prognostic factors for the outcome of root canal treatment may operate at individual root, tooth or subject levels. At these different levels, the relationship between a prognostic factor and treatment outcome might be attenuated by different confounder profiles. Thus, prognostic factors may play different roles in predicting outcome at these three levels (102). The hierarchical structure of the data may only be accounted for by a multi-level random effects modelling approach (102) or marginal effect models (17, 21, 22).

Outcome of root canal retreatment using radiographically judged periapical healing as a measure of success

A systematic review (9) of 17 studies published between 1961 and 2005 reported that the pooled estimated success rates of root canal retreatment completed 2–4 years previously, ranged between 70% and 80% based on strict radiographic criteria for success. Whereas, the estimated weighted pooled success rates of primary treatments completed 2 to 4 years prior to review was reported by another systematic review to range between 76% and 86% (8).

The above figures seem to support the commonly held belief (14, 15, 26, 28) that primary treatment is associated with better outcome than retreatment, possibly due to the difference in the nature (23) and location of root canal infection (103). A meta-analysis (9) of seven studies reported that the relative proportion of roots/teeth with retreatment *versus* primary treatment was low (range 4% to 51%). The statistical comparison of this data (based on strict criteria) might therefore be under-powered in the meta-analysis; showing that primary treatment was associated with higher odds of success (OR = 1.3; 95% CI: 0.8, 2.1) but the difference was not significant (P = 0.4). Interestingly, a recent prospective study (21) revealed a similar odds ratio (OR = 1.3; 95% CI: 0.9, 1.8) when comparing the outcomes of the two types of treatment. A further meta-analysis (9) performed on data from teeth with pre-operative periapical lesions (14, 17, 24, 26), revealed the odds ratio to be slightly higher at 1.6 (95% CI: 0.8, 3.6) but the result was not statistically significant at the 5% level. It could be concluded that the *small* differences in success rate between primary treatment and retreatment are clinically genuine but that there was insufficient statistical power to show a definitive difference.

Two randomized controlled trials (11, 12) compared the outcome of surgical *versus* non-surgical retreatment and were included in a Cochrane review (104). Both reported that surgical retreatment was associated with higher success rates than root canal retreatment, *one-year* after treatment, although the differences were not significant in the study by Danin *et al*. (1996) (11). At *four-years* after treatment, Kvist & Reit (1999) (12) failed to show any difference. They hypothesized that surgical retreatment resulted in more rapid initial bone-fill but were associated with a higher risk of "late failures". In agreement with Del Fabbro *et al*. (2007) (104), a more recent systematic review and meta-analyses stratified their analyses by the duration of follow-up and also concluded that there was no significant difference in the outcomes of non-surgical retreatment and Endodontic surgery (105).

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Overview of prognostic factors for resolution of periapical disease by root canal retreatment

The prognostic factors for resolution of periapical disease following root canal retreatment may be classified into pre-, intra- and post-operative factors; the strength of evidence for potential prognostic factors was found to be weak in a recent systematic review (9). However, a recent prospective study in London (UK) has found that the effects of all significant influencing factors, except "type of irrigant", were found to be the same for both primary treatment and retreatment (21). The evidence for each of the potential influencing factor is presented sequentially below.

Pre-operative factors

Gender

None of the previous studies reporting on the influence of gender on retreatment have found any significant association between gender and success rate (14, 18, 20, 21, 31, 37, 106).

Age

The effect of the patient's age on retreatment outcome has been analysed by evaluating age as a continuous variable (17, 21) or categorised by decade (32, 37); or by division into two groups (18, 20). Age was not found to have a significant influence on retreatment outcome in all but one study (32). Imura *et al.* (2007) (32) reported that age had a significant effect on the outcome of retreatment; the age group 50–59 was associated with a higher success rate compared with all other age bands pooled into one category. In their final multiple regression model, only one age band was analysed, the selection of which was data-driven and without any clinical justification. In fact, their summary data revealed no obvious, linear or non-linear trends in the success rates by different age bands.

Dichotomizing or categorizing continuous predictors is considered unnecessary and is unsupported on statistical grounds (107). The disadvantages include loss of information (such as detection of non-linear relationships with outcome), loss of statistical power, and increased probability of false positive results. The choice of thresholds should have a clinical basis or be consistent with previously recognized cut-off-points (107). In the absence of an a *priori* cut-off-point, the most common and acceptable approach is to take the sample median (107). The arbitrary selection of cut-off-points may lead to the notion of testing more than one value and choosing that which, in some sense, gives the most satisfactory pre-conceived result; it is worse still if the cut-off-points are selected using a data-dependent method (107).

The last strategy appeared to be adopted by Imura *et al*. (2007) (32) rendering the outcome unreliable.

General medical health

The effect of general health on retreatment outcome has been poorly investigated. One study (108) only included healthy patients. Without stratifying the analyses for primary treatment and retreatment, another study (109) reported that conditions associated with impaired non-specific immune response significantly reduced the success rates of root canal treatment on teeth associated with periapical lesions. However, a recent prospective study (21) failed to reveal any specific medical conditions or therapies to have a significant influence on periapical healing following retreatment. The conditions investigated included: diabetes; history of allergic reaction; systemic steroid therapy, long-term antibiotics, thyroxin therapy, hormone replacement therapy; and coronary heart disease. The analyses were however, compromised by the small proportion of patients included with systemic diseases. The authors reported the subjective observation that the rate and pattern of periapical healing were similar amongst teeth within the same patient but could vary substantially between patients. This was though statistically supported by the significant clustering effect of multiple teeth within the same patients in their study (21).

Tooth type

There is a widespread perception amongst dentists that the simpler anatomy of single-rooted teeth makes their management more amenable and their outcomes better and more predictable (110). However, previous studies (14, 18, 20, 21, 26, 28, 31–33, 35, 36) did not find any significant influence of this factor on retreatment outcome. Interestingly, Allen *et al*. (1989) (33) reported that maxillary teeth were associated with a significantly higher success rate compared to mandibular teeth. This difference was, however not significant when only molar teeth were included in the analysis. The importance of controlling the pre-operative status of teeth was demonstrated by Ng *et al*. (In press a) (21). In their uni-variable analyses, tooth/root type were found to have a significant association with success rate but this effect reduced once the analyses were adjusted for presence and size of pre-operative periapical lesion in a multiple regression model. The findings appear to infer that the complex canal anatomy associated with molar teeth does not negatively influence the outcome of root canal retreatment. Perhaps more important is the issue of apical anatomy (111) and its infection (103, 112) which may vary less between tooth types.

Periapical status

The findings on the effect of periapical status on retreatment outcome have been relatively consistent. Teeth with a periapical lesion are associated with significantly lower success rates of retreatment than those without a lesion (11, 14–21, 24, 26, 29, 31, 34, 35, 36, 108,113). Using single variable analysis, a recent meta-analysis (9) and a prospective study (21) have reported a 6–7 fold difference in the odds of success between treatments on teeth with or without a periapical lesion. However, the magnitude of effect was found to be reduced to 2 fold after adjusting the result for other significant prognostic factors (21).

The strategy for handling the data on periapical lesion size may influence the observed effect of periapical lesion size on treatment outcome. Periapical lesion size has been analysed either as a continuous variable (17, 21, 29), or categorized into bands (14, 15, 26, 108). Despite the recording of lesion size by predetermined size bands, the analysis is sometimes further dichotomized for convenience. The thresholds for dichotomization have varied between 2 mm (15) and 5 mm (14, 26, 108) but none of the studies had justified their selection strategy.

Periapical lesion size has been found to have a significant influence on outcome of retreatment (16, 21, 35–37); with higher success rates for smaller lesions. Analysis of the size of lesion as continuous data showed a reduction in the odds of success by 14% for every 1 mm increase in the diameter of the lesion (21). In contrast, some studies (11, 14, 108) have not found a statistically significant difference. The discrepancy in findings could be attributed to lack of statistical power, differences in criteria for success, duration of follow-up, and the nature of dichotomization of the size of lesion for analysis. The sample sizes in two of the studies (11, 108) were insufficient to detect a true effect. The intuitive impression that larger lesions may require longer to heal completely, tends to be corroborated by Sjögren *et al.* (1990) (14) using strict criteria for outcome as well as an extended follow-up period, which found no difference in success rates. The negative influence of large lesion size has a ready and acceptable biological explanation; in that the diversity of bacteria (by number of species and their relative richness) is greater in teeth with larger periapical lesions (114). The infection was more likely to persist in those canals with a higher number of bacteria pre-operatively (115). Larger lesions may represent longer-standing root canal infections that may have penetrated deeper into dentinal tubules and accessory anatomy in the complex canal system (116) where mechanical and chemical decontamination procedures may not readily reach. Larger lesions may also represent cystic transformation, potentially rendering non-

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Other pre-operative clinical signs and symptoms

Most of the other investigated pre-operative factors (pain, tooth tenderness to percussion, soft tissue tenderness to palpation, soft tissue swelling, soft tissue sinus, periodontal probing defect of endodontic origin, root resorption) are in fact different clinical manifestations of periapical disease (21). They may therefore act as surrogate measures or complement "presence and size of periapical lesion" in measuring the effect of severity of periapical disease within a broad continuous spectrum. Of these, only presence of pre-operative pain (15), sinus tract (21) and apical resorption (75) were found to be significant prognostic factors that significantly reduced the success of retreatments. In contrast, Chugal *et al*. (2001) (29) reported that "presence of sinus" did not add any prognostic value to that provided by "presence and size of lesion". The discrepant finding may be attributed to the much smaller sample size (200 teeth, 441 roots) in their study when compared to the data in Ng *et al*. (In press a) (21). Similarly, the "Toronto study" (20, 82) using multiple logistic regression analyses to account for confounding, and limiting their analyses to teeth with apical periodontitis, found that the presence of "pre-operative clinical signs and symptoms" did not influence retreatment outcome. Unfortunately, the factor "clinical signs and symptoms" investigated in the "Toronto study" was not clearly defined and the associated sample sizes were also small.

Interestingly, Ng *et al*. (In press a) (21) reported that although pre-operative swelling was excluded during the building of their final logistic regression model, this factor was found to have prognostic value even when its effect was adjusted for "presence and size of periapical lesion". It may therefore be reasonable to speculate that its presence does indeed have a significant "clinical" prognostic value.

The biological explanation for the negative impact of sinus tract and periapical swelling on periapical healing is interesting to speculate on as both represent suppuration, either in the acute or chronic form. The finding is not readily explained by the type and quantity of the implicated intra-radicular bacteria, which are predominantly Gram-negative and fastidious species (*P. endodontalis, L. buccalis, P. gingivalis, F. nucleatum*) (114, 118–121). These species have not been reported to be resistant to root canal decontamination procedures unless of course they are beyond the reach of the procedure. Other species associated with refractory cases presenting with persistent sinus tracts include *Actinomyces* (122) and other unidentified coccal- and fungi-form micro-organsims (123), which are implicated in extra-radicular infections. A sinus tract may facilitate an alternative nutrient or bacterial supply to maintain both an extra-radicular periapical infection as well as a residual infection in the apical root anatomy, possibly explaining its negative influence on the success of treatment, independent of the presence and size of periapical lesion.

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A conceivable scenario is that suppurative conditions represent proliferation of the apical microbiota into the periapical tissues where they may encounter one of three responses. A compromised immune response may be unable to mount an effective defence response and allow direct penetration and invasion by bacteria into the host (124). A normal immune response consisting of an abundance of PMN infiltration may result in rapid suppuration and a temporary overwhelming of the *local* defences resulting in a swelling (125). A combination of virulent organisms and weakened immune response may lead to a spreading infection, first locally and then through cellulitis to further reaches. This overwhelming of the host defences may also signal the potential for future treatment failure. A third response may consist of an exaggerated host reaction due to immune hypersensitivity, a condition in which there is potential for perpetuation of the host-bacterial interaction and therefore delayed healing or treatment failure (126, 127).

Time interval between primary treatment and retreatment

A persistent radiographic periapical radiolucency without any other clinical signs and symptoms after primary treatment may represent a healing lesion and cannot automatically be regarded as treatment failure without reference to the duration following treatment. The persistence of apical bacterial biofilms even after contemporary intra-canal debridement measures (103) suggests that periapical healing involves an on-going interaction between the host and the microbial flora; the outcome of healing being determined by either the perpetuation or resolution of this interaction. Clinically, it may be hypothesised that the case for failure supposedly increases with the persistence of such an interaction after a follow-up duration of 3 or more years (75). Thus it may seem reasonable to speculate that the longer the interval between primary treatment and retreatment with persistence of the lesion, the greater the risk of failure. However, three studies (18, 20, 33) investigating the effect of this interval on outcome, all concurred that it had no significant effect. Three other studies also provided insight into this problem by virtue of the fact that they limited inclusion of teeth to those that had received primary treatment at least 2 years (35, 36, 108) or 4-5 years (16) previously. Their reported success rates (75%, 62%, 74%, respectively) revealed no obvious trends, providing no direct support for the above speculation. The inference may be that time alone is not the key element in the outcome but the nature of the interaction between the bacteria and the host. This in turn leads to the natural inference that knowledge of the nature of the apical microbiota, the nature of the host response, and the interaction between them may be the keys to future treatment strategies.

Pre-operative canal contents

The success rates of retreatment related to the prior presence of different foreign materials in the root canal system is only reported in two studies (21, 33). One study (33) included surgical retreatment cases (54% of the samples) and found that the presence of pre-operative "cement" root filling material was associated with significantly lower success rates than the presence of "gutta-percha" or "silver point" root filling material. Not unsurprisingly, teeth with separated instruments, pre-operatively, were associated with lower success rates than those with "gutta-percha" root fillings (21). However, Gorni & Gagliani (2004) (19) reported that the success rate of treatment on teeth with pre-operative separated instruments was 96%, which is *on par* with the reported pooled success rate (94%) of retreatment on teeth without apical periodontitis (9). Clinically, the factors, "type of foreign material", "presence of fractured instrument", "fate of foreign material" and lastly, "ability to achieve patency at the canal terminus" are all in the same statistical confounding pathway (21). The study concluded that as long as patency could be achieved at the canal terminus, success of retreatment would not be affected by the type of foreign material whether it was removed or bypassed. In this study (21), only half of the fractured instruments were successfully removed or bypassed, explaining their association with lower success rates. Their finding was consistent with the 49–53% of fractured instrument removal rate by postgraduate students in Athens, Greece (128) or dentists in Wuhan, China (129). Higher rates of instrument removal (87%) (130) and success rates (91%) (19) have been reported by experienced specialists.

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Pre-operative procedural error in canal preparation

Pre-operative procedural errors may impede or complicate retreatment. The errors investigated have included: obstruction, canal morphology alteration (transportation, straightening, stripping), iatrogenic root perforation, or internal resorption (19). The last condition was, obviously unrelated to the previous treatment. They found that success of retreatment was compromised if the root canal morphology was altered unfavourably by the primary treatment (19).

The evidence on the effect of pre-existing perforations is contradictory and may possibly be related to the material used for repair. The occurrence of root perforations was found to compromise the outcome of retreatment significantly by both the Toronto (18, 20) and London Eastman (21) studies, consistent with Gorni & Gagliani (2004) (19). However, on the positive side, Main *et al.* (2004) (131) reported that periradicular radiolucencies associated with pre-existing perforations repaired with mineral trioxide aggregate cement resolved completely in all cases. This finding was in agreement with the latest report from the "Toronto study" (20) comparing perforation repair with MTA® or glass ionomer cement. Unfortunately, the above studies did not analyse further the specific prognostic factors for teeth with perforations. A narrative review (132) concluded that the time lapsed before defect repair, location and size of perforation, and adequacy of perforation seal were reported to be important factors, based on *in vitro* findings, animal studies and one case-series.

<u>Quality of pre-existing root fillings</u>

Persisting apical disease associated with teeth containing radiographically adequate root fillings may be caused by intra-radicular infection, extra-radicular infection, a true cyst, or a foreign body reaction (117). Of these, only the first would respond to non-surgical root canal retreatment (117). Studies (11, 18, 20, 21) comparing the success rates of retreatment on teeth with satisfactory *versus* unsatisfactory pre-existing root fillings have returned conflicting reports. Danin *et al.* (1996) (11) found no significant influence due to the apical extent of pre-existing root fillings but only had a sample size of 18 teeth. This finding was in contrast to the Toronto study (18, 20) where the success rate for teeth with pre-existing root filling with satisfactory length and density was significantly lower (19%–22%). The discrepancy may be attributed to the fact that the latter study used tooth as a unit of outcome assessment, and only included teeth with periapical lesions in the analysis. Two explanations were advanced for the observation by the authors of the Toronto study (18, 20): 1) in teeth with adequate pre-operative root filling, the persisting infection may have been less susceptible to routine retreatment procedures; and 2) the persistent lesion may have been caused by extra-radicular infection, a true cyst or foreign body reaction unresponsive to retreatment. Although Ng *et al.* (In press a) (21) also found that the success rates for roots with satisfactory pre-existing root fillings (absence of voids and extended to within 2 mm of the radiographic apex) were 6% lower than for those with unsatisfactory pre-existing root fillings, the difference was not significant even after adjusting for the presence of a periapical lesion.

Ng *et al.* (In press a) (21) further found that under-extended pre-existing root fillings in teeth with compromised outcomes may be caused by either natural or iatrogenic blockages that could not be negotiated to the apical terminus during retreatment. This was supported by the fact that short root fillings (>2 mm short of canal terminus) after retreatment were 5% more frequently present in roots with unsatisfactory pre-operative root fillings than in roots with satisfactory pre-operative root fillings.

Intra-operative factors

Qualification of operators

Published studies on retreatment outcome have involved operators of different qualification and skill mixes, although the most frequently involved group was undergraduate students (14, 16, 24, 34–36, 113) followed by specialists (11, 15, 17, 26, 28) and then postgraduate students (18–21, 29). The operators in another two studies (33, 37) were a mixed group of dentists (undergraduate & postgraduate students, specialists) and a single dentist, respectively. The outcome of root canal retreatment as influenced by educational and experience background of the operators (specialist *versus* postgraduate students; first *versus* second year postgraduate students) was compared by Ng *et al.* (In press a) (21). They found staff (faculty) members achieved the highest success rates, followed by 2nd year and then 1st year postgraduate students, although the differences were not statistically significant. They reported no obvious influence attributable to differences in morphological tooth type or pre-operative periapical status of the teeth managed by various operator groups. These observations concur with the important influence of the clinical background of operators on the technical outcome of endodontic procedures, demonstrated in laboratory studies (133, 134). Clearly technical skills play an important role but there is a lack of appropriate tools or methodology to objectively quantify operator skills, which include a complex constellation of cognitive, technical and clinical skills. The role of technical refinement must surely be balanced against the overall understanding of the biological problem, and crucially the motivation and integrity with which the procedure is performed.

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Use of rubber dam isolation during treatment

The use of rubber dam in modern root canal treatment is so widely accepted that the absence of systematic data on its influence on root canal treatment outcome comes as a considerable surprise. One study on retreatment (37) had analysed the influence of rubber dam compared to cotton roll isolation and found significantly higher success rates with the former approach. Perhaps as a consequence, the principal justification for rubber dam use is based on medico-legal implications of root canal instrument inhalation by the patient (5).

Use of magnification and illumination

The value of magnification and illumination during root canal treatment has been repeatedly reinforced by endodontists (135) but a recent systematic review failed to draw any objective conclusions on their influence as no article was identified in the current literature that satisfied their inclusion criteria (136). A recent prospective study (21) investigated this factor but found only an insignificant influence on the final outcome. Use of a microscope may assist location of the second mesio-buccal canal in maxillary molars (64%), but this only made a small difference to the success rates associated with mesio-buccal roots when a periapical lesion was present (21). The true benefit of a microscope can only be verified through a randomised controlled trial but nevertheless, the suggestion is quite strong that a microscope is unlikely to make a significant impact on the critical step of apical infection control; since it is not viewable.

Type of instruments for canal preparation

The root canal system may be mechanically prepared to a requisite size and taper (137) using a variety of instruments of different cutting designs, tips, tapers, and materials of construction. Their efficacy is often tested in laboratory studies and the instruments and their utility may have well characterised properties (138). Investigation of the influence of type of instrument used for canal enlargement has been undertaken only in one non-randomised prospective study but the outcome is likely to be confounded by many factors including the protocol adopted for teaching technical skills (21). In this study, the better success rates for hand or rotary NiTi instruments compared with stainless steel instruments (21) were attributable to the fact that tactile skills training was achieved through a preliminary focus on the use of stainless steel files to develop tactile sensitivity and consistency. Only on demonstration of this competency did the trainees progress to NiTi instruments. More importantly, such senior students may also have had a better understanding of the biological rationale for root canal treatment. The ability to gain and maintain apical patency as well as to avoid procedural errors was better instilled in the senior students, whilst in selected cases, NiTi instruments appear capable of achieving the same in primary root canal treatment undertaken by undergraduates (139).

Apical extent of instrumentation

A key tenet of the European Society of Endodontology (2006) guidelines (5) is that root canal debridement must be extended to the terminus of the canal system; which is expressed variously as extension to the "apical constriction", or to "0.5 to 2 mm from the radiographic apex", or to the "cemento-dentinal junction". This guideline is broadly supported by the fact that outcome of retreatment is compromised by canal obstruction or failure to achieve patency to the canal terminus (21, 75, 113). After adjusting the results for periapical status and other significant prognostic factors, Ng *et al.* (In press a) (21) reported a 2-fold reduction in the success of retreatment when the patency to the canal terminus was not achieved. Statistically framed another way, there was a 12% reduction in the odds of success with every millimetre of the canal system from the terminus that remained "un-instrumented" (21). This finding was consistent with that of Chugal *et al.* (2003) (140) who investigated the outcome of *primary* root canal treatment. In contrast, Sjögren *et al.* (1990) (14) and Gorni & Gagliani (2004) (19) reported that the level of instrumentation had no significant influence on the outcome of retreatment on teeth with apical periodontitis. Curiously, Sjögren *et al.* (1990) (14) reported contradictory findings on primary treatment *versus* retreatment that may simply be related to the insufficient sample size in the latter group. It could be speculated that the lack of mechanical negotiability of canals may be due to the presence of obstructions caused by "denticles", tertiary dentine, acute branching or a fine plexus of apical canals, dentine/organic debris, separated instruments or root canal filling material. None of the previous studies distinguished between the various causes of such obstruction. The first four examples of *mechanical* obstruction may still allow irrigants to penetrate apically beyond them during treatment.

During instrumentation, extension of the instruments beyond the canal terminus has been described as "apical disturbance". Bergenholtz *et al.* (1979a) (35) found that the majority of failures occurring among 'cleaned roots' (with apical disturbance) were complicated by overfilling during retreatment. Juxtaposed against this is the observation that the use of "patency filing" to maintain the opening of the canal terminus (a form of apical disturbance, albeit controlled), resulted in an 80% success rate for root canal retreatment based on strict criteria (21).

Apical size of canal preparation

The continued debate on the optimal size of apical preparation remains topical in the absence of definitive evidence: the findings from relevant *in vitro* and clinical studies have been reviewed before (141). So far, four clinical outcome studies have considered the issue or have systematically investigated the effect of apical size of canal preparation (17, 21, 75, 142) on retreatment outcome. Unfortunately, the former three studies (17, 75, 142) did not stratify their analyses by primary treatment and retreatment; furthermore, their data contained only a small proportion of retreatment cases (30%, 9%, 16%, respectively). Although none of the four studies had designed their investigation with apical canal size as their principal focus and neither had they found a statistically significant influence from this factor, all four studies reported the same inverse trend of decreasing success rates with an increase in the size of apical preparation. Ng *et al.* (In press a) (21) reported that their investigation of the influence of apical size of preparation was confounded by their clinical protocol that all canals should be prepared to a minimum ISO size 30, except for cases with very acute or double curvatures. Their adopted protocol further precluded unnecessary over-enlargement of the canal apically beyond ISO size 30. Investigation of the influence of apical size of preparation was therefore further confounded by the initial apical size of the canal before preparation; no further enlargement was recommended for those canals having an initial apical size 30 or larger. It was speculated that canal preparation to larger apical sizes may compromise treatment success by generation of more apical dentine debris, which in the absence of an adequate irrigation regimen serves to block apical canal exits that may still be contaminated with bacteria. Continued generation of dentine debris, in the absence of sufficient irrigation, leads to what is termed “dentine mud” which ultimately creates a blockage. The impatient or neophyte endodontist fails to resist the temptation to force the instrument back to length resulting in the classically described procedural errors of apical transportation, canal straightening and perforation. An alternative mechanism is required to explain the higher failures in initially large canals; it is likely that immature roots present a different debridement challenge, where the canal shape is not amenable to planing of the main portions of the canal by conventional instruments. Perhaps an intracanal brush may be a more suitable cleaning device in such teeth. The findings from the above studies therefore do not concur with views that more effective bacterial debridement may be achieved with larger apical preparations (143–145).

Taper of canal preparation

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The issue of apical preparation size should be considered together with that of the size and taper of the rest of the canal preparation. Again, there is a paucity of sufficient direct evidence for the influence of degree of canal taper on root canal treatment outcome. The ESE guidelines (5) recommend only that canal preparation should be tapered from crown to apex without stipulating any particular degree of taper. Three studies have analysed the influence of canal preparation taper on primary treatment and retreatment outcome, although again, none had focussed their investigation on this factor (17, 21, 146) and only Ng *et al.* (In press a) (21) had stratified their analyses for primary treatment and retreatment. Smith *et al.* (1993) (146) using loose criteria for determination of success, found that a "flared" preparation (wide taper) resulted in a significantly higher success rate compared with a "conical" preparation (narrow taper); the exact degree of taper was not reported and the effects of confounders were not controlled. In contrast, Hoskinson *et al.* (2002) (17) and Ng *et al.* (In press a) (21) using strict criteria, did not find any significant difference in treatment outcome between narrow (.05) and wide (.10) canal tapers. The controlled use of stainless steel instruments in a step-back technique may create .05 (1 mm step back) or .10 (0.5 mm step back) tapers, although, of course, uncontrolled use of such instruments may generate a variety of shapes. Ng *et al.* (In press a) (21) also compared these (.05 & .10) preparation tapers with .02, .04, .06, and .08, tapers (generally achieved by using greater taper nickel-titanium instruments) and found no significant effect on treatment outcome. They cautioned that their investigation of the influence of canal preparation taper without randomisation could be confounded by the initial size of canal, type of instrument used and operator experience.

Triangulation of the data on the effects of canal preparation size and taper on re-treatment outcome, may intuitively lead to the conclusion that as far as current best evidence indicates, it is not necessary to over-enlarge the canal to achieve periapical healing. An apical preparation size of ISO 30 with a .05 taper for stainless steel instrumentation or .06 taper for NiTi instrumentation is sufficient. Precisely what biological and hydrodynamic mechanisms underpin such sufficiency is more difficult to define. Although a number of laboratory studies (147–149) have investigated the interaction between canal dimensions and irrigation or obturation dynamics, the precise physical, chemical or biological mechanisms that ultimately enable periapical healing remain unknown, although collaborations with fluid dynamics specialists (149) and (micro)biologists (23) may ultimately yield a clearer picture.

Technical errors during canal preparation

Procedural errors during root canal preparation include canal blockage, ledge formation, apical zipping and transportation, straightening of canal curvature, tooth or root perforation at the pulp chamber or radicular level, and separation of instruments. Of these, the effects of changes in canal shape (ledge formation, apical zipping and transportation) have not been specifically investigated and reported, whilst the effect of canal blockage was explored in the previous section (*Apical extent of canal preparation*). This section discusses the effect of iatrogenic perforation and instrument separation.

Root canal retreatments with iatrogenic perforations may result in significantly lower success rates (21, 32). However, one study (32) had pooled their data on iatrogenic perforations, instrument separation and inter-appointment flare-up for analysis, confusing the cause of the reduced success rate. The factors affecting the outcome of management of perforations were discussed previously (*Pre-operative procedural error in canal preparation)*.

Instrument separation during retreatment has been found to reduce the success rate significantly (21, 32, 75), however, the reported prevalence of instrument separation was very low (0.5 – 0.9%) in these studies precluding an analysis of causative factors (21, 32). A case-control study (31) compared teeth with retained separated instruments after primary treatment or retreatment performed by endodontists with those without such retained separated instrument as controls; amongst the teeth with periapical lesions, the success rate of teeth with retained instruments was 6% lower than the controls but in statistical terms not significantly. The stage of canal debridement at which instrument separation occurred and the justification for their retention may have implications on the outcome but these issues were not discussed in their paper. The corono-apical location of a separated instrument and whether the instrument was successfully bypassed were found to have no effect on treatment outcome. The number of cases with instruments at the various corono-apical levels in the canal was small and unevenly distributed; therefore the statistical power may have been insufficient. In their report, retained instruments were most prevalent in the apical third (77%). This was consistent with the findings from another study, that overall, separated NiTi-instrument removal-rate was 53%; the favourable factors for removal were straight root canals, anterior teeth, location coronal to the canal curvature, fragments longer than 5 mm and hand NiTi K-files (129). Unfortunately, these findings were not correlated with periapical healing.

Irrigant

Different chemical agents have been used as irrigants for root canal treatment, singly or in various combinations, both in clinical practice and in the studies reviewed. They have included solutions of: water, saline, local anaesthetic, sodium hypochlorite, iodine, chloramine, sulphuric acid, EDTA, hydrogen peroxide, organic acid, Savlon®, urea peroxide and a quaternary ammonium compound (Biosept®) (9). Most of the studies had used sodium hypochlorite as an irrigant (9, 150) regardless of whether it was primary treatment or retreatment. This is consistent with the ESE guidelines (5) for irrigation which recommends a solution possessing disinfectant and tissue-dissolving properties.

A recent prospective study (21) systematically investigated the effect of the irrigant on the success rates of root canal retreatment, which although not a randomized controlled trial, revealed interesting new findings on the effects of irrigants. Whilst a higher concentration of sodium hypochlorite made negligible difference to treatment outcome, the additional use of other specific irrigants had a significant influence on success rates (21). The finding of a lack of improvement in periapical healing with the use of a higher concentration NaOCl solution is consistent with previous clinical/microbiological findings (151, 152). Comparing 0.5% to 5.0% NaOCl solution for irrigation, it was found that concentration of solution, *per se*, did not appear to increase the proportion of teeth, either rendered culture-negative (151) or associated with periapical healing (152). As iodine and sodium hypochlorite are both halogen-releasing agents and attack common key protein groups (153), the finding that the additional use of 10% povidone-iodine for irrigation had no additional influence on treatment success was as expected. Surprisingly, however, the additional use of 0.2% chlorhexidine solution for irrigation was found to *reduce* the success of treatment significantly (21). This finding was in complete contrast to previous reports (154, 155) on its equivalent or superior *in vivo* antibacterial efficacy when compared with sodium hypochlorite solution. The use of chlorhexidine as a final irrigant following sodium hypochlorite irrigation had been recommended some years ago (156) and was justified on several grounds, including its substantivity in root dentine (157), relative lack of toxicity (158) and broad-spectrum efficacy (153). Not until recently, has alternate irrigation with sodium hypochlorite and chlorhexidine solution raised serious concerns because of their interaction product. The interaction product is an insoluble precipitate containing para-chloro-aniline, which is cytotoxic and carcinogenic (159, 160). Apart from mutually depleting the active moiety in the two solutions for bacterial inactivation, the precipitate may cause persistent irritation to the periapical tissue, and block dentinal tubules and accessory anatomy, possibly explaining the observed lower success rate when chlorhexidine was used as an additional irrigant.

Ng *et al*. (In press a) (21) also found that the additional use of EDTA had a profound effect on improving radiographically observed periapical healing associated with root canal retreatment (OR = 2.3 [1.4, 3.8]). The observed synergistic effect of sodium hypochlorite and EDTA had been previously demonstrated in terms of bacterial load reduction (161) but not periapical healing. The long term (≥ 2 years) outcome of their cases stratified by canal disinfection protocols (Byström's PhD thesis 1986) (162) did not support their microbiological findings. Their reported success rate for alternate irrigation with sodium hypochlorite and EDTA solutions (67%) was low when compared to the success rate for irrigation using saline (91%), 0.5% sodium hypochlorite (92%) or 5% sodium hypochlorite (86%) solutions (162). The reported outcome data were unexpected as pre-obturation negative bacterial culture was achieved in all cases. Given the complexity of their study design (clinical and microbiologic), their sample size was restricted to 11–15 teeth per group limiting their outcome data. The synergistic effect of the two disinfectants has been attributed to the chelating properties of the sodium salts of EDTA and their roles have been reviewed by Zehnder (2006) (163). EDTA solution assists negotiation of narrow or sclerosed canals by demineralisation of root dentine and helps removal of compacted debris from non-instrumented canal anatomy. It may also facilitate deeper penetration of sodium hypochlorite solution into dentine by opening dentinal tubules and removing the smear layer from the instrumented surface, and lastly may help detach or breakup biofilms adhering to root canal walls (150). In retreatment cases, the previously instrumented canals may contain *contaminated* debris, smear layer, un-negotiable calcifications or iatrogenic blockages, and lastly contaminated filling materials. The additional use of EDTA irrigation may help by aiding removal of such contaminated materials, and opening up accessory anatomy and blocked canal exits.

Medicament

Most previous retreatment outcome studies have not standardised the type of root canal medicament used in the inter-appointment period, but the use of a number of medicaments has been reported. The list was consistent with that recommended in the ESE guidelines for a medicament with disinfectant properties and included: calcium hydroxide, creosote, and iodine solutions (9). However, there is an absence of studies investigating the influence of this factor on retreatment outcome.

Recently, the use of a mixture of calcium hydroxide and chlorhexidine has been tested based on the speculation that the mixture would be more effective against *E. faecalis* (164–166). The rate of complete healing after retreatment using this medicament was 64% (167) which is much lower than the previously reported pooled success rate of 77% (9).

Root canal bacterial culture results prior to obturation

In the distant past, in various centres of endodontic excellence, completion of root canal treatment by obturation would only be triggered by a negative culture test result confirming absence of bacteria in the sample-able part of the root canal system (168–170). This practice has, unfortunately, fallen out of clinical favour because of the perceived predictability and good prognosis of root canal treatment without microbiological sampling. Sampling procedures are considered lengthy, difficult, inaccurate, requiring laboratory support and having low benefit/cost ratio (171, 172).

At the time of writing, data on the effect of culture results on retreatment were only available from two studies (16, 113). Results of meta-analyses of their data showed that canals with negative culture results prior to obturation were associated with 57% higher success rates than those with positive culture results (odds ratio = 4.3–4.8) but the difference was not statistically significant regardless of whether the analyses were restricted to the data on teeth with pre-operative periapical lesion or not (9).

Root filling material and technique

The inter-relationship between the core root filling material, sealer (for filling the gaps between the core material and canal surface) and technique for their placement, complicates the investigation of the effect of root filling material and technique on treatment outcome. In previous studies on retreatment outcome, the most commonly used core root filling material was gutta-percha with various types of sealer or gutta-percha softened in chloroform (chloropercha) (9). The sealers used may be classified into zinc oxide eugenol-based, glass ionomer-based and resin-based types (9).

Two studies investigating the effects of root filling material and placement techniques on retreatment outcome, found no significant influence attributable to these factors (15, 75). The effect of sealer on the outcome of retreatment has not been specifically investigated (9).

Cold lateral compaction, as one of the most established and widely accepted technique for placement of gutta-percha root filling material is normally used as the control group for comparison with other techniques. Van Nieuwenhuysen *et al.* (1994) (37) found that the use of a single-cone technique was associated with a lower success rate, whilst the use of warm vertical compaction achieved similar healing rates for retreatment in the “Toronto study” (18, 20) as well as in the “London

Eastman study" (21). In the context of retreatment, there is a lack of firm evidence to support the view that the putatively improved filling of the irregular canal space using thermoplasticised gutta-percha placement would have a substantially beneficial influence on treatment outcome.

Apical extent of root filling

Of the many intra-operative factors, this has been the most frequently and thoroughly investigated, presumably because it offers a readily measurable outcome, retrospectively. In these previous studies, the apical extent of root fillings has been classified into three categories for statistical analyses: more than 2 mm short of radiographic apex (short), 0–2 mm within the radiographic apex (flush) and extended beyond the radiographic apex (long) (9). The rationale for this stratification has not been specifically justified in previous studies but it is possible to offer a rational explanation based on average length measurements of root-end anatomy. Some studies have defined acceptable apical extension of root filling material as that ending within 1 mm of the radiographic apex (flush) (142). Friedman's group dichotomized apical extension into adequate (flush) and inadequate (short or long) categories (15, 18, 20). The adoption of radiographic root apex as the reference for measuring the apical extent of root fillings has been criticized because of the poor correlation between the location of this point and the terminus of the canal (173). The London Eastman study (21), instead used the location of canal terminus determined by electronic apex locators (EALs) as the reference point (EAL 'zero' reading).

Without stratifying the analysis by the presence of periapical lesion, the apical extent of root filling was found to have a significant influence on the success rates of retreatment in a recent systematic review (9) and prospective study (21). Flush root fillings were associated with the highest success rates (15, 18, 20, 21, 75), whilst long root fillings (24, 35, 36, 113) were associated with the lowest success rates. However, no significant difference in success rates of retreatments was found between teeth with short or long root fillings, regardless of whether the results were adjusted for the presence of pre-operative periapical lesion (21).

Curiously, whilst Sjögren *et al.* (1990) (14) found the extent of root filling to have a significant influence on outcome of primary treatment on teeth with periapical lesions, they did not find such a relationship for retreatment. The reported lack of statistical significance may have been due to insufficient sample size (204 roots undergoing primary treatment; 94 roots undergoing retreatment). The authors stressed that all cases with short root fillings and pre-operative periapical lesions were classified amongst those that could not be instrumented to their full length. It was also noted that the retreatment cases with flush root fillings (67%) were associated with a much lower success rate than their primary treatment (94%) counterparts. It could be speculated that the canal termini in retreatment cases may have been blocked by dentine and pulpal debris during the primary treatment. Perhaps, given this complication, a direct comparison between flush root fillings in primary treatment and retreatment cases may require different evaluation measures, possibly involving the use of electronic apex locators, although the different behaviour of EALs under these circumstances should be borne in mind (174).

Conflicting findings were reported on the effect of apical extent of root fillings from the different phases of the "Toronto study" on outcomes of retreatment on teeth with periapical lesions. When the apical extent of root fillings were categorized into short, flush and long, they were found to have no significant effect on treatment outcome (18). A significant association was, however found after combining long and short root-fillings into one category under the label of "inadequate" root filling (18). The odds ratio for adequate root fillings (OR = 6.8; 95% CI: 1.2, 38.6) based on the data from phases 1&2 of their study (18) had a very wide confidence interval, indicating imprecision in the estimation. In contrast, when data from phases 1–2 (18) and phases 3–4 (20) of the Toronto study were pooled for analyses, this relationship was no longer statistically significant. This illustrates the potential for spurious results obtained from analyses using relatively small sample sizes. The use of "tooth" as unit of assessment may also render analyses of this root-level variable problematic.

The previous, mostly retrospective studies did not and could not distinguish between the effects of apical extent of instrumentation *versus* the apical extent of obturation. The London Eastman study (21) was able to separate the effect of these two factors and found them both to independently and significantly affect periapical healing. The factors did though correlate with each other, consistent with the fact that canals are normally filled to the same extent as canal preparation. A single measure "apical extent of root filling" could therefore inform about both the apical extent of canal cleaning, as well as obturation, except when there is overextension of instruments or extrusion of cleaning agents during canal preparation without root filling extrusion or root filling material extrusion during obturation without apical disturbance during preparation.

Extrusion of cleaning, medication or filling materials beyond the apical terminus into the surrounding tissues may result in delayed healing or even treatment failure due to a foreign body reaction (175–178). Magnesium and silicon from the talc-contaminated extruded gutta-percha were found to induce a foreign body reaction, resulting in treatment failure (176). An animal study has shown that large pieces of subcutaneously implanted gutta-percha in guinea pigs were well encapsulated in collagenous capsules, but fine particles of gutta-percha induced an intense, localised tissue response (178). The inference that perhaps extrusion of large pieces of gutta-percha may not impact on periapical healing was not supported by data from previous studies (21, 24, 35, 36, 113). The discrepancy may possibly be accounted for by bacterial contamination of the extruded gutta-percha in the clinical data.

Radiographic evidence of “sealer puffs” extruding through the main apical foramina and lateral/accessory canals has been pursued with vigour in the strong and undaunted belief of its value as “good practice” by some endodontists. Their perception is that this sign is a surrogate measure of root canal system cleanliness (179) and ardently argue that healing would follow, albeit with some delay. The published evidence on the effects of sealer extrusion into the periapical tissues has been contradictory. Friedman *et al.* (1995) (15) who did not stratify their analyses for primary treatment and retreatment, found that extrusion of a glass ionomer-based sealer significantly reduced success rates. In contrast, Ng *et al.* (In press a) (21) reported that extrusion of a zinc oxide eugenol based-sealer had no significant effect on periapical healing. The discrepancy may be attributed to the difference in sealer type and the duration of treatment follow-up: 6–18 months by Friedman *et al.* (1995) (15) compared with 24–48 months by Ng *et al.* (In press a) (21). The radiographic assessment of the presence or resorption of sealer may be complicated by the radiolucent property of its basic components and the insufficient sensitivity of the radiographic method to detect small traces of it (21). It is possible that in some cases, the radiographic disappearance of extruded sealer may simply be due to resorption of the radio-opaque additive, barium sulphate or its uptake by macrophages, still resident in the vicinity (176).

A mixed sample of primary treatment and retreatment cases showed that extruded glass ionomer-based (15), zinc oxide eugenol-based (180), silicone-based (180) sealers or Endomethasone® (181) were not found to be resorbed/absorbed by periapical tissues after one year. Traces of calcium hydroxide-based sealer (Sealapex®) could still be detected after three years (182). In the latter study, treatments were carried out on primary molar teeth and the canals were obturated with Sealapex® without gutta-percha. With longer duration of follow-up, complete resorption of extruded zinc-oxide eugenol-based sealers (Procosol®, Roth Elite®) (183) and a resin-based sealer (AH Plus, Dentsply/DeTrey, Konstanz, Germany) (184) was demonstrated in 69% and 45%, of the cases after 4 and 5 years, respectively. Extruded zinc oxide eugenol-based sealer was radiographically detectable in 65% of retreatment cases after 2–4 years (21).

Ng *et al.* (In press a) (21) advanced two explanations for the difference between the effect of extruded core gutta-percha and zinc oxide/eugenol sealer: the latter is antibacterial and may kill residual microorganisms, whilst it is also more soluble and readily removed by host cells compared to gutta-percha.

Quality of root filling

Another much investigated parameter of obturation in retrospective studies has been the radiographic measure of "quality of root filling". The rationale for complete obturation of the root canal system is to prevent re-contamination by colonization from the residual infection or newly invading bacteria. Both are putatively prevented by a "tight" seal with the canal wall and an absence of voids within the body of the material. Quality of root filling may therefore be regarded either as poor root filling technique or as a surrogate measure of the quality of the entire root canal treatment, since good obturation is reliant upon properly executed preliminary steps in canal preparation. A recent systematic review (9) reported that the criteria for judging the quality of root fillings have not been well defined in previous studies (14, 17, 18, 37). An unsatisfactory root filling has been defined as "inadequate seal", "poor apical seal" or "radiographic presence of voids"; whilst Van Nieuwenhuysen *et al*. (1994) (37) also considered the apical extent of the root filling. This subjective assessment has not been standardized or calibrated, nor tested for variability in assessment by inter- and intra-observer agreement. Nevertheless, satisfactory root fillings *were* found to be associated with significantly higher success rates than unsatisfactory root fillings for retreatment (14, 18, 37). A recent prospective study with only a small proportion (0.5%) of cases with voids within the apical 5 mm of the root fillings, reported that the influence of this factor on retreatment outcome could not be analysed (21).

Acute exacerbation during treatment

The aetiological factors for inter-appointment "flare-up" or pain have not been precisely determined and several hypothetical mechanisms involving chemical, mechanical or microbial injury to the periradicular tissues, as well as psychological influences have been suggested as contributory to post-preparation pain (126, 127). Although this factor has not been specifically studied in the context of periapical healing, acute "flare-ups" during primary root canal treatment or retreatment (data not stratified) were not found to be significantly associated with periapical healing in two studies (14, 142). In contrast, the London Eastman study (21) found that pain or swelling occurred in 18% of retreatment cases after chemo-mechanical debridement, and was found to significantly reduce success as measured by periapical healing. This interesting finding may be explained by the hypothesis that “flare-ups” were caused by extrusion of contaminated material during canal preparation. Such material may elicit a foreign body reaction or (transient) extra-radicular infection, resulting in treatment failure in a proportion of such cases. Alternatively, acute symptoms may be the result of incomplete chemo-mechanical debridement at the first appointment leading to a shift in canal microbial ecology favouring the growth of more virulent micro-organisms and thence leading to post-preparation pain and treatment failure. The exact biological mechanisms of failure in these cases remain obscure and warrant further investigation.

Number of treatment visits

The effect of number of treatment visits on periapical healing remains an on-going controversy, fuelled by debate between specialists and dentists arguing for single visit treatment on the basis of cost-effectiveness and business sense against academics and some specialists arguing for multiple visit treatments, based on biological rationale (185). The main thread of argument for multiple visit treatments has been that primary debridement is not completely effective in eliminating all the adherent bacterial biofilm (103) and the residual bacteria may multiply and recolonise the canal system (161, 162). It is therefore considered desirable to use the inter-appointment period to dress the canal with a long-lasting or slow-release antibacterial agent capable of destroying or incapacitating residual bacteria, as well as to take the opportunity to gauge the initial periapical response before root filling. Calcium hydroxide has served in this capacity for many years because of its ability to dissolve organic tissue, kill bacteria, detoxify antigenic material and act as a slow release agent because of its low solubility-product in an aqueous environment. However, its antibacterial ability has come under close scrutiny recently, with advocates suggesting that the material is not suitable for purpose (186). A final resolution to this debate is awaited based on robust clinical evidence.

A recent systematic review on outcome of root canal retreatment reported that most previous studies on periapical healing outcome have performed all treatment over multiple visits (9). Only three studies compared the success rates of single- and multiple-visit *re*treatments (18, 20, 37). Van Nieuwenhuysen *et al.* (1994) (37) found that the outcome of retreatment was significantly improved by multiple visits and better still if the canal preparation and disinfection were completed in the first visit. The data analyses from Phases 1 & 2 and Phases 3 & 4 of the “Toronto study” (18,

20) gave contradictory outcomes. The former (18) did not reveal any significant difference but the latter (20) found single-visit treatments to be associated with significantly higher "healed" rates.

The debate about the merits of single or multiple visit treatments will continue unabated given the respective strengths of the motivational drivers amongst the opposing groups. The issue may only be resolved by properly documented, large randomised controlled trials (which are currently unavailable) because unrecorded confounders (operator skill, biological or technical case complexity and patient compliance) underlying the factor "number of treatment visits" would continue to play out their biasing effect in non-randomised studies.

Post-operative (root canal treatment) factors

Quality and type of coronal restoration after root canal treatment

The placement of a coronal restoration after root filling is the final step in the management of teeth undergoing root canal retreatment. Its importance was supported by the results of a systematic review and meta-analysis (9) which pooled data from 2 studies (17, 18). Teeth with satisfactory coronal restorations were found to have significantly better periapical healing compared with those with unsatisfactory restorations (OR = 3.31; 95% CI: 1.07, 10.30) (9). The term "satisfactory restorations" has only been defined in one study (17): a restoration with no evidence of marginal discrepancy, discolouration or recurrent caries with absence of a history of decementation.

Given that one of the roles of coronal restorations is to prevent post-operative root canal re-infection, the criteria for unsatisfactory restoration given in Hoskinson *et al.* (2002) (17) could not infer coronal leakage when the inner core was still intact. Consequently, the London Eastman study (21) adopted a different classification and definition for unsatisfactory restorations in order to depict obvious and potential coronal leakage more effectively. The two groups of unsatisfactory restorations were defined as those with: 1) obvious signs of exposed root filling; and 2) potential leakage indicated by marginal defects and history of de-cementation. It is perhaps this strategy that contributed to the finding of an extremely profound effect (OR = 10.7; 95% CI: 3.7, 31.5) of this factor on the outcome.

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A number of investigations have been performed based on comparisons between the types of post-root canal treatment restorations, including: permanent versus temporary restorations (15, 18, 20, 21, 33); crown versus plastic restorations

(14, 15, 20, 21); presence versus absence of posts (15); and non-abutment versus abutment (14, 21). Teeth that had been permanently restored were associated with significantly higher success rates than their temporarily restored counterparts in some studies (15, 18, 33) but not in others (21, 187). The *type* of permanent restoration (14, 15, 20, 21) was found to have no significant influence on the outcome of retreatment. Two studies (21, 187) reported that the type of restoration (temporary *versus* permanent) had no significant influence on periapical healing after adjusting the results for pre-operative periapical status. This observation may be attributed to the underlying reasons for delaying the placement of permanent restorations by dentist or patient. The reasons include the fact that: 1) these teeth may be associated with persistent signs or symptoms of persistent apical periodontitis following treatment; or 2) some referring dentists may defer placement of final restoration on teeth with pre-operative periapical lesion until there is radiographic evidence of periapical healing.

It has often been recommended that it would be wise to provide a sub-seal over the root filling in case of loss of a permanent or temporary restoration; the sub-seal would be glass ionomer (GIC) or zinc oxide eugenol cement (188–191). The placement of a GIC or zinc oxide eugenol (IRM®) cement lining coronal to the gutta-percha filling and underneath the permanent core in order to provide additional antibacterial coronal seal, was found to have no beneficial effect on treatment success in a prospective study (21).

In summary, the above findings overall support the ESE guidelines (5) that an adequate restoration *should be placed* after root canal treatment to prevent subsequent bacterial recontamination. Therefore the provision of a good quality coronal restoration, regardless of type, should be considered the final part of the root canal treatment procedure following obturation.

Use of root treated teeth as abutments for prostheses and occlusal contacts

Mechanical stress on teeth is a function of their role in restorations as well as the pattern of occlusal loading both in static and dynamic occlusion, i.e., whether teeth are involved as single units or bridge/denture abutments and whether they have holding or guiding contacts. It is reasonable to expect that bridge and denture abutments may be placed under unfavourable loads, as may last-standing teeth in the dental arch (192, 193). Such teeth may therefore be expected to have lower success rates through development of cracks and fractures due to fatigue. Although this observation has been confirmed for teeth functioning as bridge abutments compared with those restored as individual units following primary root canal treatment (14), such a relationship has not been specifically investigated in retreatment cases.

Outcome of root canal retreatment using tooth survival as the measure of success

A systematic review of 14 studies published between 1993 and 2007, on tooth survival following non-surgical root canal treatment (194), identified only two studies (45, 86) that had included some cases undergoing retreatment, the other 12 studies had only investigated primary root canal treatment. A further two studies (22, 93) specifically evaluating tooth survival following retreatment have been published since the systematic review. The former (93) included a large cohort of teeth (n=4744) on which the retreatments were performed by endodontists participating in the Delta Dental Insurance plan, a scheme that insures approximately 15 million individuals in the USA. The latter study (22) had included a smaller cohort (n=858 teeth) in whom the retreatments were provided by endodontic postgraduate students (UCL Eastman Dental Institute, London, UK). Their data were prospectively collected to evaluate the outcome of root canal treatment. The two studies reported that 89% (93) and 95% (22) of teeth had survived 5 or 4 years following retreatment, respectively. Most of the lost teeth had been extracted within 2–3 years following retreatment (22, 93). These figures are similar to the pooled two to ten year survival rates for primary treatment (87%–97%) (194). A prospective study (22) found no significant difference in the 4 year survival rates between teeth undergoing primary treatment (95.3%) or retreatment (95.4%). The two types of treatments also shared the same set of prognostic factors for tooth survival (22). The most common reasons for tooth extraction following retreatment were: persistent clinical signs and symptoms (39%); tooth or root fracture (29%); and failure of coronal restoration (22%) (22).

Overview of prognostic factors for tooth survival following root canal re-treatment

A search of the literature identified only one study to have systematically investigated the prognostic factors for tooth survival after root canal retreatment (22). The problem even in this sole study was that the investigation was compromised by the low event rate (small proportion of teeth extracted during the study period); nevertheless some investigations were possible and are reported below.

Patient factors

Ng *et al*. (In press b) (22) found that teeth in patients suffering from diabetes or receiving systemic steroid therapy had a higher chance of being extracted after retreatment. The negative influence of diabetes on tooth survival is consistent with the report by Mindiola *et al*. (2006) (195), whilst the influence of steroid therapy had never been reported previously. It may be argued that patients suffering from diabetes were more susceptible to periodontal disease (196) or had a lower success rate of root canal treatment (30), which in turn could be the reason for tooth extraction. They however reported that over 50% of such teeth were extracted due to persistent pain. Some of these observations may be explained by the presence of neuropathy, a debilitating painful complication of diabetes (197). It was further, interesting to note that systemic steroid therapy is often prescribed to control such chronic pain (198–200).

Tooth morphological type and location

Tooth types may vary in susceptibility to tooth fracture, a common reason for tooth loss after treatment. Ng *et al*. (22) however, found that tooth *type* had no significant influence on survival. Maxillary premolars and mandibular molars were found to have the highest frequency of extraction, with tooth fracture being the most common reason. The observation is consistent with previous reports on fracture incidence of maxillary premolars and mandibular molars (201, 202). The factors, "proximal contacts" and "terminal (last standing) teeth" were found to affect tooth survival significantly by Ng *et al*. (22), but were significantly correlated to "molar teeth". Most of the extractions of terminal teeth or teeth with one or less proximal contact were due to tooth fracture. The observation may be explained by the unfavourable distribution of occlusal force and higher non-axial stress on terminal teeth and those with less than 2 proximal contacts. Other possible reasons explaining their higher rate of loss are that: 1) failure of root canal treatment on a terminal tooth may be accepted more willingly because of little perceived aesthetic value; 2) clinicians may be less likely to offer further treatment on terminal molar teeth due to difficult access. It therefore seems important to ensure favourable distribution of occlusal forces when designing restorations for molar teeth, teeth with one or less adjacent teeth, and terminal teeth following retreatment.

Pre-operative conditions of teeth

The presence of pre-operative periapical lesions, which is the most significant prognostic factor for periapical healing, was found to have no significant influence on tooth survival (22). On the other hand, pre-operative periodontal probing defects of endodontic origin, pre-operative pain and pre-operative sinus tracts, were found to reduce tooth survival (22). These observations are consistent with a previous report that the mere presence of a periapical lesion was not a sufficient reason for dentists and patients to opt for active treatment (203). The negative impact of pre-operative pain on survival outcome, highlights the importance of accurate pain diagnosis. In some instances, the pain may be of non-endodontic origin, and therefore persist after re-treatment (70). In other instances, pre-operative pain of endodontic origin may persist following treatment, as a result of peripheral or central sensitisation. Therefore effective pain diagnosis and management for patients presenting with pre-operative pain are crucial.

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The presence of pre-operative cervical resorption and perforation were also found to significantly reduce tooth survival (22). This was as expected because tooth fracture and re-infection due to leakage are likely sequelae in such cases. In the presence of re-infection, clinicians are more inclined to suggest extraction due to the intuitive perception of poor long-term prognosis of such teeth.

Intra-operative factors

Amongst all the intra-operative factors, “lack of patency at apical foramen” and “extrusion of gutta-percha root filling” were found to reduce tooth survival (22). They found that extraction of teeth with these conditions was more likely to be due to persistent endodontic problems as both of them were also prognostic factors for treatment success based on periapical healing. In the presence of persistent problems and knowing that the treatment objective of cleaning to the canal terminus could not be achieved, patients and dentists may be more likely to opt for extraction sooner than later.

Post-operative restorative factors

Protection of teeth with crowns or cast restorations had not been found to influence treatment success based on periapical healing although placement of good cores had. In contrast, placement of crowns or cast restorations *was* found to improve tooth survival (22). This suggests that crowns and cast restorations help prevent tooth fracture whilst the mere placement of a satisfactory core would be sufficient to prevent re-infection after treatment. Unfortunately, they were not able to investigate the inter-relationship between tooth morphological type, the extent of tooth tissue loss after treatment and the type of final restoration. Although the direct and injudicious clinical inference from their result is that cast restorations should preferably be placed on all teeth after root canal treatment, this is probably a gross exaggeration of the true need. Fabrication of a full coverage cast restoration requires further removal of tooth tissue from an already weakened tooth. On the basis of laboratory (89, 204) and clinical findings (22), posterior teeth with compromised marginal ridges (mesial or distal), together with evidence of heavy occusal loading evidenced by faceting, may benefit from cast cuspal coverage restorations. The restoration design should attempt to preserve as much remaining tooth tissue as possible; the implication is that the so-called non-aesthetic but technically demanding partial veneer onlays and partial coverage crowns would be the restorations of choice for root treated teeth. In anterior teeth, the missing tooth tissue may often be replaced with plastic adhesive restorative material. A crown is only indicated when intra-radicular retention becomes necessary.

The use of cast post & cores for retention of restorations was also found to reduce tooth survival (22). It may be speculated that the presence of posts has different effects on anterior and posterior teeth as they are subjected to different directions and amount of occlusal force. It was reported that only 12% of the extracted teeth with cast post & cores were incisors or canines. Therefore, the inference is that the use of such retention should be particularly avoided in premolar and molar teeth. Alternative treatment options should therefore be considered for molar or premolar teeth lacking sufficient tooth structure.

Ng *et al.* (In press b) (22) observed that teeth functioning as prosthesis abutments had poorer survival but the number of teeth (n = 94) functioning as abutments was too small in their sample to demonstrate a statistically significant effect. As before, the explanation may reside in the excessive and unfavourable distribution of occlusal stresses on abutment teeth. If possible, root-treated teeth should be avoided as abutments for prostheses or in provision of occlusal guidance in excursive movements.

Concluding remarks

This paper presented a critical appraisal and synthesis of the available literature reporting on the clinical outcome of root canal retreatment and their prognostic factors for periapical healing and tooth survival. The reported findings were analysed, interpreted and synthesized from both clinical and biological perspectives. Current best evidence indicates that the outcome of non-surgical retreatment was only slightly less favourable than that of primary treatment and not significantly different. The factors potentially compromising outcomes are mainly those preventing re-access to the apical anatomy and the residual infection remaining therein. The prognostic factors were similar for primary root canal treatment and retreatment.

Modern techniques and biological awareness contribute to excellent potential outcomes for teeth undergoing root canal retreatment.

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Table 1 Comparison of reported proportion of samples with successful periapical healing based on "tooth" or "root" as the unit of measure

	Percentage of molar teeth	Estimated success rate using tooth as unit measure	Estimated success rate using root as unit measure
Hoskinson *et al.* (2002) (17)	80%	77%	75%
Ng *et al.* (In press a) (21)	50%	77%	81%

Table 2 Criteria for determination of periapical status

Strindberg (1956) (75)	Bender *et al.* (1966a&b) (39, 40)	Friedman & Mor (2004) (41)
Success: ***Clinical:*** No symptoms ***Radiographic:*** The contours, width and structure of the periodontal margin were normal, or The periodontal contours were widened mainly around the excess filling.	**Success:** ***Clinical:*** Absence of pain / swelling Disappearance of fistula No loss of function No evidence of tissue destruction ***Radiographic:*** An eliminated or arrested area of rarefaction after a post-treatment interval of 6 months to 2 years	**Healed:** ***Clinical:*** Normal presentation ***Radiographic:*** Normal presentation
Failure: ***Clinical:*** Presence of symptoms ***Radiographic:*** A decrease in the periradicular rarefaction, or Unchanged periradicular rarefaction, or An appearance of new rarefaction or an increase in the initial rarefaction.		**Diseased:** Radiolucency has emerged or persisted without change, even when the clinical presentation is normal, or Clinical signs or symptoms are present, even if the radiographic presentation is normal.
Uncertain: ***Radiographic:*** There were ambiguous or technically unsatisfactory control radiographs which could not for some reason be repeated; or The tooth was extracted prior to the 3-year follow-up owing to the unsuccessful treatment of another root of the tooth.		**Healing:** ***Clinical:*** Normal presentation ***Radiographic:*** Reduced radiolucency.