Marco Esposito, Luca Sbricoli, Jacopo Buti, Umberto Uccioli, Marco Tallarico

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Randomised controlled trial

ENDODONTIC RETREATMENT OF TEETH WITH UNCERTAIN ENDODONTIC PROGNOSIS *VERSUS* DENTAL IMPLANTS: 5-YEAR RESULTS FROM A RANDOMISED CONTROLLED TRIAL

MARCO ESPOSITO, DDS, PhD
Freelance researcher and Associate Professor, Department of Biomaterials, The Sahlgrenska Academy at Göteborg University, Göteborg, Sweden

LUCA SBRICOLI, DDS, PhD
Researcher, Department of Neurosciences, University of Padua, and private practice in Padua, Italy

JACOPO BUTI, DDS, PhD, MPerio RCSEd
Associate Professor, Unit of Periodontology, UCL Eastman Dental Institute, London, UK

UMBERTO UCCIOLI, DDS
Private practice in Frosinone, Italy

MARCO TALLARICO, DDS, MSc
Private practice in Rome and Adjunct professor, Aldent University, Tirana, Albania

Correspondence to:
Marco Esposito
Casella Postale 34, 20862 Arcore (MB), Italy
E-mail: espositomarco@hotmail.com

PURPOSE. To ascertain whether it is better to endodontically retreat a previously endodontically treated tooth with periapical pathology and/or symptoms and an uncertain prognosis, or to replace the tooth with a single implant-supported crown.

MATERIALS AND METHODS. Twenty patients requiring treatment of a previously endodontically treated tooth with periapical pathology and/or symptoms of endodontic origin and an uncertain prognosis, as judged by the recruiting investigator, were randomly allocated to endodontic retreatment (endo group; 10 patients) or tooth extraction and replacement with an implant-supported crown (implant group; 10 patients) according to a parallel-group design at a single centre. Patients were followed up to 5 years after treatment completion. Outcome measures were: procedure failure; complications; marginal bone level changes at both teeth and implants; radiographic endodontic success (teeth only); number of patient visits and days to complete treatment; chairside time; costs; and aesthetics, as assessed using the pink aesthetic score (PES) for the soft tissues and the white aesthetic score (WES) for the tooth/crown by independent assessors.

RESULTS. One patient from the endo group dropped out. One endodontically retreated tooth fractured. There were no statistically significant differences in treatment failure between groups (difference in proportions = 0.1; 95% CI -0.18 to 0.35; P = 1.00). Three endo group patients had one complication each *versus* one complication in the implant group, the difference not being statistically significant (difference in proportions = 0.2; 95% CI -0.17 to 0.51; P = 0.582). The mean marginal bone levels at endo retreatment/implant insertion were 2.10 ± 0.66 mm for the endo and 0.05 ± 0.15 mm for the implant group. Five years after treatment completion, teeth lost on average 0.60 ± 0.96 mm and implants 0.56 ± 0.77 mm, the difference not being statistically significant (mean difference = -0.05 mm; 95% CI: -0.95 to 0.86; P = 0.914). Of the four teeth that originally showed periapical radiolucency, one was lost, two displayed complete healing, and one showed radiographic improvement. There were no statistically significant differences in the number of patient visits (endo = 6.7 ± 0.7; implant = 6.1 ± 0.7; mean difference = 0.6; 95% CI: -0.1 to 1.3 P = 0.106). However, it took significantly more days (endo = 61 ± 13.0; implant = 191.4 ± 75.0; mean difference = -130.4; 95% CI: -184.5 to -76.4; P < 0.001) but less chairside time (endo = 628 ± 41.4 min; implant = 328.5 ± 196.4 min; mean difference = -299.5; 95% CI: -441.3 to 1.0; P = < 0.001) to complete the rehabilitation. Implant treatment was significantly more expensive (endo = 1440 ± 549.7; implant = 2099 ± 170.3; mean difference = 659; 95% CI: 257.2 to 1060.8; P = 0.004).
Five years after treatment completion, mean PES were 12.3 ± (1.3) and 8.9 ± 2.2 and mean WES were 8.1 ± 1.4 and 7.1 ± 1.7 in the endo group and implant group, respectively. Soft tissues aesthetics (PES) was significantly better at endodontically retreated teeth (mean difference -3.4; 95% CI -5.1 to -1.6; P (t-test) = 0.001), whereas no significant differences were observed between treatments in tooth aesthetics (WES) (mean difference = -1.0; 95% CI -2.6 to 0.5; P (t-test) = 0.178).

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CONCLUSIONS. These results suggest that both endodontic retreatment and replacement of previously endodontically treated teeth with persistant pathology and dubious endodontic prognosis yielded similar medium-term success rates. Soft tissue aesthetics and treatment completion time were better with endodontic retreatment, whereas implant rehabilitation required half the chairside time but was significantly more expensive. Much larger patient populations and longer follow-ups are needed to fully explore this issue, but this study indicated the less invasive endodontic retreatment as the primary therapeutic option.

CONFLICT OF INTEREST STATEMENT. Mozo-Grau/Ticare (Valladolid, Spain), the manufacturer of the implants used in this investigation, donated the implants and partially funded this trial; however, data belonged to the authors and the sponsor did not interfere with the conduct of the trial or the publication of its results in any way.

INTRODUCTION

In the presence of endodontically treated teeth having still a periapical or lateral radiolucency and symptoms of an active endodontic infection, showing an uncertain prognosis because of the complexity of the endodontic retreatment procedures, dentists have to decide whether to retreat the tooth endodontically or to extract it. In case of extraction, various therapeutic options are available, ranging from no treatment to replacement with a removable or fixed prosthesis. For many patients, it is likely that the preferred option would be a fixed prosthesis that restores function and aesthetics; however, it is not clear which is the most cost-effective way of achieving this goal.

Apart from previous publications reporting earlier results of this study[1,2] there have been no randomised controlled trials (RCTs) comparing endodontic retreatment with tooth extraction and replacement with an implant-supported crown. Despite the complete lack of reliable evidence in the literature, several reviews, both systematic and narrative, have been published with the aim of identifying the best treatment alternative[3-6]. In summary, they concluded that both treatments were successful, but further research is required, since no reliable study has been published to date.

In this context, it would be useful to determine whether better clinical outcomes could be achieved by retreating teeth that have already been treated endodontically but display persistent endodontic infection and uncertain prognosis, or whether it would be more beneficial to replace them with implant-supported crowns. Hence, the aim of this RCT was to compare outcome measures in endodontic retreatment *vs.* implant-supported crown in previously endodontically treated teeth with periapical pathology and/or symptoms and an uncertain prognosis up to 10 years after loading. This article, which is reported according to the CONSORT statement to improve the quality of reports of parallel-group randomised trials (http://www.consort-statement.org/), presents the data collected at 5 years of follow-up; previous articles have presented data at 1-[1] and 3-year[2] follow-ups.

MATERIALS AND METHODS

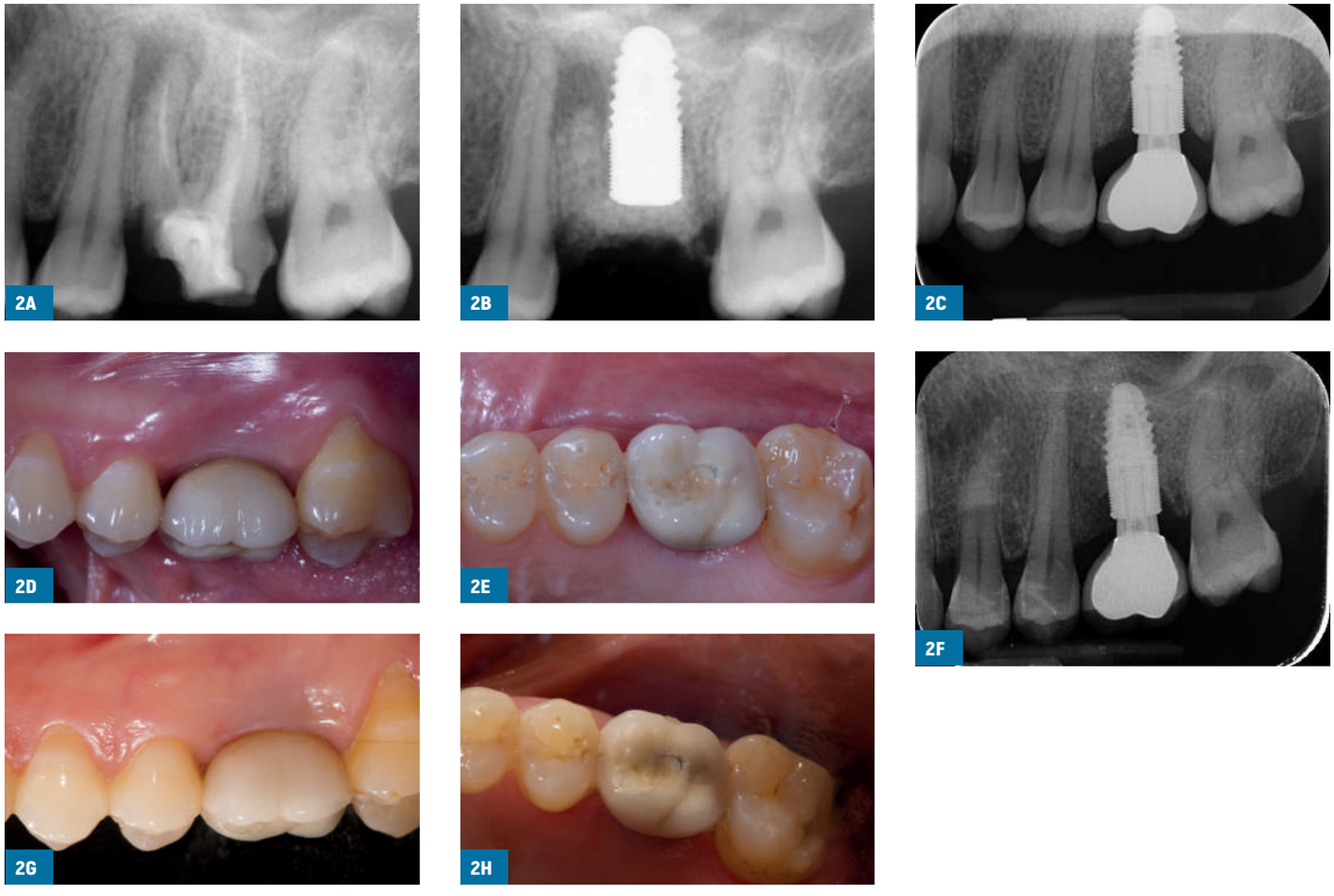
The study was originally designed as a multicentre randomised controlled trial of parallel-group design with two arms and independent outcome assessment when possible (blinding was not possible due to the nature of the trial). Teeth randomised to the endo group were to be endodontically retreated (**FIGS. 1A-G**), whereas teeth allocated to the implant group were to be extracted and replaced by implant-supported crowns (**FIGS. 2A-H**). However,

FIGS. 1A-G: *Treatment sequence of a representative patient randomly allocated to the endodontic retreatment group: preoperative radiograph of maxillary left first molar with inadequate root canal filling and symptomatic apical periodontitis, involving a painful response to biting and percussion. The massive loss of dentine and risk of calcified fourth canal associated with a periapical lesion could possibly affect the prognosis (a); radiograph (b), vestibular (c) and occlusal (d) pictures taken at treatment completion (root canal filling with warm gutta-percha and stratified lithium disilicate crown) used for radiographic and aesthetic evaluation; radiograph at the 5-year checkup showing improvement in the periapical lesion (e); buccal (f) and occlusal (g) views 5 years after treatment completion used for aesthetic evaluation.*

only one of the two centres which provided 1 year data[1] actually provided the 3-[2] and 5-year data, so the trial became reliant on data from a single centre.

Patient selection

Any patient with at least one previously endodontically treated permanent tooth, persistent radiographic pathology and/or symptoms (e.g., pain, fistula, abscess) of endodontic origin and an uncertain prognosis, as judged by the recruiting investigator, who required a crown, inlay or onlay, was to be included in the study. Teeth had to be periodontally healthy, with less than 4 mm of bone loss from the cemento-enamel junction (CEJ), and eligible for rehabilitation as a single unit (not to be included in a fixed prosthesis). Only one tooth per patient was included in the study. Patients had to be at least 18 years old and able to understand and sign informed consent to document that they understood the scope of the study (including procedures, follow-up evaluations, and any potential risks involved). Patients were informed as to the nature of the study, apprised of treatment alternatives, and invited to ask any questions pertaining to the trial. Preoperative periapical radiographs were taken to ascertain the condition of the tooth to be included in the study.



FIGS. 2A-H: *Treatment sequence of a representative patient randomly allocated to the tooth extraction and implant rehabilitation: previously treated maxillary left first molar with incomplete root canal filling involving a painful response to biting and percussion with a large periapical lesion, and underfilled canal with a post at the mesial canal (a); baseline radiograph taken after implant placement and augmentation procedure (b); radiograph taken immediately after delivery of the definitive screw-retained, metal-ceramic crown (c); buccal (d) and occlusal (e) views upon fitting of the definitive crown; periapical radiograph (f); buccal (g) and occlusal (h) views 5 years after treatment completion.*

Exclusion criteria were:

- General contraindications to endodontic/implant treatment;
- Immunosuppressed/immunocompromised status;
- Irradiation of the head and/or neck;
- Uncontrolled diabetes;
- Pregnancy or lactation;
- Any symptomatic tooth whose symptoms were not certainly of endodontic origin;
- Teeth with clear signs of vertical root fracture and scheduled for extraction;
- Untreated periodontal disease and/or mesial or distal bone loss more than 4 mm from CEJ at the study tooth;
- Poor oral hygiene and motivation;
- Addiction to alcohol or drugs;
- Psychiatric problems;
- Unrealistic expectations;

- Wisdom teeth;
- Previous or ongoing treatment with intravenous aminobisphosphonates;
- Referral for endodontic retreatment alone (follow-up could not be carried out at treatment centre);
- Inability to commit to 10-year follow-up;
- Participation in other clinical trials that would interfere with present protocol.

Patients were divided into three groups based on the number of cigarettes they declared smoking per day: non-smokers, moderate smokers (up to 10 cigarettes per day) and heavy smokers (more than 10 cigarettes per day).
Patients were recruited and treated at one single private practice (Dr. Tallarico). Originally, 12 centres agreed to participate in the study, but only two centres actually recruited and treated patients and reported data to 1 year after treatment completion. Unfortunately, only one centre provided the 3- and 5-year data. As per the original protocol, each centre had to treat 20 patients (10 in each group). Having determined that the patient was eligible for this study, and after informed consent was signed, a sequentially numbered envelope containing the treatment option (endodontic retreatment or tooth extraction and placement of an implant-supported crown) was opened and the treatment plan was finalised according to the outcome of the randomization. If the patient decided to withdraw from the study after having been randomly allocated to the treatment, this information was to be recorded together with the reasons for doing so.
The following information had to be recorded prior to commencing treatment:
a) Tooth position and number of root canals;
b) Presence of signs and symptoms
    0 = no symptom
    1 = provoked pain
    2 = spontaneous pain
    3 = fistula
    4 = abscess;
c) Radiographic appearance
    0 = no periapical or lateral lesion
    1 = periapical or lateral lesion;
d) Previous endodontic treatment
    0 = previously filled root with filling looking good on radiographs
    1 = previously filled root with filling looking defective on radiographs (underfilling, overfilling, broken instrument, perforations, calcification, apical stops, stripping, external or internal transportation, internal or external resorption, etc.)

Clinical procedures

Operators were free to treat patients in the way they considered most appropriate. The research protocol did not affect individual operators exerting their preference as regards how to perform endodontic (e.g., non-surgical; in one or multiple sessions; or apicectomies) or implant treatment (e.g., augmentation procedures; immediate post-extraction or delayed implants; flapless implant placement; 1 or 2-stage procedures; immediate, early or conventional loading; healing periods; cemented or screw-retained implant-supported crown, etc.). After random allocation to endodontic retreatment or implant rehabilitation, each investigator was free to choose the treatment considered to be in the best interests of the patient. Ideally, the fastest and simplest treatment procedure, as judged by the treating dentist, was to be pre-

ferred; however, the decision remained in the hands of the individual operator who, based on their experience, clinical need, and patient preference, decided the best course of action on a case-by-case basis.
Patients rinsed with 0.2% chlorhexidine mouthwash for 1 minute prior to any intervention.

Endodontic procedures

Teeth were isolated with a rubber dam and reopened to gain access to the root canal as required. The working length was estimated on a periapical radiograph. Root canal posts, when present, were removed using ultrasound instruments or a bur, attempting to limit dentine removal. If there were fractured endodontic instruments in the canal, they were removed with ultrasound tools or, if this was not possible, they were bypassed. Obturation material was removed manually or mechanically using appropriate solvents for gutta-percha or cement. Once the correct working length had been determined using an apex locator and/or periapical radiograph, the canal was prepared using manual stainless steel instruments or rotating nickel-titanium instruments, attempting to prepare within 2 mm from the radiographic apex. When probing did not reach the apex, the canal was to be prepared to as great a depth as possible. Canals were irrigated with 5% sodium hypochlorite, with or without the aid of an ultrasound device. Ethylenediaminetetraacetic acid (EDTA) was used, especially in calcified canals. If the anatomy of the canal had been altered by previous treatments, manual h-files, k-files and Gates Glidden drills were used as required. Operators were free to decide whether to close the canals in the same session or after medication with calcium hydroxide for one week. Before closing the canals, they were cleaned with 17% liquid EDTA to remove the dentine smear. After a final cleaning with 5% sodium hypochlorite, canals were dried with standard sterile paper cones. Root canals were filled with gutta-percha cones tipped in cement according to the technique preferred by the operator - either with warm or cold lateral condensation or with vertical warm condensation. In the event of perforation, the area was to be cleaned and closed with either mineral trioxide aggregate (MTA) or eugenol-zinc oxide cement, before or after canal obturation. Teeth were to be reconstructed as soon as possible, and their access cavity definitively obturated within 2 weeks to minimise the risk of tooth fracture.
If the operator decided to perform an apicectomy with retrograde obturation, vestibular flaps were to be elevated, and root apexes to be cut in an oblique direction, cleaned with an appropriate ultrasound tip and closed with either MTA or eugenol-zinc oxide cement. When canal filling or apicectomy had been completed, a standardised periapical radiograph was to be taken (baseline radiograph) and evaluated by the clinicians, who were to report the following information (later rechecked by an independent outcome assessor):

- Complex canal anatomy — yes / no
- Modified canal anatomy — yes / no
- Apical diameter wider than instrument size 40 — yes / no
- Broken instrument in the canal — none / removed / bypassed
- Perforation — none / floor / canal
- Canal — found / not found
- Level of the gutta-percha filling in the apical third:
  - 0) ideal (0 to 2 mm from the apex)
  - 1) overfilling (any material beyond the apex)
  - 2) underfilling (more than 2 mm from the apex).

Multiradiculated teeth were graded according to the canal with the worst outcome, in the following order: underfilling (worst outcome), overfilling and ideal (best outcome).

- Quality of filling in the apical third:
  0) adequate (no visible space between the gutta-percha and the canal walls)
  1) inadequate (visible space between the gutta-percha and the canal walls).

Access to the pulp chamber was provisionally closed, to be definitively closed within 2 weeks. After endodontic therapy, patients were prescribed ibuprofen 400 mg (or paracetamol 1 g for patients with stomach problems or allergic to ibuprofen) but patients were instructed not to take them in absence of pain.

Implant therapy

Maxillary sinus lift and vertical or horizontal augmentation procedures could be performed, if required, prior to or at implant placement, to obtain sufficient bone volumes to allow implant placement. When grafting was performed, a synthetic, fully resorbable granular bone substitute (MG-Osteodrive, Mozo-Grau/Ticare, Valladolid, Spain) made of calcium-based inorganic compounds was used, together with resorbable barriers made of collagen from bovine tendon fibres (MG-Reguarde, Mozo-Grau/Ticare) at the discretion of the operator. The following prophylactic therapy was prescribed: amoxicillin 2 g one hour prior to augmentation, followed by 1 g every 8 h for 7 days. Patients allergic to penicillin were prescribed clindamycin 600 mg 1 hour prior to implant placement, followed by 300 mg clindamycin every 8 h for 7 days.

Implant installation technique

Self-tapping cylindrical titanium implants (MG-Inhex, Mozo-Grau/Ticare) with conical apex, internal connection and RBM (Resorbable Blast Media) surface were used. Operators were free to choose implant lengths (8, 10, 11.5, 13 and 15 mm) and diameters (3.3, 3.75, 4.25 and 5 mm) according to clinical indications and their preference. Immediate post-extraction implants or implants which were grafted at insertion were placed under a 7-day antibiotic prophylaxis regimen, as previously described, whereas all other implants were placed after a single administration of 2 g of amoxicillin (or 600 mg of clindamycin) one hour prior to placement.

Drills with increasing diameters were used to prepare the implant site, as suggested by the manufacturer. Implants were placed with their most coronal portion flush to the crestal level, with the exception of post-extraction implants, which were placed about 2 mm below the highest crestal peak. Motors were set with a torque of 35 Ncm, and resistance to implant insertion was recorded as up to or greater than 35 Ncm. Residual gaps between the implant surface and bone walls were filled with a granular bone substitute (MG-Osteodrive), and a resorbable barrier (MG-Reguarde) was placed to cover the grafted area. In cases of transcrestal sinus lift, the working drill length was set 1 mm shorter than the height of the residual alveolar crest. After implant site preparation, expanding-condensing osteotomes (Sinus lift Osteotomes, Salvin Dental Specialties, Charlotte, NC, USA) were used to fracture the sinus floor bone. The maxillary sinus epithelium was checked for perforation with the Valsalva manoeuvre immediately after sinus floor fracture. In cases of residual bone height lower than or equal to 2 mm less than the length of the planned implant, bone grafting was avoided and collagen sponge (Parasorb Cone, RESORBA Medical, Nürnberg, Germany) was inserted using the osteotome as a plugger. Slight elevation of the sinus epithelium was achieved secondary to the hydraulic pressure created by the collagen sponge. Finally, the implant was placed as previously described.

Operators were free to choose between submerged or non-submerged techniques. If a submerged technique was used, the wound was completely closed over the implant; however, in

cases of post-extraction implants, the wound was left partially open over the resorbable barrier. Implants could be loaded immediately, early or conventionally, in occlusion or infraocclusion, at the discretion of the operator. After implant placement, baseline periapical radiographs were taken of the implants. Patients were prescribed ibuprofen 400 mg (or paracetamol 1 g for patients with stomach problems or allergy to ibuprofen), but they were instructed not to take them in the absence of pain. Patients were also prescribed 0.12% chlorhexidine mouthwash for use 1 minute twice a day for 2 weeks. Within 1 week all patients were recalled and checked, and oral hygiene instructions were reinforced. Sutures were removed 7 to 10 days after implant placement.

Prosthetic procedures

All implants/teeth were to be restored as single units and not splinted under prosthetic reconstructions with other implants/teeth. Operators were free to deliver provisional full acrylic crowns before the definitive metal-ceramic or full ceramic crowns, which could be either cemented or screw-retained. Dr. Tallarico used standard MG-INHEX Hex preparable titanium abutments for crowns, which were provisionally cemented with Temp-Bond (Kerr, Orange, CA, USA).

After fitting of the definitive crowns (implant group)/completion of the restoration procedures (endo group), clinical pictures and standardised periapical radiographs of the study implants and teeth were taken, and implants were manually tested for stability.

Patients were recalled every 6 months for maintenance throughout the entire study period. Investigators could decide to recall patients more frequently (every 3 to 4 months) if necessary.

Outcome measures

This study tested the null hypothesis that there would be no differences in clinical outcomes between the two procedures, against the alternative hypothesis of a difference.

The primary outcome measure was failure of the procedure:

- for dental implants, failure was defined as implant mobility, implant fracture and/or any infection dictating implant removal. The stability of each individual implant was measured manually with a torque of 20 Ncm upon fitting of the final restoration and later on using the handles of two metal instruments;
- for restored teeth, failure was dictated when a tooth had to be extracted, or if it was no longer able to perform its masticatory function. Tooth extraction could be due to any cause, including endodontic abscess, root fracture, periodontal issues, etc.

Secondary outcome measures were the following.

- Any biological or biomechanical complication at implants or teeth at any time during the entire observation period. Postoperative pain was considered a complication if still present in a spontaneous form one week after treatment. Examples of complications considered were: nerve injury, fistula, peri-implantitis, periapical radiolucency, abscess, caries, metal screw fracture, crown loosening, root fracture, ceramic fracture, etc.
- Marginal bone level changes at both implants and teeth. Digital periapical radiographs of both teeth and implants were taken using the paralleling technique, employing commercially available film holders (Rinn XCP; Dentsply Rinn, Elgin, IL, USA), and, for teeth only, with individual stents made of hard silicone used for bite registration to standardise repositioning of the film holder. Radiographs were to be taken just after implant placement/endodontic retreatment, upon fitting of definitive implant-supported crowns, and 1, 3 and 5 years after completion of the treatment. In the event of an

unreadable radiograph, the radiograph was to be taken again. Marginal bone levels were measured using ImageJ (National Institutes of Health, USA) software. The software was calibrated for each single image using the known length or diameter of dental implants. For teeth, the images were calibrated by means of the known dimensions of the Digora Optime (Soredex, Tuusula, Finland) active area, or the dimensions of the active area of the RVG sensor (RVG 6100 Digital Radiography System, Carestream Health, Rochester, NY, USA). Measurements of the mesial and distal bone crest levels adjacent to each tooth/implant were made to the nearest 0.01 mm. The reference points for the linear measurements were either the CEJ, when visible, for teeth; or the edge of restorations and the coronal margin of the collar for implants; and the most coronal point of bone-to-implant/tooth contact. Bone levels were measured at both mesial and distal sides and averaged.

- Radiographic endodontic success (for teeth only) was assessed by an independent assessor, who compared the postoperative radiographs with those obtained at 1, 3 and 5 years after treatment completion. Radiographs were viewed on a computer screen in pairs (baseline and follow-up radiographs of the same tooth). Radiographic alterations were reported in the following way: complete healing (no visible periapical radiolucency); improvement (reduction of the periapical lesion); or no changes/worsening (radiolucency remained unaltered or increased over time).
- Number of clinical sessions required to complete the treatment (fitting of the final crown for implants) and to manage any complications arising during follow-up (routine check-ups/hygiene were not counted).
- Days required to complete the procedure. The number of days necessary from the start to the end of the treatment (either end of endodontic therapy, including any reconstruction of the tooth crown, or fitting of the definitive crown for implants).
- Chairside time. The number of minutes spent by the patient on the chair until treatment completion (either end of endodontic therapy, including any reconstruction of the tooth crown, or fitting of the definitive crown for implants) and to resolve any arising complications (routine check-ups/hygiene were not counted).
- Treatment costs. The total cost of each procedure up to fitting of the final restorations, calculated according to the individual dental practice's official price list (not the actual cost paid by the patient). The total costs required to fix any complications arising up to 5 years after treatment completion were also to be added.
- Aesthetic evaluation of the vestibular and occlusal clinical pictures, including the mesial and distal adjacent teeth, taken at the end of the treatment, 1, 3 and 5 years after treatment completion, and performed on a computer screen by an independent dentist. Aesthetics were assessed using both the pink aesthetic score (PES)[7] and the white aesthetic score (WES)[8]. In brief, the PES was used to assess seven variables, namely: mesial papilla, distal papilla, soft tissue level, soft tissue contour, alveolar process deficiencies, soft tissue colour and texture; a 0-1-2 scoring system was used, 0 being the lowest and 2 being the highest value, with a maximum achievable score of 14 per dental unit. With the WES score, five variables were evaluated: tooth form, tooth volume/outline, colour (hue/value), surface texture, and translucency; a 0-1-2 scoring system was used, 0 being the lowest and 2 being the highest value, with a maximum achievable score of 10 per dental unit.

At the only participating centre, a local blind outcome assessor (Dr. Anna Vaccarella) recorded the following outcome measures: implant stability; number of patient visits and days to com-

plete treatment; chairside time; and cost. Complications were dealt with and reported directly by Dr. Tallarico. One independent dentist (Dr. Trullenque-Eriksson up to the third year of follow-up and thereafter Dr. Sbricoli), not involved in the treatment of the patients, evaluated radiographic endodontic success, aesthetics and marginal bone levels. Due to the nature of the study, the outcome assessors could not be blinded.

Sample size and randomization

A sample size was estimated, taking into account a hypothetical difference in implant/tooth failures from 1% to 5%. A two-group continuity-corrected chi-squared test with a 0.050 two-sided significance level would have 80% power to detect a difference between a proportion of 0.050 and a proportion of 0.010 (odds ratio of 0.192) if the sample size in each group was 333. Most likely this was a gross underestimation of the sample size, but was, nevertheless, still far too large in relation to our predicted recruitment capacity. Initially, 12 centres agreed to participate to this trial, each centre had to recruit 20 patients to be equally allocated to both interventions, and therefore a total of 240 patients (120 in each group) were to be included. Twelve computer-generated restricted randomization lists were created. Only one investigator (Dr. Esposito), who was not involved in the selection and treatment of the patients, knew the random sequence and had access to the randomization list, stored on a password-protected laptop computer. The randomization codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. After the patient provided their consent to participation in the trial, the envelope corresponding to the patient recruitment number was opened in order to determine whether the tooth was to be endodontically retreated or extracted. Therefore, treatment allocation was concealed from the investigators in charge of enrolling and treating the patients.

Statistical analysis

All data analysis was performed, according to a pre-established analysis plan, by a clinician with expertise in statistics (Dr. Trullenque-Eriksson up to the third year of follow-up, and thereafter by Dr. Buti). The patient was the statistical unit of the analyses. Differences in the proportions of patients with failures and complications (dichotomous outcomes) were compared between the two groups using Fisher's exact probability test. Between-group differences in patient means for continuous outcomes (bone levels; bone level changes; number of visits and days to complete the treatment; chairside time; costs; and aesthetics scores) were compared using t-tests. Differences in marginal bone levels over time were compared using paired t-tests. The plan had initially been to carry out a subgroup analysis to compare outcomes in teeth with single or multiple canals; however, this was not performed since the number of patients recruited was too small. All statistical comparisons were conducted at the 0.05 level of significance.

RESULTS

During initial monitoring it was noticed that most of the centres were not recruiting, and soon 10 centres withdrew without having treated a single case. Only two centres managed to recruit and treat patients according to the study protocol and deliver the 1-year data, but only one centre delivered the 3- and 5-year data.

Twenty-two patients were screened, and 20 patients were consecutively enrolled in the trial. Two patients were not included because they declined to participate in the study. All patients were treated according to the allocated interventions.

One patient from the endo group dropped out and was last seen 3 years after treatment com-

pletion; she moved to another town and we repeatedly asked her to go another dentist to have periapical radiographs and clinical pictures taken, but she refused. Subjectively, she reported no problems. All other radiographs and clinical pictures were taken as per the protocol, and data pertaining to all patients remaining in the trial were included in the statistical analyses.

The main deviation from the research protocol was that one patient, who received a provisional crown on an immediately loaded post-extraction implant, became pregnant 2 months after loading, and received her definitive crown 13 months after implant placement. She also refused one additionally planned implant, so the definitive restoration was a hybrid prosthesis joining one implant with one tooth instead of a single crown. In addition, two patients from the implant group attended their 5-year follow-up check-up with a 4-month delay owing to the general lockdown in response to the Covid-19 pandemic.

Patients were recruited and treated from February 2012 to November 2014. The follow-up of all patients was to 5 years after definitive treatment completion. Patient demographics are presented in **TABLE 1**. Before treatment, the only imbalance between the two groups was in gender distribution, with more females in the implant group. The treatment characteristics of teeth and implants are summarised in **TABLE 2A** and **TABLE 2B**, respectively.

- *Failures*: One upper first molar fractured between endodontic sessions, before the canals were definitively obturated; the tooth was extracted and the patient refused additional treatments. The difference in proportions of failures between groups was not statistically significant (difference in proportions = 0.1; 95% CI -0.18 to 0.35; P [Fisher's exact test] = 1.00).
- *Complications*: Three patients from the endo group were affected by one complication each *versus* a single complication in the implant group, the difference not being statistically significant (difference in proportions = 0.2; 95% CI -0.17 to 0.51; P [Fisher's exact test] = 0.5820). Apart from the tooth fracture described above, the other two complications in the endo group were one case of crown de-cementation, which was observed at 3-year follow-up, and moderate pain being reported by another at tooth 36 at 5-year follow-up. The former was re-cemented and the occlusion adjusted, while the latter was found to be affected by gingivitis and bled on probing; oral hygiene was reinforced and the patient was instructed to use 1% chlorhexidine gel twice a day for 1 week, and the gingivitis regressed. The one complication arising in the implant group was an abutment screw loosening at 5-year follow-up. The old screw was replaced by a new one.
- *Marginal bone level changes*: At baseline (completion of the endo retreatment for teeth, placement for implants) the average bone level was 2.10 ± 0.66 mm around teeth *versus* 0.05 ± 0.15 mm at implants. Five years after treatment completion, the average bone levels around teeth was 2.83 ± 0.60 mm *versus* 0.60 ± 0.63 mm at implants (**TABLE 3**). Bone loss at 5 years after treatment completion was 0.60 ± 0.96 mm at teeth and 0.56 ± 0.77 mm at implants, the difference not being statistically significant (mean difference = -0.05 mm; 95% CI: -0.95 to 0.86; P [t-test] = 0.914; **TABLE 3**).
- *Radiographic endodontic success (teeth only):* Before treatment, four teeth out the 10 allocated to endodontic retreatment showed a periapical/lateral lesion. Five years after completion of the treatment, of these four teeth, one had been lost, while two showed complete healing and one improvement on radiograph. None was symptomatic.
- *Number of appointments*: The mean number of patient visits per group was 6.7 ± 0.7 for teeth and for 6.1 ± 0.7 for implants, the difference not being statistically significant (mean difference = 0.6; 95% CI: -0.1 to 1.3 P [t-test] = 0.106).
- *Number of days to complete treatment*: The mean number of days to complete treatment in each group was 61 ± 13.0 for teeth and 191.4 ± 75.0 for implants, the difference

TABLE 1 BASELINE PATIENT CHARACTERISTICS

	Endo (n = 10)	Implant (n = 10)
Females	2	7
Mean age at implant insertion (range)	48.6 (39-64)	45.2 (34-64)
Non-smokers	9	9
Smoking up to 10 cigarettes/day	1	1
Smoking more than 10 cigarettes/day	0	0
Upper central incisors	2	0
Lower central incisors	0	0
Upper lateral incisors	0	0
Lower lateral incisors	0	0
Upper canines	0	0
Lower canines	0	2
Upper first premolars	1	0
Lower first premolars	0	0
Upper second premolars	1	1
Lower second premolars	0	0
Upper first molars	3	5
Lower first molars	3	1
Upper second molars	0	0
Lower second molars	0	1
Teeth with one canal	3	2
Teeth with two canals	1	1
Teeth with three or more canals	6	7
Teeth restored with posts	4	5
Symptomatic teeth	9	8
Provoked pain	8	6
Spontaneous pain	1	1
Fistula	0	1
Abscess	0	0
Teeth with a radiographic periapical or lateral lesion	4	6

being statistically significant (mean difference = -130.4; 95% CI: -184.5 to -76.4; P [t-test] < 0.001).

- *Chairside time*: The mean number of minutes spent by patients in the chair while treatment was completed and any arising complications were fixed was 628 ± 41.4 for teeth and for 328.5 ± 196.4 for implants, the difference being statistically significant (mean difference = -299.5; 95% CI: -441.3 to 1.0; P [t-test] = < 0.001).
- *Costs*: Costs were calculated based on the official prices of the practice and not on the actual costs charged to the patients, since all patients received highly discounted ra-

TABLE 2A TREATMENT CHARACTERISTICS OF ENDODONTICALLY RETREATED TEETH

	Teeth (n = 10*)
Surgical endodontic retreatment	0
Manual instrumentation of the canal	2
Mechanical instrumentation of the canal	8
Complications during endodontic treatment	1 (tooth fracture)
Used intermediate medication with calcium hydroxide	4
Canals closed with warm lateral condensation	0
Canals closed with warm vertical condensation	9
Simple canal anatomy	7
Complex canal anatomy	3
Modified canal anatomy	2
Apical diameter wider than instrument size 40	2
Removed broken instrument	0
Perforation of the floor of tooth chamber or canal	0
Number of teeth with one or more canals not found	2
Ideal apical (0–2 mm from the apex)	8
Overfilling	1
Underfilling (more than 2 mm from the apex)	0
Adequate filling of the apical third (no visible spaces)	9
Inadequate filling of the apical third (visible spaces)	0
Prosthetic rehabilitation with post	9
Prosthetic rehabilitation with metal-ceramic or ceramic crown	9

** One tooth fractured during the endodontic retreatment and could not therefore be included in all fields.*

TABLE 2B TREATMENT CHARACTERISTICS OF IMPLANTS

	Implants (n = 10)
Pre-implant placement ridge preservation/augmentation procedures	0
Implants inserted flapless	5
Implants of length 10.0 mm	1
Implants of length 11.5 mm	6
Implants of length 13.0 mm	3
Implants of diameter 3.3 mm	1
Implants of diameter 3.75 mm	3
Implants of diameter 4.25 mm	0
Implants of diameter 5.0 mm	6
Insertion torque greater than 35 Ncm	10
Post-extraction implants	4
Mean vertical buccal bone loss at post-extraction implants [SD]	0 mm
Mean horizontal implant–buccal bone gap in mm [SD]	0.80 ± 1.23 mm
Augmentation procedures at implant placement	7
In post-extraction implant gaps	2
In both the gap and buccal to post-extraction implants	2
Crestal sinus lift without bone substitute	3
Implants loaded immediately	2
Implants non-submerged and delayed loaded	2
Implants submerged and delayed loaded	6

tes. The average cost for endodontic retreatment, including the restoration procedures and remedying any complications was 1440 ± 549.7, whereas the average cost for implant treatment was 2099 ± 170.3. Implant treatment was significantly more expensive (mean difference = 659; 95% CI: 257.2 to 1060.8; P [t-test] = 0.004).

- *Aesthetics (PES and WES scores)*: 5 years after treatment completion, the average PES + WES score, was 20.4 ± 2.2 for teeth and 16 ± 3.4 for implants, the difference being statistically significantly different (mean difference = -4.4; 95% CI -7.2 to -1.5; P [t-test] = 0.005; **TABLES 4A, 4B**). Soft tissues aesthetics (PES) were significantly better at endodontically retreated teeth (mean difference -3.4; 95% CI -5.1 to -1.6; P [t-test] = 0.001). When analysing the individual PES score domains (**TABLE 4A**), the difference was statistically significant and clinically more evident for mesial and distal papilla, soft tissue contour and alveolar process deficiencies. No significant differences in tooth aesthe-

TABLE 3 MARGINAL BONE LEVELS AND CHANGES AT 1, 3 AND 5 YEARS AFTER TREATMENT COMPLETION BY STUDY GROUP

	Teeth			Implants			Mean difference (SE)	95% CI of the difference	P-value from unpaired sample t-test
	N	Mean	(SD)	N	Mean	(SD)			
At completion of the endo retreatment/ implant placement	9	2.10	(0.66)	10	0.05	(0.15)	2.05 (0.23)	1.54 to 2.56	< 0.001*
At implant loading	-			10		(0.43)	-	-	-
1 year after treatment completion	9	2.67	(0.71)	10	0.76	(0.67)	1.91 (0.32)	1.24 to 2.58	< 0.001*
3 year after treatment completion	9	2.33	(0.68)	10	0.67	(0.64)	1.66 (0.30)	1.02 to 2.29	< 0.001*
5 year after treatment completion	8	2.83	(0.60)	10	0.60	(0.63)	2.22 (0.32)	1.54 to 2.91	< 0.001*
Mean changes baseline – 1 year	9	0.57	(0.54)	10	0.72	(0.69)	-0.14 (0.29)	-0.75 to 0.46	0.631
Mean changes baseline – 3 years	9	0.23	(0.82)	10	0.62	(0.68)	-0.39 (0.34)	-1.12 to 0.33	0.267
Mean changes baseline – 5 years	8	0.60	(0.96)	10	0.56	(0.77)	-0.05 (0.42)	-0.95 to 0.86	0.914
P-value from paired t-test from baseline to 1 year	0.012*			0.01*					
95% CI of the difference (1 year)	0.16 to 0.99			0.22 to 1.21					
P-value from paired t-test from placement to 3 years	0.426			0.018*					
95% CI of the difference (3 years)	-0.40 to 0.86			0.14 to 1.11					
P-value from paired t-test from placement to 5 years	0.121			0.048*					
95% CI of the difference (5 years)	-0.21 to 1.41			0.01 to 1.10					

**Statistically significant difference*

TABLE 4A PES SCORES 5 YEARS AFTER TREATMENT COMPLETION BY STUDY GROUPS AND BY DIFFERENT AESTHETIC DOMAINS; SD IN PARENTHESES

	Mesial papilla	Distal papilla	Soft tissue level	Soft tissue contour	Alveolar process deficiencies	Soft tissue colour	Soft tissue texture	Total PES score
Teeth = 8	1.9 (0.4)	1.9 (0.4)	1.6 (0.5)	1.8 (0.5)	2.0 (0)	1.5 (0.8)	1.6 (0.5)	12.3 (1.3)
Implants = 10	0.9 (0.7)	1.0 (0.8)	1.7 (0.5)	1.1 (0.3)	1.1 (0.8)	1.6 (0.5)	1.5 (0.5)	8.9 (2.2)
Difference (SE)	-1.0 (0.3)	-0.9 (0.3)	0.1 (0.2)	-0.7 (0.2)	-0.9 (0.2)	0.1 (0.3)	-0.1 (0.6)	-3.4 (0.8)
P-value	0.003*	0.009*	0.758	0.005*	<0.001*	0.755	0.621	0.001*

**Statistically significant differences*

TABLE 4B WES AND TOTAL PES + WES SCORES 5 YEARS AFTER TREATMENT COMPLETION BY STUDY GROUP AND BY DIFFERENT AESTHETIC DOMAINS; SD IN PARENTHESES

	Tooth form	Tooth volume/ outline	Colour hue/ value	Surface texture	Translucency	Total WES score	Total PES+WES score
Teeth = 8	1.8 (0.5)	1.6 (0.5)	1.6 (0.5)	1.6 (0.5)	1.5 (0.5)	8.1 (1.4)	20.4 (2.2)
Implants = 10	1.2 (0.6)	1.7 (0.5)	1.4 (0.5)	1.5 (0.7)	1.3 (0.5)	7.1 (1.7)	16 (3.4)
Difference (SE)	-0.6 (0.3)	0.1 (0.2)	-0.2 (0.3)	-0.1 (0.3)	-0.2 (0.2)	-1.0 (0.7)	-4.4 (1.3)
P-value	0.049*	0.758	0.373	0.671	0.424	0.178	0.005*

** Statistically significant differences*

tics (WES) (mean difference = -1.0; 95% CI -2.6 to 0.5; P [t-test] = 0.178) were observed between treatments. However, more specifically, tooth form was statistically significantly better at endodontic retreated teeth.

DISCUSSION

This trial was designed to investigate one of the most discussed dilemmas in dentistry, namely whether it is better to endodontically retreat a tooth with previous endodontic treatment but persistent pathology and uncertain prognosis, or to extract and replace it with an implant-supported crown. In our, admittedly small, sample there was only one treatment failure (fracture of a first upper molar during endodontic retreatment) and few complications in the 5 years after treatment completion in both groups.

Although there no differences were observed in terms of the number of patient visits to the clinic, we did note several statistically and clinically significant differences between the two procedures. However, it is important to bear in mind that the number of patients included was very small, so it is difficult to generalize the results, and our conclusions should be considered more as working hypotheses than evidence-based truths. That being said, in terms of aesthetics, treated teeth scored considerably higher than implants with respect to soft tissues (pink), while there was virtually no difference in aesthetic outcomes between the natural and synthetic crowns (white). The largest differences observed at 5 years after therapy completion regarded mesial and distal papillae, soft tissue contour, alveolar process deficiencies, and tooth form hence, if aesthetics is a patient's priority, endodontic retreatment might be the best treatment choice, especially considering that an implant can still be placed at a later stage if needed.

Other differences between groups were the fewer days needed to complete endodontic retreatment and rehabilitation, whereas chairside time was almost double that needed for implant-based rehabilitation; these factors should be explained to patients, who can then make an informed choice as to which treatment they would prefer, according to their own needs and predispositions. Expense may also be an influential factor in this regard; calculated on the basis of the official prices of the private practice, costs were higher for implant rehabilitation, but this is to be expected. In this case, however, we should note that the calculated costs do not reflect the actual cost paid by our patients, who received considerable discounts for their participation in the research. Furthermore, the costs we cite

are only a very rough estimate, and may not accurately reflect those of other practices, either in Italy or abroad.

Regarding peri-implant marginal bone levels, no differences in bone loss were observed between teeth and implants; however, the methods used to estimate bone levels at teeth were less reliable than those for implants, and our radiographic comparison of bone levels between teeth and implants should be interpreted with caution.

The radiographic healing of endodontic lesions obviously applied to endodontically retreated teeth only. At baseline only four out of 10 teeth had visible radiolucent lesions. Of these teeth, 5 years after completion of the therapy, one had been lost due to fracture, two showed complete healing and one a radiographic improvement. Radiographic healing improvement observed on periapical radiographs was expected and in accordance with another study[9], though longer follow-ups will be still informative.

Meanwhile, our data supports the notion that there might be no major differences in medium-term clinical outcomes of endodontic retreatment of previously endodontically treated teeth with persistent pathology and dubious long-term prognosis as compared to tooth extraction followed by replacement with an implant-supported crown. However, clinicians may care to note that soft tissues aesthetics, costs and time needed to complete the treatment all point in favour of endodontic retreatment.

As there have not yet been any other RCTs testing similar hypotheses, no meaningful comparison with similar studies can be attempted. Nevertheless, if our results are confirmed by larger trials, they would indicate that it might be preferable to start with a less invasive endodontic retreatment approach as the primary treatment option, keeping the implant option as a rescue treatment in case of endodontic retreatment failure.

The main limitations of the present trial are the insufficient sample size and the difficulties in precisely estimating bone levels at natural teeth. The insufficient sample size can only be resolved by conducting similar trials with much larger sample sizes. However, according to our experience this will not be an easy task. In fact, although we were eager to fully exploit the opportunity generously provided by the sponsor to compare endodontic retreatment with implant replacement, and 12 centres enthusiastically decided to join the protocol, when clinicians were at the randomization stage, this limited their decisions and 10 centres pulled out of the trial. In addition, one of the two centres who provided the 1-year data, did not provide any data at 3 and 5 years, all of which badly affected the original sample size. Another factor that those planning similar trials in the future may like to bear in mind is that bone level assessment at endodontically treated teeth was complex and possibly not fully reliable; this was due to three main factors: i) the difficulty in identifying reference points (the CEJ or the margin of a restoration); ii) the lack of known distances for calibrating the assessments; and iii) the use of different equipment for taking periapical digital radiographs although the use of radiographic stent may have partially resolved this issue).

Indeed, this trial could be considered emblematic of the problems typically linked to clinical trials; in order to conduct proper clinical research, it is necessary to have a valid question to answer, a detailed and thoroughly planned research protocol, a generous and detached sponsor, and unbiased operators genuinely interested in testing the initial hypothesis. In many cases, however, experienced operators already believe that they know which the best treatment option is for their patients, despite the lack of scientific evidence and the fact that an equal number of clinicians may hold the diametrically opposing view. They may, therefore, as in our case, be unwilling to allocate the treatment randomly; when beliefs are so firmly entrenched, it is difficult to find solid ground on which to run unbiased research.

On a more positive note, this RCT is the only one comparing the two treatment options to be

published so far; we hope that with this study as a precedent, other researchers could be prompted to test similar hypotheses. Such studies are difficult to conduct, for the reasons mentioned above, but are badly needed if we are to make evidence-based decisions on the correct approach to adopt when dealing with teeth with uncertain prognosis.
Since in the present investigation both procedures were tested in real clinical conditions, and patient inclusion criteria were broad, results can be generalized with confidence to a wider population with similar characteristics.

CONCLUSIONS

Our preliminary results suggest that both endodontic retreatment and implant replacement of previously endodontically treated teeth with persisting pathology and a dubious endodontic prognosis provided similar medium-term success rates. That being said, soft tissue aesthetics and total treatment time were more favourable in endodontic retreatment, whereas implant rehabilitation required half the chairside time of endodontic retreatment but was more expensive. Much larger patient populations and longer follow-ups are needed to fully answer our initial question, but based on our results it might be better to consider the less invasive endodontic retreatment as the primary therapeutic option.

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