Mestrado Integrado em Medicina Dentária

Faculdade de Medicina da Universidade de Coimbra

Long-Term Prognosis of Endodontic Microsurgery: a Systematic Review

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Long-Term Prognosis of Endodontic Microsurgery: a Systematic Review

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I. Abstract

Background: Root canal treatment might not succeed because of the complexity of the root canal system or technical errors. If nonsurgical endodontic retreatment (NSER) is not expected to be effective on the removal of the cause of prior failures, surgical endodontic retreatment (SER) is an alternative approach to the extraction of the tooth. Endodontic microsurgery (EMS) is characterized by modern microsurgical techniques that integrate the use of an operation microscope or an endoscope, root-end cavity preparation with ultrasonic tips and more biocompatible root-end filling materials.

Objective: The objective of this study is to evaluate the long-term clinical and radiographic outcome of endodontic microsurgery in teeth diagnosed with secondary apical periodontitis.

Materials and methods: A comprehensive literature search was performed on two electronic databases, *Pubmed* and *The Cochrane Library*, to answer the PICO question: “What is the long-term clinical and radiographic outcome of endodontic microsurgery (EMS) in teeth diagnosed with secondary apical periodontitis through radiographic evaluation?”. Inclusion and exclusion criteria were defined a priori to select the best longitudinal evidence with a follow-up ≥ 2 years.

Results: A total of 573 articles were obtained from which 10 fulfil inclusion criteria: 6 prospective clinical studies (PCS) and 4 randomized clinical trials (RCT). The overall success rate ranged from 69.3% to 93.3%. Regarding the follow-up time, the minimum was 2 years and the maximum was 10 to 13 years. Several potential prognostic factors were assessed during each trial in order to evaluate its influence on the outcome of EMS. Nevertheless, only 5 showed statistically significant differences concerning the EMS outcome: smoking habits; tooth location and type; absence/presence of dentinal defect; interproximal bone level; and root-end filling material.

Conclusion: This systematic literature review found strong evidence reporting high success rates and predictability of the EMS procedure performed under modern surgical techniques. However, in order to accomplish a more reliable data on the outcome of EMS through the development of a high-quality meta-analysis in the future, there is a need to implement more homogeneous prospective trials reporting outcome on EMS through the establishment of guidelines, particularly, concerning case selection, definition of success and dropout reporting.

Keywords: root canal therapy; endodontic microsurgery; surgical endodontic retreatment: treatment outcome; success rate; endoscope; root-end filling; systematic review.

II. Introduction

Root canal treatment might not succeed because of the complexity of the root canal system, technical errors or apical cysts. If nonsurgical endodontic retreatment (NSER) is not expected to be effective on the removal of the cause of prior failures, surgical endodontic retreatment (SER) is an alternative approach to the extraction of the tooth (1). These situations include: infection in apically unreachable areas, extra-radicular infection, foreign body reactions or radicular cysts (2), when the NSER is associated with complications, is refused by the patient, or is supposed to be technically challenging (3).

Endodontic microsurgery (EMS) is characterized by modern microsurgical techniques that integrate the use of an operation microscope (4) or an endoscope (5), root-end cavity preparation with ultrasonic tips and more biocompatible root-end filling materials (2,6).

Over the years, the use of magnification devices has become an increasingly common practice in dentistry (7). During the endodontic microsurgery procedure, the operator can easily identify root apices and anatomical details such as isthmuses, root microfractures, canal fins and lateral canals. Combined with the microscope or endoscope, the use of ultrasonic tips enables a conservative surgical approach, for the reason that this technology allows the operator a better control during the procedure and decreases the risk of perforation by increasing the capacity to remain localized in the centre of the canal compared to the microhandpiece (8). With the aim of preventing outgrowth of bacteria and promote periapical tissue healing (9), an ideal root-end filling material must have biocompatibility, dimensional stability (4) and resistance to resorption (9). Besides, it should be bactericidal, bacteriostatic, easy to manage and offer an exceptional seal capacity (4,9).

The outcome evaluation of EMS is based on the combination of specific clinical and radiographic healing criteria. Several parameters are required to be evaluated in order to establish clinical success, such as: existence or absence of signs and/or symptoms, tenderness to percussion or palpation, mobility and function. Also, sinus tract formation or periodontal pocket development must be examined (10). Currently, the radiographic outcome classification defined by Rud *et al.* (11) and Molven *et al.* (12) is known to be broadly accepted for clinical practice, due to its solid correlation between radiographic and histologic findings from 120 teeth (11) and its high interobserver agreement after isolated examinations (2,12). Therefore, this classification is divided into 4 categories (appendix 1): complete healing (re-formation of the lamina dura); incomplete healing (scar tissue); uncertain healing; and unsatisfactory healing (10).

Furthermore, the use of Cone Beam Computed Tomography (CBCT) can be, in the next future, an excellent alternative to evaluate long-term healing of EMS in 3 dimensions (1), as it demonstrate to be more sensitive and specific than periapical radiographs in assessing periapical radiolucencies (13). In line with this, the “Penn 3D criteria” (appendix 2) of assessment emerge with 3 categories: complete healing; limited healing; and unsatisfactory healing (14). Kim *et al.* (8) also developed a classification with the purpose of making prediction of the probability of endodontic microsurgical success depending upon the pre-existing condition of the tooth (appendix 3).

The prognosis of EMS can be influenced by several variables, for instance: differences in the procedures and materials; clinical and radiographic evaluation; patient-related factors (demography and systemic condition); type, number and location of the tooth involved; the quality of earlier root canal treatment or re-treatment; and the type of coronal restorations. It is difficult to make a direct comparison between different studies about this subject when there is an obvious heterogeneity for these variables and for the evaluation of the treatment success and failure rate among the studies (7).

For these reasons, there is a need to overcome the heterogeneity of evidence about the prognosis of EMS (15) through the differentiation of the studies according to their methodological rigor (16), with the aim of decreasing the large variety of reported outcome (15). Also, the development of this review aims to achieve a more reliable outcome result through the search of studies with high level of external validity of the results, particularly, concerning the follow-up period evaluated and the conditions in which EMS was performed. In this sense, studies with a long-term follow up (5) and whose EMS was performed under slightly different conditions (for instance, with respect to the operator) (16) will be ideal. In this way, we expect to solve some limitations of previous reviews on the short-term outcome of EMS (17–19) and disclose more reliable and pragmatic evidence to use in a private practice clinical context.

Kang *et al.* (18) developed a systematic review and meta-analysis with the purpose of evaluating and comparing the clinical and radiographic outcomes of nonsurgical endodontic retreatment and endodontic microsurgery and presented 92% of overall pooled success rate for EMS. Nonetheless, this review included studies with a minimum sample size of 20 teeth . (18) which may not be enough to reach clinically meaningful results (16). Moreover, a systematic review and meta-analysis developed by Seltzer *et al.* (20) concluded that endodontic microsurgery showed significantly better prognosis than traditional root-end surgery (TRS), with a 94% success rate to treat apical periodontitis through EMS. However, such conclusion is based on studies with a minimum follow-up period of 6 months . (20). During the last two decades, many studies have reported on the outcome of EMS, notwithstanding with only short-term (≤ 2 years) follow-up (21–26). Short-term observation may overestimate the prognosis because 5% to 25% of teeth assessed as healed at the short-term have been reported to revert healing when observed at 3-years or longer after EMS (5,27–29). Moreover, the proportion of cases assessed as “uncertain healing” at 1-year follow-up that will progress to “complete healing” when assessed at 5-years is variable and dependent upon the root-end filling material (5,29,30). Evidence on long-term outcome of EMS is extremely important to give reliable information to treatment providers in order to have a sound rationale to discuss treatment options with their patients. This clinical evidence is expected to improve the identification of factors with impact in prognosis and possibly will have a better intertwining with patient-centered outcomes.

The purpose of this study is to evaluate the clinical and radiographic long-term outcome of endodontic microsurgery in teeth diagnosed with secondary apical periodontitis through radiographic evaluation.

III. Materials and methods

Before literature search, a specialized framework based on evidence was used, known as PICO question (population, intervention, comparison, outcome). This question was formulated as following: “What is the long-term clinical and radiographic outcome of endodontic microsurgery (EMS) in teeth diagnosed with secondary apical periodontitis through radiographic evaluation?”.

A preliminary search of the JBI Database of Systematic Reviews and Implementation Reports, the Cochrane Database of Systematic Reviews, PROSPERO and MEDLINE revealed that currently there is no other review (published or in progress) on this topic.

The Cochrane handbook methodology for systematic reviews was used to complete this review.

1. Searching criteria

The inclusion and exclusion criteria allowed to make a rigorous selection of all the clinical studies that evaluated the clinical and radiographic outcomes after endodontic microsurgery.

Inclusion criteria:

1. Clinical studies in humans.
2. Publication from January 1990 to May 2020 (monthly updated since October 2019).
3. Randomized clinical trials (RCTs) on EMS.
4. Prospective clinical studies (PCSs) on EMS.
5. A minimum follow-up period of 2 years.
6. Teeth with indication to perform EMS (periapical lesion, secondary apical periodontitis, extrusion of root canal filling material resulting from primary endodontic treatment, or persistent extra-radicular infection).
7. The treatment procedure pursued the modern technique using magnification devices (microscope and endoscope) and ultrasonic root-end preparation.
8. Well-established clinical and radiographic success criteria, using conventional periapical radiography or CBCT.
9. The success rate for EMS was given.

Exclusion criteria:

1. Studies that included patients aged under 18 years.
2. Retrospective clinical trials, cases of series, or reviews on EMS.
3. Studies with samples of teeth that were subject to root resections and amputations, or that present root perforations or fractures.
4. The procedure was not described with clarity or did not sustain the modern technique portrayed above.
5. The follow-up period was less than 2 years.
6. Studies in which the follow-up only included a periapical radiography or clinical evaluation.
7. Studies that did not assess the outcome on apical microsurgery using specific clinical and radiographic criteria.
8. The success rate for EMS was not given.

2. Searching method

An initial search, limited to PubMed has been undertaken to identify articles on this topic, followed by analysis of the text words contained in the titles or/and abstracts, and of the index terms used to describe these articles. This informed the development of a search strategy including identified keywords and index terms which were tailored for each information source. After that, two electronic databases were searched: *Pubmed* (appendix 4) and *The Cochrane Library* (appendix 5).

The MeSH terms used were: “periapical diseases”; “root canal therapy”; “apicoectomy”; “retreatment”; “microsurgery”; “treatment outcome”; and “Retrograde Obturation”. Additionally, the following terms were applied: “root-end filling”; “surgical endodontic retreatment”; “apical surgery”; “periapical surgery”; “retrograde surgery”; “endodontic surgery”; “root-end surgery”; “root-end cavity preparation”; “periradicular surgery”; “root-end resection”; “apicectomy”; “radiographic outcome”; “success rate”; and “radiographic success rate”.

3. Study selection

The selection of the studies ended in May of 2020. All resulting articles were separately scanned by two reviewers (JMS, DP). Following the search, all identified citations were uploaded into Mendeley Desktop 1.19.4 and duplicates removed.

After that, this process was followed. On the first step, the titles were read to exclude the articles that did not gather the criteria for abstract assessment. If there were distinct opinions between the reviewers, the article was selected for abstract evaluation. On the second step, the reading of the abstracts of the chosen studies was carried out with the aim of selecting the articles according to the inclusion and exclusion criteria previously determined. If there were distinct opinions between the reviewers, the article was selected for full-text review. Finally, on the third step, the selected articles were fully read, in order to select only those that met all the inclusion criteria described above. Communication with some authors was attempt to access relevant supplementary data to avoid any kind of assumption.

4. Data extraction

During the data extraction process, an excel table was made up containing the following topics: study type; sample size; number of re-surgery or orthogonal retreatment cases; clinical and radiographic criteria; clinical and radiographic success rates; recall rate; follow-up period; technique and material employed; and finally, main results, limitations and conclusions of the study.

5. Quality assessment

Two Cochrane risk-of-bias assessment tools were used. The RoB 2 tool was applied to randomized controlled trials and the ROBINS-I tool was applied to non-randomized studies (https://www.riskofbias.info). The assessments were performed independently by two authors (JMS, DP). Eligible studies were assessed for methodological validity prior to inclusion in the review.

IV. Results

The article selection method of the electronic databases search is presented in Figure I. There were 573 articles identified after database searching, 1 of which was added through other source. A total of 120 records were selected after title reading was performed. Following abstract and full-text reading, a total of 110 articles were excluded according to the exclusion criteria previously established. The reasons for the exclusion are showed in appendix 6. The most frequent causes of exclusion were an insufficient follow-up period (44 articles) and an unwanted study design (31 articles).

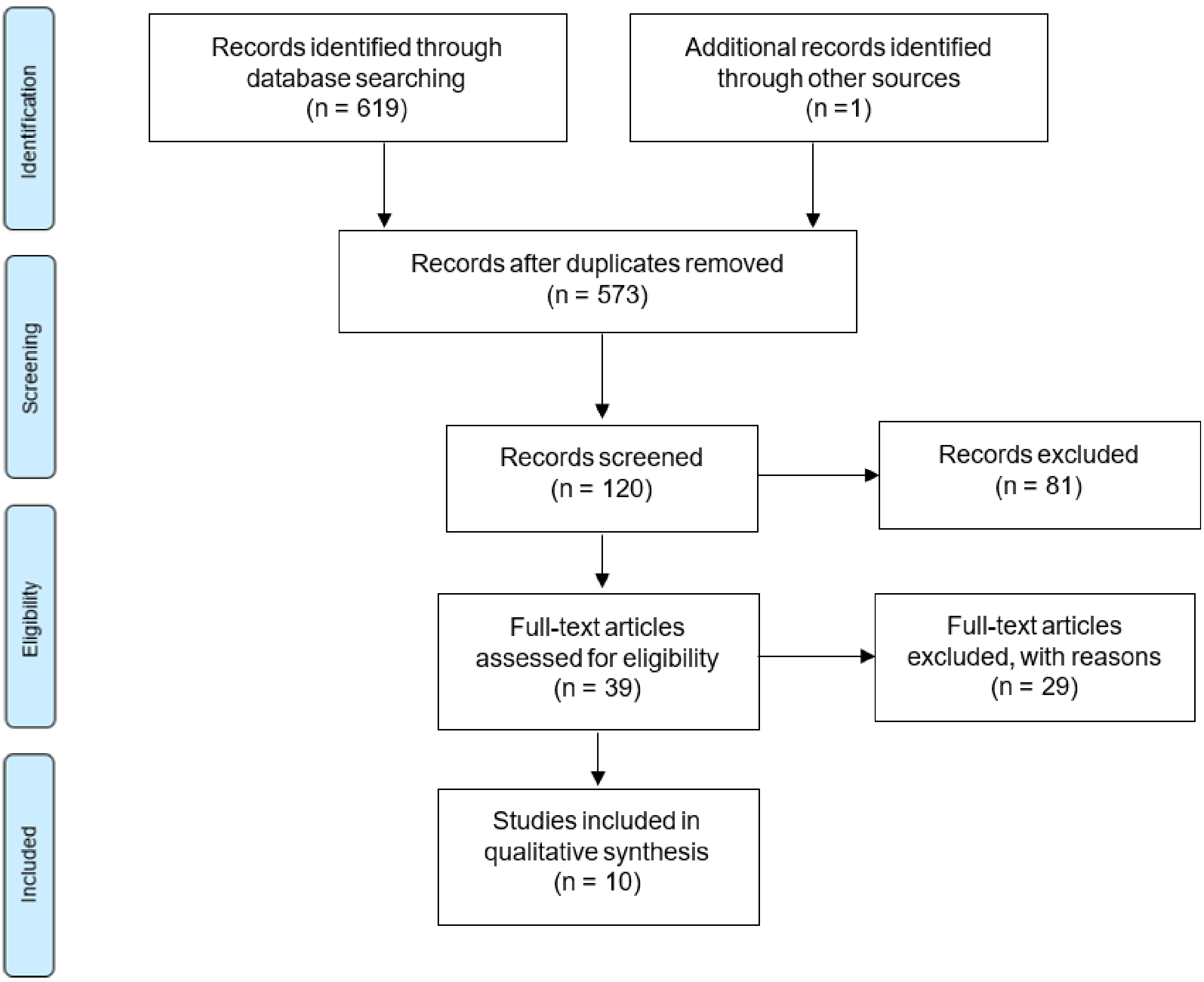

Figure I – Flowchart of the article selection method according to The PRISMA Statement (52).

There were 10 articles that met all the inclusion criteria after full-text assessment and were subject matter to data extraction, methodologic quality assessment, and data synthesis and analysis. Table I summarizes a few information concerning the included studies in the systematic review.

Table I – Studies included in the review and the success rate.

Study	Study design	No. of patients	No. of teeth	Follow-up (years)	Material	Recall Rate (%)	Sucess rate	Survival rate*
Truschnegg *et al.,* 2020 (31)	PCS	73	87	10 to 13	IRM	72.9%	75,80%	79%
von Arx *et al.,* 2019 (1)	PCS	NA	119	10	MTA or MTA white	61%	81,50%	88.2%
Kim *et al.,* 2016 (9)	RCT	NA	260	4	ProRoot MTA or Super EBA	70%	89,50%	91,6%
Caliskan *et al.,* 2016 (32)	PCS	108	108	2 to 6	ProRoot MTA	83.3%	80%	100%
Tawil *et al.,* 2015 (33)	PCS	NA	155	3	Gray ProRoot MTA or SuperEBA	85%	69,30%	100%
von Arx *et al.,* 2014 (30)	PCS	339	339	5	MTA or COMP	79.9%	84,50%	89,1%
Song *et al.,* 2012 (34)	RCT	NA	172	6 to 10	IRM, Super EBA or ProRoot MTA	61%	93,30%	100%
von Arx *et al.,* 2012 (5)	PCS	194	194	5	SuperEBA, ProRoot MTA or Retroplast	87.6%	75,90%	93.4%
Taschieri *et al.,* 2008 (7)	RCT	70	113	2	SuperEBA	89.3%	91%	100%
Chong *et al.,* 2003 (35)	RCT	183	183	2	MTA or IRM	59%	89,80%	100%

Prospective Clinical Study (PCS); Randomized Clinical Trial (RCT); Not Available (NA); zinc oxide-eugenol intermediate restorative cement (IRM); Mineral trioxide aggregate (MTA); dentin-bonded adhesive resin composite (COMP); Super ethoxybenzoic acid (SuperEBA).
*rate not reported in the articles, calculated based on available values.

Of the 10 included studies, 6 PCSs (1,5,30–34) and 4 RCTs (7,9,34,35) were selected. The minimum sample size amongst all studies was 87 teeth (31), while the maximum was 339 treated teeth (30). Concerning the follow-up time, the minimum follow-up period was 2 years (7,32,35) and the maximum was 10 to 13 years (31). Several types of materials were used for outcome evaluation, such as: Mineral Trioxide Aggregate (MTA) (1,5,9,30,32–35); Super ethoxybenzoic acid (SuperEBA) (5,7,9,33,34); zinc oxide-eugenol intermediate restorative cement (IRM) (31,34,35); and resin-based cements (5,30). Regarding the recall rate of the studies, the lowest was 59% (35), while the highest was 89.3% (7).

All studies (1,5,7,9,30–35) applied the classification defined by Rud *et al.* (11) and Molven *et al.* (12) for outcome assessment. The overall success rate ranged from 69.3% (33) to 93.3% (34). However, numerous potential prognostic factors were assessed during each trial (Table II) in order to evaluate its influence on the outcome of EMS through statistical analysis.

The potential prognostic factors fall into 3 groups: patient-related (ie, age; sex (1,5,30–34); smoking and alcohol habits (5,31)); tooth-related (clinical signs/symptoms (5); tooth location and type (1,5,7,30–34); previous nonsurgical (32) or surgical endodontic treatment (1,5,30–32); size (5,31,32) and histopathology (32) of periapical lesions; quality of root canal filling (5,32); absence/presence of a post (5,30,32,33); lesion type (A-F) (34); interproximal bone level (5); absence/presence of dentinal defect (33)); and treatment-related (ie, type of magnification device (microscope vs. endoscope) (7); antibiotic prescription (5,31,32); root-end filling material (1,5,9,30,33–35); postoperative healing course (32,34)).

None of the included studies reported statistically significant differences in the following potential prognostic factors: age; sex (1,5,30–34); clinical signs/symptoms (5); previous nonsurgical (32) or surgical endodontic treatment (1,5,30–32); size (5,31,32) and histopathology (32) of periapical lesions; apical extent of root canal filling (5,32); absence/presence of a post (5,30,32,33); lesion type (A-F) (34); type of magnification device (microscope vs. endoscope) (7); antibiotic prescription (5,31,32); and postoperative healing course (32,34).

However, statistically significant differences were found for 5 potential prognostic factors evaluated among the studies.

Truschnegg *et al.,* 2020 (31) showed a lower success rate in smokers (33.3%) when compared to non-smoking patients (80.4%).Tawil *et al.,* 2015 (33) was the only study that evaluated de effect of root dentinal defects in the EMS outcome; the success rate was lower for the group of teeth with dentinal defects (31.5%) compared with the group of intact teeth (97.3%).

With regard to the tooth type factor, von Arx *et al.,* 2019 (1) showed a higher success rate for maxillary molars (95.2%) compared to maxillary premolars (66.7%). Nevertheless, no other study reported significant differences regarding this factor (5,7,9,30–35).

von Arx *et al.,* 2012 (5) reported significant difference concerning the interproximal bone level of the tooth, showing higher success rate when the mesial and distal interproximal bone level was ≤ 3 mm from the cementoenamel junction or the restoration margin of the tooth.

Finally, with regard to the root-end filling material, von Arx *et al.*, 2014 (30) reported a higher success rate for MTA (92.5%) compared with COMP (76.6%), moreover, in other study (5) the same author also found statistically significant differences between the MTA group (86.4%) and the SuperEBA group (67.3%), with higher success rate for MTA. However, Kim *et al.,* 2016 (9) and Tawil *et al.,* 2015 (33) did not reported significant differences in the outcome when MTA and SuperEBA were compared.

Lastly, a survival rate was calculated based on available values in all studies. This rate ranged from 79% (31) to 100% (7,32-35).

All 4 RCTs were subject matter to quality assessment through the risk of bias evaluation according with the RoB 2 tool (“Risk of bias tool for randomized trials”), as recommended by Cochrane (36). All the evaluated domains are shown in Figure II. The overall risk of bias was low in 3 studies (7,9,35) and showed some concerns in the study performed by Song *et al.,* 2012 (34).

Table II – Summary of the included studies for results analysis.

Study	Study design	Material	Evaluated Parameters	Follow-up (years)	Sample size		Previous treatments		Success Rate (%)			Recall Rate (%)	Results: Prognostic Factors
										Radiographic			
					No. Patients	No. Teeth	No. Re-surgery	No. Orthogonal retreatment	Clinical	Healed (Complete + Incomplete healing)	Non healed (Uncertain + Unsatisfactory healing)		
Truschnegg *et al.*, 2020 (31)	PCS	IRM	1. Age 2. Sex 3. Smoking and alcohol habits 4. Tooth location 5. Previous endodontic surgery 6. Size of the pre and postoperative lesion 7. Perioperative antibiotics	10 to 13	73	87	19	0	79.0	75.8	24.2	72.9	**No significant differences**: Age, sex, alcohol habits, tooth location, previous endodontic surgery, size of the pre and postoperative lesion, or perioperative antibiotics. **Significant differences: Smokers** (lower success rate).
von Arx *et al.*, 2019 (1)	PCS	MTA, MTA white	1. Sex 2. Age 3. Tooth type **4. Type of MTA (ProRoot) used (gray vs white)** 5. Surgery (first-time vs repeat surgery)	10	NA	119	12	NA	NA	Overall rate: 81.5 MTA Group: 84.1 MTA white Group: 80.0	Overall rate: 18.5 MTA Group: 15.9 MTA white Group: 20.0	61.0	**No significant differences:** Age, sex, type of MTA, or first-time versus repeat surgery. **Significant differences:** Tooth type (Higher success rate for **maxillary molars** compared to maxillary premolars).
Kim *et al.*, 2016 (9)	RCT	ProRootMTA, Super EBA	**1. Type of material**	4	NA	260	NA	NA	NA	Overall rate: 89.5 ProRoot MTA Group: 91.6 SuperEBA Group: 89.9	Overall rate: 10.5 ProRoot MTA Group: 8.4 SuperEBA Group: 10.1	70.0	**No significant differences:** Type of material.
Caliskan *et al.*, 2016 (32)	PCS	ProRoot MTA	1. Sex 2. Age 3. Tooth location and type 4. Quality of the root canal filling 5. Presence or absence of a post 6. Previous endodontic treatment or retreatment 7. Previous nonsurgical or surgical endodontic treatment 8. Size and histopathology of periapical lesions 9. Antibiotic therapy 10. Postoperative healing course	2 to 6 (**56%** of the included cases were observed **3–6 years after EMS**)	108	108	18	42	NA	80.0	20.0	83.3	**No significant differences:** Sex, age, tooth location and type, quality of the root canal filling, presence or absence of a post, previous endodontic treatment or retreatment, previous nonsurgical or surgical endodontic treatment, size and histopathology of periapical lesions, antibiotic therapy, or postoperative healing course.
Tawil *et al.*, 2015 (33)	PCS	Gray ProRoot MTA, SuperEBA	1. Sex 2. Age 3. Tooth location 4. Presence vs Absence of dentinal defect 5. Root-end filling material (Super EBA vs. MTA)	3 (median follow-up time of **35.7 months**)	NA	155	NA	NA	NA	Overall rate: 69.3 Dentinal defect Group: 31.5 Intact Group: 97.3	Overall rate: 30.7 Dentinal defect Group: 68.5 Intact Group: 2.7	85.2	**No significant differences:** Sex, Age, tooth location, or root-end filling material (Super EBA vs. MTA) **Significant differences:** Presence of **dentinal defect** (lower success rate)

Prospective Clinical Study (PCS); Randomized Clinical Trial (RCT); Not Available (NA); zinc oxide-eugenol intermediate restorative cement (IRM); Mineral trioxide aggregate (MTA); dentin-bonded adhesive resin composite (COMP); Super ethoxybenzoic acid (SuperEBA).

Study	Study design	Material	Evaluated Parameters	Follow -up (years)	Sample size		Previous treatments		Success Rate (%)			Recall Rate (%)	Results: Prognostic Factors
										Radiographic			
					No. Patients	No. Teeth	No. Re-surgery	No. Orthogonal retreatment	Clinical	Healed (Complete + Incomplete healing)	Non healed (Uncertain + Unsatisfactory healing)		
von Arx *et al.*, 2014 (30)	PCS	MTA, dentin-bonded adhesive resin composite (COMP)	1. Type of material (MTA or COMP) 2. Age 3. Sex 4. Tooth type (maxillary anterior, premolar, and molar or mandibular anterior, premolar, and molar) 5. Presence or absence of post/screw 6. Type of surgery (first-time surgery or repeat surgery).	5	339	339	31	NA	NA	Overall rate: 84.5 MTA Group: 92.5 COMP Group:76.6	Overall rate: 15.5 MTA Group: 7.5 COMP Group: 23.4	79.9	**No significant differences:** Age, sex, type of tooth treated, presence of post/screw, or type of surgery (first-time vs repeat surgery). **Significant differences:** Type of material (higher success rate for **MTA** treated teeth)
Song *et al.*, 2012 (34)	RCT	IRM, Super EBA, ProRoot MTA	1. Age 2. Sex 3. Tooth type 4. Tooth location 5. Lesion type (A-F) 6. Type of material	6 to 10 (6 years - 37 7 years -24 8 years - 27 9 years - 14 10 years – 2)	NA	172	NA	NA	NA	93.3	6.7	60.5	NA
von Arx *et al.*, 2012 (5)	PCS	SuperEBA, ProRoot MTA, Retroplast	1. Patient related (ie, age, sex, and smoking) 2. Tooth related (ie, tooth type, pain, clinical signs/symptoms, size of periapical lesion, interproximal bone level, apical extent of root canal filling, post, and previous apical surgery) 3. Treatment related (ie, antibiotic prescription, root-end filling material, and initial postoperative healing)	5	194	194	16	NA	85.3	Overall rate: 75.9 ProRoot MTA Group: 86.4 SuperEBA Group: 67.3 Retroplast Group: 75.3	Overall rate: 24.1 ProRoot MTA Group: 13.6 SuperEBA Group: 32.7 Retroplast Group: 24.7	87.6	**No significant differences:** Patient related factors, tooth related factors (ie, tooth type, pain, clinical signs/symptoms, size of periapical lesion, apical extent of root canal filling, post, and previous apical surgery), or treatment related factors (ie, antibiotic prescription, and initial postoperative healing). **Significant differences:** Interproximal bone level (higher success rate when the mesial and distal **interproximal bone level was ≤ 3 mm** from the cementoenamel junction (or restoration margin), or type of material (higher success rate for **ProRoot MTA** when compared to SuperEBA).
Taschieri *et al.*, 2008 (7)	RCT	SuperEBA	1. Type of magnification device (microscope vs. endoscope) 2. Tooth location	2	70	113	NA	113	NA	91.0	9.0	89.3	**No significant differences:** Type of magnification device (microscope vs. endoscope), or tooth location (arch)
Chong *et al.*, 2003 (35)	RCT	MTA, IRM	1. Type of material (MTA or IRM)	2	183	183	NA	NA	NA	Overall rate: 89.8 MTA Group: 91.8 IRM Group: 87.2	Overall rate: 10.2 MTA Group: 8.2 IRM Group: 12.8	59.0	**No significant differences:** Type of material

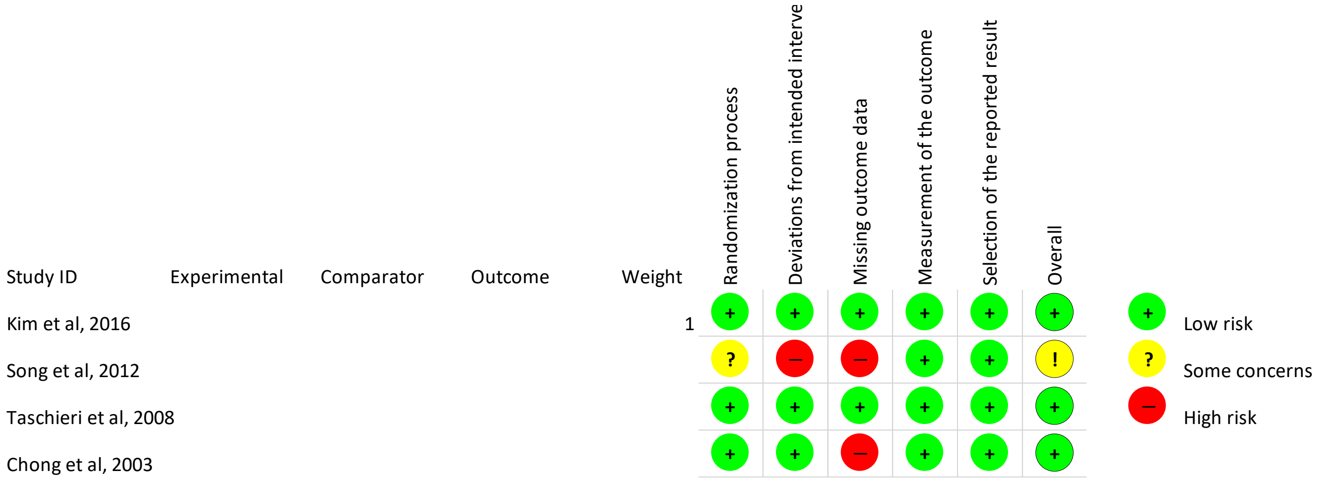

Figure II – Risk of bias summary of the included RCTs.

The 6 remain PCSs were subject matter to quality assessment through the risk of bias evaluation according with the tool ROBINS-I ("Risk of bias in non-randomized studies – Of Interventions"), as proposed by Cochrane (37). The scores are summarized in Table III. The pre intervention bias was shown to be mainly low risk. At the intervention, a low risk of bias was revealed among all studies. Finally, at the post intervention domain, the risk of bias varied into low to moderate, particularly, concerning the measuring outcomes.

Table 3 - Risk of bias summary of the included PCSs.

	Domains							
	Pre intervention		At intervention	Post intervention				
Study	Bias due to Confounding	Bias in Selecting Participants for the Study	Bias in Classifying Interventions	Bias due to Deviations from Intended Intervention	Bias due to Missing Data	Bias in Measuring Outcomes	Bias in Selecting Reported Result	Overall RcB Judgment
Truschnegg et al, 2020 (31)	Moderate	Low	Low	Low	Low	Low	Low	Low
von Arx et al, 2019 (1)	Low	Low	Low	Low	Low	Low	Low	Low
Caliskan et al, 2016 29)	Moderate	Low	Low	Low	Low	Moderate	Low	Low
Tawil et al, 2015 (33)	Low	Low	Low	Low	Low	Moderate	Moderate	Low
von Arx et al, 2014 (30)	Low	Low	Low	Low	Low	Moderate	Low	Low
von Arx et al, 2012 (5)	Low	Low	Low	Low	Low	Low	Low	Low

V. Discussion

The main objective of outcome assessment after an endodontic treatment is to observe healing or improvement of apical periodontitis (38). Based on the results of this review, 2 to 13 years after intervention, the overall success rate of EMS ranged from 69.3% (33) to 93.3% (34); there was a 24% difference between the minimum and the maximum clinical and radiographic success rate. This wide value range might be explained by the methodological design of the studies. Tawil *et al.,* 2015 (33) aimed to evaluate the post-surgical periapical healing response of roots with dentinal defects, diagnosed with the support of transillumination, when compared with intact roots; therefore, this study included a group of teeth with root dentinal defects, which had an extremely low success rate compared to the other group of evaluated teeth; besides, the authors considered incomplete healed classified cases as non-healed. For these reasons, a significant decrease in the overall success rate was verified. On the other hand, Song *et al.,* 2012 (34) just presented the outcome of the teeth considered as healed at the short-term follow-up (ranging from less than 1 year to 5 years) (39), which makes 39.5% its real recall rate, instead of 60.5%, this fact may possibly had led to an overestimation of the outcome results.

Between all the potential prognostic factors evaluated, only 5 presented statistically significant differences regarding the EMS outcome: smoking habits (31); tooth location and type (1); absence/presence of dentinal defect (33); interproximal bone level (5); and root-end filling material (5,30). The impact of a root-end filling material was the most frequently analysed intraoperative factor among the included studies.

Modern endodontic approaches do not contemplate the use of amalgam as root-end filling material due to its potential disadvantages (40); therefore, none of the included studies resorted to its use. Moreover, the use of gutta-percha alone or Glass Ionomer Cement (GIC) for EMS was not reported in these studies. In the present review, the root-end filling materials used for outcome evaluation were the following: Zinc oxide-eugenol intermediate restorative cement (IRM) (31,34,35); Super ethoxybenzoic acid (SuperEBA) (5,7,9,33,34); resin-based cements (5,30); and Mineral Trioxide Aggregate (MTA) (1,5,9,30,32–35).

Zinc oxide eugenol (ZOE) is characterized by a combination of eugenol liquid and zinc oxide powder. In order to improve its mechanical properties, ZOE has been modified into other materials, for instance, Intermediate Restorative Material (IRM) and Super Ethoxybenzoic Acid (SuperEBA), without eugenol. Potential disadvantages of these cements have been described, such as: tissue irritation; moisture sensitivity (34); high solubility; and challenging handling properties (40). Also, SuperEBA has a particular issue related with a possible development of air bubbles resulting in shrinkage when an inadequate powder-to-liquid proportion is used for the filling, which might cause microleakage in a long-term period (34). Truschnegg *et al.,* 2020

(31), Song *et al.,* 2012 (34), and Chong *et al.,* 2003 (35) used IRM as root-end filling material. Chong *et al.,* 2003 (35) was the only study showing comparative results on the EMS outcome between IRM and other material; even though the success rate was higher in the MTA group, no statistically significant difference was found. On the other hand, Kim *et al.,* 2016 (9), Tawil *et al.,* 2015 (33), Song *et al.,* 2012 (34), von Arx *et al.,* 2012 (5), and Taschieri *et al.,* 2008 (7) used SuperEBA as retrograde filling material. von Arx *et al.*, 2012 (5) was the only author who found statistically significant differences between the MTA group (86.4%) and the SuperEBA group (67.3%), with higher success rate for MTA.

In the present study, there were 2 articles (5,30) that evaluated the EMS outcome when a dentine bonding agent was used. Both of them presented a lower success rate in comparison with MTA; however, only one (30) showed statistically significant difference between the two root-end-filling materials. These results may be explained by the necessity of a dry field during the etch/prime/bond process (20); and the requirement of moisture control of such material (40), which can be difficult during the EMS procedure.

In the late 90s, MTA, the first generation hydraulic calcium-silicate cements was introduced in dentistry (40), and later on the second generation emerged with Biodentine, which improved some limitations of MTA, such as the induction of discoloration, the extended setting time and the retarded hydratation (41,42), through the replacement of bismuth oxide (Bi2O3) for zirconium oxide (ZrO2) as radiopacifier agent. These materials received widespread interest due to its high biocompatibility (43). In the present study, most of the included studies used MTA as root-end filling material (1,5,9,30,32–35). Indeed, MTA showed higher success values compared to SuperEBA (5) and COMP (30); these outcome results can be supported by the characteristics described above. Even so, there are some clinical concerns regarding MTA, such as: the probability of washing out because of its long setting time (2h 45min); and the fact of having a sandy consistency after its mix with sterile water, which makes it more difficult to handle, deliver to the operative site, and condense adequately (40).

Recently, new tricalcium silicate-based materials that maintain the desirable properties of prior bioceramic materials and overcome its disadvantages have been developed. The presence of calcium phosphate improves the setting properties of these materials, establishing a crystalline structure comparable with the tooth and bone apatite (44).This type of materials present putty consistency and a faster setting time, becoming easier to handle and deliver to the operative site (45). However, the scientific evidence that supports its clinical use as a root-end filling material remains scarce. In fact, some studies reporting its use were excluded from our review, due to its short follow-up period of 1 year (4,6) and to its retrospective study design (46). Despite their short follow-up periods, Safi *et al.* (4) and Zhou *et al.* (6) reported promising overall success rates evaluated through 2-dimensional periapical radiographies for Root Repair Materials (RRM) of 92% and 94,4%, respectively.

With regard to quality assessment, the risk of bias was calculated for all studies included, either RCTs or PCSs. A low overall risk of bias was obtained for all studies, Song *et al.,* 2012 (34). One of our greatest concerns is related to the risk of bias due to missing data. In fact, there were some studies that included extracted teeth in the statistical analysis (1,7,28,32); however, there were several authors who considered teeth extracted during the follow-up as a dropout, because the reason for extraction is unknow or not related with EMS, such as fracture or prosthetic reasons (5,9,30). Contemplating the patient-centered outcome, this information should not be disposable, since tooth retention is a major concern and missing extraction data will lead to an overestimation of the expected EMS outcome, independently of the reason for extraction. Another important concern is associated with risk of bias due to measuring outcomes. Most of the studies had 2 or more observers (1,5,7,9,30–35), blinded (5,7) and an interobserver variability was assessed (1,9,32,34,35). All studies used the radiographic outcome classification defined by Rud *et al.* (11) and Molven *et al.* (12); nevertheless, one study (33) classified incomplete healing cases as non-healed, which compromised this domain in the risk of bias evaluation. Indeed, an underestimation of the EMS outcome may had occurred, as explained above.

Concerning the follow-up period after an endodontic microsurgery, the amount of time required for the outcome assessment remains questionable (15). There is a need to overcome this particular issue in order to accomplish a long-term predictability of the treated teeth and to make a weighted therapeutic decision (34).

The *European Society of Endodontology (ESE)* defines that regular clinical and radiographic follow-ups for a minimum observation period of 1 year are appropriate; however, longer periods may be necessary when complete healing is not accomplished or in other specific cases. Regarding the outcome assessment of surgical endodontic procedures, *ESE* defends that when a radiolucent area, defined as “surgical defect” or “scar”, persists after 1 year, must be monitored for the next 4 years (38). According to *American Association of Endodontists (AAE)* the outcome assessment should be performed for 1 year or beyond (47).

There is previous evidence reporting reversal to disease after 4 years following traditional endodontic surgery which supports that a short follow-up period could be not enough to identify a recurrence of apical periodontitis (15). However, such findings were not reported in studies with a modern microsurgical approach (9,33,35).

Recent long-term follow-up studies sought after statistically significant differences in the outcome of EMS when long-term follow-up is compared to the outcome at a short-term follow-up period. Von Arx *et al.* (1), showed a significantly lower success rate after 10 years (81.5%) compared with the rates after 1 and 5 years (91.6% and 91.4%, respectively).

However, no statistically significant differences were found when 1- and 5-years follow-up when compared. On the other hand, Kim *et al.* (9) demonstrated a slightly reduction (4.8%) in the overall success rate at 4-year follow-up; but there was no statistically significant difference between 1- and 4-year follow-up periods. In fact, the authors attributed the lower recall rate of the 1-year follow-up of the success group at the 4-year follow-up, as the main cause of this decrease. Two studies (33,35) showed that significant information about healing patterns was revealed 1 year after EMS. Furthermore, Von Arx *et al.* (30) confirmed that cases rated as healed after 1 year remained so in 93.9% of cases after 5 years, with higher predictive value for MTA group (96.7%) in comparison with the COMP group (90.7%). Nevertheless, the classification of uncertain healing at a short-term follow-up appears to be the least predictable of all at a long-term follow-up (32,48).

Some studies suggest that the regression would possibly be counterbalanced by teeth that could be classified as healed at the long-term follow-up but were failures at the short-term (5,34).

For all the reasons described above, we believe that 1-year follow-up may be sufficient to estimate the predictability of EMS outcome at a long-term follow-up; nevertheless, uncertain healing cases at 1-year should continue to be carefully followed and the root-end material used must be considered. On the other hand, long-term follow-up studies allow the achievement of a more reliable patient-centered outcome, due to the possibility of existence of data concerning the survival rate and increase the knowledge of the risk-factors involved in long-term failures, such as root fracture (1), prosthodontic considerations (5), endodontic or periodontological reasons (31), and crown fractures or caries (9).

In this review, strict inclusion and exclusion criteria were employed, with the aim of decreasing the heterogeneity of the included studies and, consequently, achieve the most reliable results possible. Contrary to Igor et *al.* (17), articles whose surgical procedure was not performed under endoscope or microscope were excluded. Concerning the study design, some reviews (18,19) included Retrospective Cohort Studies (RCSs), which was not permitted in this review according to the exclusion criteria. Finally, the last strength of this study is the fact that all studies used the same radiographic outcome classification (11,12), which allowed to make an easier comparison of the outcome results.

Some limitations were found in this study. First, only studies with a long-term follow-up period were included, which compromised the quality of some of them, since the longer the follow-up, the higher the dropout rate (3,34), which might lead to an inherent loss of scientific validity of some conclusions (34). Second, it was challenging to make an objective data interpretation due to the lack of criteria consistency among the studies; there is a need to establish guidelines to report outcome targeted to studies on EMS. Lastly, despite of the current trend of search for comparative outcome results between 2-Dimensional and 3-

Dimensional outcome measurement, the inclusion of such studies (49–51) was not possible due to a short follow-up time (51), a retrospective study design (50), or to the clinical and radiographic criteria applied (49).

Several concerns were found regarding the external validity of the results achieved. First, all included studies were mainly carried out by specialists in a Hospital or University environment (1,5,7,9,30–35) which can lead to an overestimation of the outcome when the procedure is performed under a private clinical setting. Since the outcome has been reported to be influenced by the operator (48), there is a need to develop multicentred, pragmatic studies, in order to evaluate the outcome of EMS in distinct conditions, as what it happens on a daily basis clinical practice. Furthermore, some authors established some rigorous exclusion criteria, such as: teeth with probing depth ≥ 4 mm (35); teeth that did not undergone by NSER; or teeth with traumatic injuries (7). All those criteria are focused on maximizing the efficacy of the intervention, which may contribute to overestimate the EMS outcome and, consequently, compromise the external validity of the results and transference of this evidence to everyday clinical practice (effectiveness of the intervention).

The development of a meta-analysis on the EMS outcome would be ideal, in order to pool data from multiple studies and increase the sample size and power. Nevertheless, different study designs, techniques, follow-up periods, and inclusion/exclusion criteria are still a major concern. All the included RCTs should have at least 2 variables in common (for instance, the root-end filling material) in order to be possible to proceed to a pooled statistical analysis. Unfortunately, the studies included in this systematic review present different variables among them and, therefore the conduction of a meta-analysis was not considered appropriate.

Lastly, no cost-benefit ratio regarding the root-end filling material was performed in any of the studies. This ratio might be interesting to consider on a therapeutic decision, for both the dentist and the patient.

VI. Conclusion

Despite of the limitations of this study, the long-term EMS outcome showed high success rates and predictability when performed under modern surgical techniques while associated with biocompatible and bioactive root-end filling materials. Moreover, EMS may be influenced by the following potential prognostic factors: smoking habits; tooth location and type; absence/presence of dentinal defect; interproximal bone level; and root-end filling material. Regarding the root-end filling material, MTA showed better outcome results.

An objective data interpretation was not possible to make because of the lack of criteria consistency among the studies, mainly, due to divergences on the success definition or dropout considerations, particularly, concerning the extracted teeth. In order to accomplish a more reliable data on the outcome of EMS through the development of a high-quality meta-analysis, there is a need to establish guidelines for trials reporting outcome on EMS. In this sense, future trials should be conducted by consistent and homogeneous methodology among them, particularly, concerning the reported heterogenous criteria described above.

Long-term follow-up studies allow the achievement of a patient-centered outcome, due to the possibility of existence data concerning the survival rate and the reasons for long-term failures. Furthermore, the cost-benefit ratio regarding the root-end filling material might be interesting to report on future trials.

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IX. Table index

X. Figure index

XI. Appendix

Appendix 1:

Criteria described by Rud et al (1) and Molven et al (2):

Complete Healing*	1. Re-formation of periodontal space of normal width and lamina dura to be followed around the apex. 2. Slight increase in width of apical periodontal space, but less than twice the width of non-involved parts of the root. 3. Tiny defect in the lamina dura (maximum 1mm) adjacent to the root filling. 4. Complete bone repair; bone bordering the apical area does not have the same density as surrounding non-involved bone. 5. Complete bone repair; no apical periodontal space can be discerned.
Incomplete Healing*	The rarefaction has decreased in size or remained stationary, and is characterized by: 1. Bone structures are recognized within the rarefaction; the periphery of the rarefaction is irregular and may be demarcated by a compact bone border; the rarefaction is located asymmetrically around the apex; the connection of the rarefaction with the periodontal space is angular; 2. Isolated scar tissue in the bone.
Uncertain Healing**	The rarefaction has decreased in size, and with one or more of the following characteristics: 1. The RL is larger than twice the width of periodontal space. 2. The RL is bordered by lamina-dura like bone structures. 3. The RL has a circular or semicircular periphery. 4. The RL is located symmetrically around the apex as a funnel-shaped extension of the periodontal space.
Unsatisfactory Healing**	The RL area appears enlarged or unchanged.

*Complete and incomplete/scar categories were combined as success.

** Uncertain and unsatisfactory healing were combined as failure.

Appendix 2:

Penn 3D criteria (3):

Complete healing*	1. Re-formation of periodontal space of normal width and lamina dura over the entire resected and un-resected root surfaces. 2. Slight increase in width of apical periodontal space over the resected root surface, but less than twice the width of non-involved parts of the root. 3. Small defect in the lamina dura surrounding the root-end filling. 4. Complete bone repair with discernible lamina dura; bone bordering the apical area does not have the same density as surrounding non-involved bone. 5. Complete bone repair. Hard tissue covering the resected root-end surface completely. No apical periodontal space can be discerned.
Limited Healing*	Complete healing can be observed in immediate vicinity of the resected root surface, but the site demonstrates one of the following conditions: 1. The continuity of the cortical plate is interrupted by an area of lower density. 2. A low density area remains asymmetrically located around the apex or has angular connection with the periodontal space. 3. Bone has not fully formed in the area of the former access osteotomy 4. The cortical plate is healed but bone has not fully formed in the site.
Unsatisfactory Healing**	The volume of the low density area appears enlarged or unchanged.

* Complete and limited categories were combined as success (Score of 1).

** Unsatisfactory cases received a score of 2.

Appendix 3:

Classification of endodontic microsurgical cases according to Kim *et al.* (4):

Class A*	Represents the absence of a periapical lesion, no mobility and normal pocket depth, but unresolved symptoms after nonsurgical approaches have been exhausted. Clinical symptoms are the only reason for the surgery.
Class B*	Represents the presence of a small periapical lesion together with clinical symptoms. The tooth has normal periodontal probing depth and no mobility. The teeth in this class are ideal candidates for microsurgery.
Class C*	Teeth have a large periapical lesion progressing coronally but without periodontal pocket and mobility.
Class D	Clinically similar to those in class C, but have deep periodontal pockets.
Class E	Teeth have a deep periapical lesion with an endodontic-periodontal communication to the apex but no obvious fracture.
Class F	Represents a tooth with an apical lesion and complete denudement of the buccal plate but no mobility.

*Classes A, B, and C represent no significant surgical treatment problems, and the conditions do not adversely affect treatment outcomes.

** Classes D, E, and F present serious difficulties. Although these cases are in the endodontic domain, proper and successful treatment requires not only endodontic microsurgical techniques but also concurrent bone grafting and membrane barrier techniques. The predictable and successful management of these cases is the true challenge.

Appendix 4:

The term: “(((((((periapical diseases[MeSH Terms]) OR periapical diseases) OR root-end filling) OR root canal therapy[MeSH Terms]) OR root canal therapy)) AND ((((((((((((((((apicoectomy[MeSH Terms]) OR apicoectomy) OR surgical endodontic retreatment) OR apical surgery) OR retreatment[MeSH Terms]) OR apical surgery) OR periapical surgery) OR retrograde surgery) OR endodontic surgery) OR root-end surgery) OR root-end cavity preparation) OR periradicular surgery) OR microsurgery[MeSH Terms]) OR retreatment[MeSH Terms]) OR root-end ressection) OR apicectomy)) AND (((((radiographic outcome) OR treatment outcome[MeSH Terms]) OR treatment outcome) OR success rate) OR radiographic success rate) NOT (review OR case report)” was used on Pubmed search. Limits used were studies on humans published from 1990/01/01.

Appendix 5:

The term: “[((Retrograde Obturation[MeSH descriptor]) OR (retrograde obturation) OR (root end filling)) AND ((Apicoectomy[MeSH descriptor]) OR (apicoectomy) OR (apical surgery) OR (periapical surgery) OR (Microsurgery[MeSH descriptor]) AND ((Treatment Outcome[MeSH descriptor]) OR (success rate) OR (radiographic success rate))]” was used on The Cochrane Library search. Limits used were trials and studies published from 1990/01/01.

Appendix 6:

Reasons for exclusion according to the exclusion criteria previously established:

Exclusion criteria	Articles
2	Song *et al.*, 2018 (5); Al-Nuaimi *et al.*, 2018 (6); Kruse *et al.*, 2017 (7); Kim *et al.*, 2016 (8); da Silva *et al.*, 2015 (9); Shinbori *et al.*, 2015 (10); Mente *et al.*, 2015 (11); Kang *et al.*, 2015 (12); Lui *et al.*, 2014 (13); Song *et al.*, 2014 (14); Bryce *et al.*, 2013 (15); Angiero *et al.*, 2011 (16); Taschieri *et al.*, 2011 (17); Moshonov *et al.*, 2011 (18); Song *et al.*, 2011 (19); Taschieri *et al.*, 2010 (20); Salehrabi *et al.*, 2010 (21); Gilbert *et al.*, 2010 (22); Tsesis *et al.*, 2009 (23); Jonasson *et al.*, 2008 (24); Iqbal *et al.*, 2007 (25); Oberli *et al.*, 2007 (26); Xu *et al.*, 2006 (27); Tsesis *et al.*, 2006 (28); von Arx *et al.*, 2005 (29); Oginni *et al.*, 2002 (30); Rahbaran *et al.*, 2001 (31); Testori *et al.*, 1999 (32); Danin *et al.*, 1999 (33); Rud *et al.*, 1998 (34); Mor *et al.*, 1995 (35)
3	Kruse *et al.*, 2017 (7); Kacarska *et al.*, 2017 (36); Wang *et al.*, 2017 (37); Kruse *et al.*, 2016 (38); Song *et al.*, 2013 (39); Saunders *et al.*, 2008 (40); Wang *et al.*, 2004 (41)
4	Kulakov *et al.*, 2018 (42); Kruse *et al.*, 2017 (7); Kacarska *et al.*, 2017 (36); Barone *et al.*, 2010 (43); Penarrocha *et al.*, 2007 (44); Yazdi *et al.*, 2007 (45); Leco Berrocal *et al.*, 2007 (46); Gagliani *et al.*, 2005 (47); Maddalone *et al.*, 2003 (48); Rud *et al.*, 2001 (49); Zuolo *et al.*, 2000 (50), Kvist *et al.*, 1999 (51); Rud *et al.*, 1996 (52); Sumi *et al.*, 1996 (53); Molven *et al.*, 1996 (54); Rud *et al.*, 1996 (55); Jesslen *et al.*, 1995 (56)
5	Safi *et al.*, 2019 (57); Penarrocha *et al.*, 2019 (58); Meschi *et al.*, 2018 (59); Zhou *et al.*, 2017 (60); Kacarska *et al.*, 2017 (36); von Arx *et al.*, 2016 (61); von Arx *et al.*, 2016 (62); von Arx *et al.*, 2016 (63); Jorge *et al.*, 2015 (64); Kurt *et al.*, 2014 (65); Song *et al.*, 2013 (66); Kreisler *et al.*, 2013 (67); Song *et al.*, 2012 (68); Shen *et al.*, 2012 (69); Patel *et al.*, 2012 (70); Walivaara *et al.*, 2011 (71); von Arx *et al.*, 2010 (72); Walivaara *et al.*, 2009 (73); Shearer *et al.*, 2009 (74); Taschieri *et al.*, 2008 (75); Carrillo *et al.*, 2008 (76); Garcia *et al.*, 2008 (77); Kim *et al.*, 2008 (78); Penarrocha *et al.*, 2008 (79); Taschieri *et al.*, 2007 (80); de Lange *et al.*, 2007 (81); Penarrocha *et al.*, 2007 (44); Walivaara *et al.*, 2007 (82); von Arx *et al.*, 2007 (83); Taschieri *et al.*, 2007 (84); Taschieri *et al.*, 2006 (85); Marin-Botero *et al.*, 2006 (86); Filippi *et al.*, 2006 (87); Taschieri *et al.*, 2005 (88); Marti-Bowen et al, 2005 (89); von Arx *et al.*, 2003 (90); Dietrich *et al.*, 2003 (91); Jensen *et al.*, 2002 (92); Vallecillo Capilla *et al.*, 2002 (93); von Arx *et al.*, 2001 (94); von Arx *et al.*, 1999 (95); Danin *et al.*, 1996 (96); Van Doorne *et al.*, 1996 (97); Pecora *et al.*, 1995 (98)
6	von Arx *et al.*, 2019 (99); Kulakov *et al.*, 2018 (42); Kacarska *et al.*, 2017 (36);
7	von Arx *et al.*, 2019 (99); Penarrocha *et al.*, 2019 (58); Riis *et al.*, 2018 (100); Meschi *et al.*, 2018 (59); Kulakov *et al.*, 2018 (42); Kacarska *et al.*, 2017 (36); Menendez-Nieto *et al.*, 2016 (101); Caliskan *et al.*, 2016 (102); Taschieri *et al.*, 2014 (103); von Arx *et al.*, 2011 (104); Wang *et al.*, 2004 (31); Wang *et al.*, 2004 (105);
8	Zandi *et al.*, 2019 (106); Castro *et al.*, 2018 (107); Meschi *et al.*, 2018 (59); Kulakov *et al.*, 2018 (42); Prati *et al.*, 2018 (108); Fariniuk *et al.*, 2017 (109); Kruse *et al.*, 2017 (7); Kacarska *et al.*, 2017 (36); Menendez-Nieto *et al.*, 2016 (101); Neskovic *et al.*, 2016 (110); Patel *et al.*, 2012 (70); Song *et al.*, 2011 (111); de Chevigny *et al.*, 2008 (112); Xu *et al.*, 2006 (27); Farzaneh *et al.*, 2004 (113); Sjogren *et al.*, 1997 (114)

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