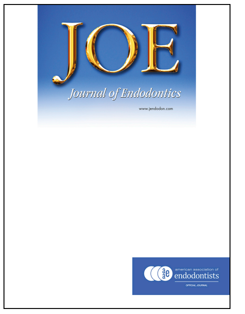

Prognostic factors and primary healing on root perforation repaired with MTA: a 14-year longitudinal study

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Prognostic factors and primary healing on root perforation repaired with MTA: a 14-year longitudinal study

Running head: Root perforations: prognostic factors on 14 years follow-up

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Prognostic factors and primary healing on root perforation repaired with MTA: a 14-year longitudinal study

ABSTRACT

Introduction: Few data are available on the long-term efficacy of mineral trioxide aggregate (MTA) in treating root canal perforations. This prospective cohort study builds on a previously reported trial to determine the outcome for teeth with root perforations treated with orthograde MTA after longer follow-up and identify potential prognostic factors. **Methods:** A prospective cohort study was performed, enrolling (1999-2009) patients with a single dental perforation treated with MTA. Preoperative, intra-operative, and postoperative information was evaluated, and the outcomes were dichotomized as healed or non-healing. Patients were followed-up yearly until 2018 for a maximum of 17 years post-treatment, with controls carried out until 14 years. Clinical and radiographic outcomes were evaluated using standardized follow-up protocols. **Results:** Of the 124 enrolled patients (median age 36.5 years, 53.2% male), 115 were healed at the first (n=110, 89%) or second (n=5, 4%) annual post-treatment check-up, while 9 subjects (7%, 4 females 18 - 65 YO) did not heal. Characteristics significantly associated with non-healing were gender, positive probing, size, and perforation site. Perforations recurred in 48 teeth during the follow-up with the estimated probability of reversal at 5, 10 and 14 years of 6% (95% CI, 2-10%), 30% (95%CI, 20-38%) and 62% (95% CI,46-73%), respectively. Positive probing had a higher reversal risk (HR=3.3, p≤0.001), and perforations >3mm were more likely to have a reversal (HR=4.1, p<0.001). **Conclusions:** The risk of reversal for healed MTA-treated root canal perforations, initially relatively low, vastly increases over time.

KEY WORDS

Root canal treatment, iatrogenic, perforation, treatment failure, MTA.

INTRODUCTION

Root canal perforations are still among the most common complications observed in modern endodontics (1). Approximately 2% to 12% of endodontically treated teeth have iatrogenic root perforations (2), and they were discovered in up to 12% of patients after non-surgical retreatment of previous root canal therapies (3). While some lesions are pathological, the vast majority result from iatrogenic events. A perforation is a break of the tooth hard tissues that causes inflammation and loss of attachment in the supporting tissues, regardless of the cause (4). If left untreated, perforations cause the root to lose integrity and the neighboring periodontal tissues to be impaired. As a result, the periradicular tissues' health and, consequently, the tooth's prognosis is jeopardized. According to Kvinnsland et al., a large percentage (53%) of such conditions occurs due to prosthodontic therapy, with 47% occurring during routine endodontic treatment (5).

Early identification, the size, form, location, and nature of the perforation, the therapy chosen, the materials used for the obturation, the host reaction, and, most significantly, the practitioner's expertise all play a role in the successful management of root canal perforations (6,7). According to Fuss & Trope, the location is likely the crucial factor impacting prognosis, with crestal root perforations most vulnerable to epithelial migration and rapid pocket formation (8). Therefore, this latter condition has the lowest repair success rate (9). Since bleeding typically makes access to the perforated region complex, viewing the perforation location itself might be challenging. Even for the most skilled endodontist, repairing root perforations can indeed be difficult.

Mineral trioxide aggregate (MTA) was the first material to obtain predictable repair and healing of root perforations. Previously-used materials had a poor prognosis, especially for relatively wide or epicrestally situated perforations (8). This outcome is mainly due to poor biocompatibility or insufficient sealing ability by the material. Both these issues were successfully overcome by MTA, a material created at Loma Linda University (California) in the early 1990s (10) that shows excellent biocompatible and sealing abilities (11,12). In fact, MTA set new benchmarks in the capabilities of endodontic materials. Some authors claimed this material to exhibit bioactive properties (13,14) even if more recent literature questioned this effect due to biases of the experimental conditions (13,15). MTA use for perforation repair was assessed by some animal studies (16,17) and a few clinical research (18–23). However, only four clinical studies address the long-term prognosis of MTA used to repair perforations (18,19,21,23).

In 2016, Gorni et al., in a prospective cohort study, evaluated the primary healing of root perforations repaired with MTA and assessed the behavior of such treatments over an 8-year follow-up (23). The present study aimed to gather additional data by adding a follow-up of up to 14 years of the same cohort. An additional aim was to determine patient/clinical characteristics affecting long-term prognosis.

MATERIALS AND METHODS

Study design

This prospective cohort research took place in the Unit of Endodontics, DMCO San Paolo, Department of Dentistry, University of Milan, Italy, from January 1999 to June 2009. In December 2018, the follow-up was closed. The research was carried out in compliance with Good Clinical Practice (GCP) principles and the current version of the

Declaration of Helsinki from 1964. All patients agreed on written informed consent to participate in the trial.

Patients

Patients with a single tooth perforation were eligible to participate, both male and female. The recruiting took place between January 1999 and June 2009. Each patient provided a complete medical and dental history. The following were used as exclusion criteria:

• To be below an age of 18.

• Women of childbearing age who do not use appropriate contraception, pregnant women, and breastfeeding mothers;

• Immune system is weakened;

• Incomplete pre-treatment or post-treatment records;

• Reluctance to take part in the research.

Diagnosis of perforations

Clinical (visualization, periodontal probing, bleeding spots on paper points) and radiographic exams were used to diagnose perforations. A strip perforation was documented as blood on the side of a paper point. The presence/location/intensity of pain, bouts of swelling/inflammation, or abscess, as well as data about the previous treatment of the concerned tooth, were noted. The location and extent/size of each perforation were identified using a periodontal probe and documented at enrollment and regular intervals after that. The size was assessed based on the root canal length in the unfrequent cases that were not apparent.

Treatment of perforations

All perforations were identified and treated on the same day they occurred. One skilled operator conducted all clinical operations utilizing magnification, either loupes (5.5 x) or surgical microscope (8x or greater). The region was debrided, cleaned, disinfected, and dried before the perforation was sealed, as follows. A mild preparation of the margins was accomplished whenever possible by ultrasound diamond-coated tips (Newtron Tips, Acteon, Merignac, France) under copious water irrigation. An irrigation with 5% NaClO solution (Ogna Pharmaceutical, Giovanni Ogna e figli S.r.l., Muggiò, Italy) was used for 1 min to obtain an optimal disinfection. The formation of a blood clot was favored by gentle compression with sterile cotton pellets. The area was dried by paper points and gentle air blow provided by a Stropko syringe (Kerr Sybronendo, Orange, CA, USA). If compression with sterile cotton pellets did not stop the bleeding from the perforation site, calcium hydroxide powder (DentaFlux, Madrid, Spain) was used to treat the site. MTA powder (ProRoot MTA DENTSPLY Maillefer - gray and white versions) was mixed with distilled water in the recommended 3:1 ratio (15, 20, 21). The material was inserted into the perforation using an MTA applicator (Dentsply-Maillefer, Ballaigues, Switzerland), and a moist cotton pellet was gently placed over the material to facilitate setting. The final filling took place after 48 to 72 hours to allow the cement setting.

Preoperative and intra-operative measurements

The following data were recorded:

- Age, gender

- Location of the tooth (anterior, premolar, or molar)
- Perforation site/location:
    - Coronal (upper third of the root canal)
    - Middle third of the root canal
    - Apical (lower third of root canal)
- Perforation size (≤1 mm, 2-3mm, >3mm)
- Probing to assess the presence of an already existent periodontal pocket, assessed on a gingival level using a dichotomous score: 'negative probing' for probing depth <4 mm, and 'positive probing' for probing depth ≥4mm. No distinction was made whether one or more aspects of the tooth exceeded the 4mm cut-off.
- Intra-oral dental radiographs were collected before perforation repair (pre-op), after repair, and at each follow-up visit.
- Demographic, clinical, and radiological data were recorded on enrollment and annual follow-up.

Outcome measures

Perforations were identified as healed when there were no -

- Clinical signs/symptoms – pain, inflammation, bleeding, absence of sinus tract;
- Loss of function;
- Periradicular periodontitis;
- Radiolucency near perforation site;
- Evidence of ongoing root resorption.

Perforation treatment was considered failed if any of the above was observed/recorded during the follow ups. The follow ups were done at 1 and 2 years to identify healed lesions. Additional follow-ups were performed every year up to 14 years after the procedure.

Statistical analyses

All calculations were performed using the open-source R statistical computing environment (24). The percentages of healed and non-healing teeth within each stratum (e.g., male) of the patient population (e.g., gender) and the characteristics of the perforations were calculated. Teeth determined to have healed at the second annual follow-up according to the previously mentioned criteria were stratified for gender, age (≤50 years vs. >50 years), location, probing result, site, and perforation size. The discrete hazard and survival functions were calculated to describe healed/non-healing over time (25). Person-time data (combining the number of persons and their time contribution) was computed from healed lesions (either first or second annual follow-up). The median length of follow-up was determined using the reverse Kaplan-Meyer method (26). A discrete-time hazard model employing the complementary log-log link was used to examine the role of patient and clinical characteristics associated with non-healing perforations (25). Univariate and multiple regression analyses were performed for the following predictors: age (≤50 and >50 years), tooth location (anterior + premolar vs. molar), perforation location (coronal vs. apical + middle third), size (≤3mm vs. >3mm) and probing.

Categorization was done based on previous studies and clinical considerations (2). In addition, exploratory graphical analyses were performed to verify the proportional hazard assumption and the presence of time-dependent effects. The functional form of baseline risk overtime was also investigated. The final multivariable model was adjusted for sex and age at treatment and included all available predictors. The model results are presented as hazard ratios (HRs) of perforation reversal and their 95% confidence intervals (CIs). The stability of the final model was verified using non-parametric bootstrap (5000 samples). We computed a bootstrap 95% confidence interval for each variable using the 2.5 and 97.5 percentiles of the bootstrap distribution. The HR was considered significant if the bootstrap 95% CI did not include 1.

Based on the multiple discrete-time hazard model, adjusted non-healing probability curves were fitted for size and probing, using the corrected group prognosis method, as follows. Survival curves were first calculated for each patient using the level of the covariate of interest (e.g., negative probing) and the patient's values for the other covariates and then averaged (27). In addition, 95% CI were estimated applying bootstrap re-sampling (1000 samples) and the percentile method.

RESULTS

Healing

One hundred and twenty-four patients (median age 36.5 years, 53.2% male) with a single root perforation following endodontic treatment were eligible and included in the study. There was no loss to follow-up until the second year. A total of 115 were found healed at first (n=110; 89%) or second (n=5; 4%) annual post-treatment follow-up, while the remaining nine subjects (4 women and 5 men aged between 18 and 65 years; 7%) were considered non-healing (**Table 1**).

A higher percentage of patients >50 years with perforations were classified as non-healing compared with those ≤50 years, although the difference was not significant (12% vs. 6% respectively, p=0.3, **Table 1**). Patients with non-healing perforations had significantly higher positive probing occurrence than healed patients (16% vs. 1% respectively, p=0.003). Overall, there was no evident association between the perforation site and healing (p=0.2). The non-healing perforations were 3% coronal, 12% middle third, and 0% in the apical region. Also, there was no significant association between perforation size and healing (p=0.16). According to the lesion size, the percentage of non-healing teeth was: 15% >3mm, 5% for 2−3 mm, and 0% for smaller perforations. All anterior teeth perforations healed, while perforations in 14% of premolars and 8% of molars did not (p=0.3).

Predictive factors for risk of reversal in healed lesions

A total of 30% of patients were still under follow-up at 14 years when the study was curtailed. The number of censored (loss-to-follow up) patients over time is presented in Figure 1. Although the maximum potential follow-up was 17 years, analyses were carried out up to 14 years as there were too few patients with the longer follow-up. The median length of follow-up was 12 years (IQR, 10–16 years). Considering the 115 teeth healed by the second year follow-up visit, perforations recurred in 48 teeth during the 14-year follow-up with the estimated probability of reversal at 5, 10, and 14 years of 6% (95% CI, 2-10%), 30% (95%CI, 20-38%) and 62% (95% CI,46-73%), respectively (Figure 1). The results of the univariate and multiple regression models regarding the associations having a greater likelihood of recurring perforations are reported in **Table 2**. Patients with a positive probing (>4 mm) indicating a previously existent periodontal pocket had a higher risk compared to patients with a negative probing (HR=3.3, $p \leq 0.001$), and patients with perforations >3mm were more likely to have reversal compared to those with smaller initial lesions (HR=4.1, $p<0.001$). A clinical example of reversal is shown in Figure 3.

The stability of the HRs estimated from the final multivariable model was verified using non-parametric bootstrap sampling. The 95% CIs of the HRs obtained with bootstrap were in accordance with those from the model (i.e., when the predictor had a significant p-value in the model, both the model and the bootstrap 95% CI did not include 1). Using the multiple regression model adjusted for the other covariates (corrected group prognosis) in patients with negative probing at 5, 10, and 14 years, the probabilities (95% CI) of lack of recurrent problems were 96.8% (96.4–97.2%), 82.4 (80.2-84.5) and 52.3% (48.3–55.9%), while only 90.1% (88.9–91.4%), 57.2 (53.3-60.8) and 18.6% (16.2–20.2%) of patients with positive probing were problem-free at the same time points (**Figure 2, left panel**) (26,27). Reversal-free probabilities at 5, 10 and 14 years for patients with a large perforation (>3mm) were 87.6% (86.5–89.0%), 48.4 (45.0-52.0) and 11.5% (9.6–12.8%), compared to 96.7% (96.4–97.1%), 81.8 (80.2-83.8) and 49.4% (46.5–53.5%) for patients with perforations smaller than 3mm (**Figure 2, right panel**).

DISCUSSION

Root canal perforations, no matter their cause, can have major consequences. Therefore, it is critical to obtain treatment of the perforation as soon as possible to preserve the affected tooth's long-term survival (4). However, even skilled endodontists find it challenging to control perforations effectively. Since its introduction, mineral trioxide aggregate has been extensively used in repairing root canal perforations, showing promising results (11,12,22). Even though MTA is one of the most investigated materials in dentistry, with impressive outcomes, the vast majority of published data is based on in vitro and animal studies. Available clinical trials are uncommon, and the first ones that have been published have tiny sample sizes, resulting in a low overall level of evidence (18,20,22).

Our study is based on the prospective follow-up of a cohort of patients that underwent perforation repair using MTA (23). The achieved follow-up (14 years) and the number of patients still present at that recall time make this one of the largest, long-term, prospective studies to investigate the behavior of treated perforations. Despite having encouraging healing rates (92%), a surprisingly high failure rate could be found after 14 years, with an estimated probability of reversal of 62%. The prognostic factors that significantly impacted the failure rates were the presence of a pre-existing periodontal pocket (probing > 4.0 mm) and the initial perforation size (>3.0 mm). In such cases, reversal probability plummeted to 81.4% and 88.5% after 14 years, respectively, for the presence of probing and a perforation larger than 3.0 mm. Kaplan-Meyer analysis applied to all examined perforation treatments showed a very low initial failure rate up to 8 years of follow-up. After that period, a relevant increase in failure rates was found. The presence of positive probing led to progressively higher failure rates during the whole follow-up. Similarly, higher failure rates were observed for large perforations (>3.0 mm) compared with smaller ones.

In a retrospective examination of healing rates of 70 perforation repairs done by six endodontic specialists, Pontius et al. observed a 90 percent success rate on a mean 3 years follow-up, in agreement with the data regarding healed lesions obtained in this study (22). Most of these perforations repairs were made using MTA. They identified as prognostic factors influencing the healing, location of the perforation, sex of the patient, and restorative status of the tooth before perforation repair. It has to be noted that the factor “sex of the patient” was at its significance limit (p=0.04), and that may have been influenced by a relatively short follow-up, the use of different filling materials and the presence of several endodontic specialists.

One of the most comprehensive clinical studies on this topic was conducted by Mente et al. (20) and updated with a larger sample size in 2014 (19). Similar to the present study, they performed a historical cohort study that followed a previously reported trial to assess the healing and failure of root perforations managed by the orthograde placement of MTA. Using the same healing criteria as in this study, the Authors found a low failure rate (85% after 9 years of follow-up) that was slightly lower than our outcomes (75% after 9 years). In agreement with our findings, the healed rate of larger perforations (size, >3 mm) was lower than that of smaller perforations. However, none of the considered prognostic factors significantly affected the outcome. The authors suggested that prognostic factors, historically considered important in the pre-MTA era, might no longer be applicable post-MTA, as it provides excellent sealing ability regardless of location and/or size (19). This concept seems to lose its efficacy over extended follow-ups, where, as highlighted in the present study, the presence of a pre-existing periodontal pocket and the perforation size dramatically increased the probability of a reversal. Krupp et al. (2013) investigated the success rate for the repair of root perforations using MTA in a retrospective study that used the same healing criteria but a lower follow-up (3.4 years) (21). Only 73% of the repaired perforations healed compared to 93% of the present study. The Authors identified two prognostic factors for healing: the presence of a preoperative lesion at the perforation site and direct contact between the perforation and the oral cavity. However, such prognostic factors could not be compared with the ones of the present study or other literature studies on MTA-treated root perforations. Main et al., in 2004, performed a study on the healing of root canal perforations treated with MTA, showing a 100% of healed lesions (18). Nevertheless, follow-up was reduced (up to 2 years), and the sample size was limited (16 subjects).

One of the main issues that were highlighted by the present study is the long-term stability of the seal provided by MTA. This material may be subjected during clinical application to an inflammatory environment with a pH as low as 5.0 (28), especially when in presence of a periodontal pocket, or consequent to large perforations entailing increased inflammatory processes. Literature data show that a low pH might delay setting processes, alter adhesion, or enhance MTA's solubility (28,29). The dissolution of MTA over time when exposed to an acidic pH, which may reflect an environment caused by microbial colonization, and these changes may facilitate the penetration of microorganisms or their metabolic products into the periapical tissues through gaps and voids along the marginal sealing (28). Future research needs to address such mechanisms and to study the interactions of the material with a colonizing biofilm to improve its performances on the long term.

One of the possible limitations of this study was that a single, experienced endodontist performed all treatments using magnification. Given the intrinsic difficulties of managing treatment of perforations, experience and good visualization of the operative site may have played a role in improving treatment outcomes. Despite that, the failure rates at the last follow-up (14 years) are not very promising. This observation may entail that material behavior over a long time might be unsatisfactory, contrarily to its short and medium-term performances.

Another possible bias was using calcium hydroxide to manage the perforation's bleeding. Increased bleeding may indicate inflammation in the tissues around the perforation; however, in most situations, little bleeding is present (30). In the present study, MTA was immediately applied to the perforation, with only a few cases requiring the application of calcium hydroxide powder prior to MTA to control bleeding, as described by Yildirim et al. (31).

CONCLUSIONS

The present study results show that the risk of recurrent problems in healed MTA-treated root canal perforations increases over time. If the reversal probability was low at 5-year follow-up (6%), it increased up to 62% after 14-years. This finding highlights the necessity to study and improve the long-term material behavior (especially under acidic conditions of the microenvironment and microbial colonization) to increase the longevity of perforation treatments. Furthermore, earlier prognosis criteria for perforated teeth may need to be re-evaluated because of this evidence.

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The authors deny any conflicts of interest related to this study.

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Table 1. Characteristics of the cohort of 124 teeth treated for perforations between 1999 and 2009 at the Unit of Endodontics, DMCO San Paolo, Milan, Italy. P-values according to Fisher's test ($p<0.05$). Analyses were performed at the second-year follow-up.

	healed N (%)	**non-healing N (%)**	**total N (%)**	**p-value**
Age				0.3
≤ 50 years	101 (94)	7 (6)	108 (87)	
>50 years	14 (88)	2 (12)	16 (13)	
Gender				1
Male	61 (92)	5 (8)	66 (53)	
Female	54 (93)	4 (7)	58 (48)	
Tooth location				0.3
Anteriors	17 (100)	0 (0)	17 (14)	
Premolars	12 (86)	2 (14)	14 (11)	
Molars	86 (92)	7 (8)	93 (75)	
Probing				**0.003**
Negative	74 (99)	1 (1)	75 (60)	
Positive	41 (84)	8 (16)	49 (40)	
Perforation site				0.2
Coronal	58 (97)	2 (3)	60 (48)	
Middle third	53 (88)	7 (12)	60 (48)	
Apical	4 (100)	0 (0)	4 (4)	
Perforation size				0.17
≤1 mm	12 (100)	0 (0)	12 (10)	
2-3 mm	74 (95)	4 (5)	78 (63)	
>3 mm	29 (85)	5 (15)	34 (27)	
Total	**115 (93)**	**9 (7)**	**124(100)**	

Table 2. Discrete-time survival analysis of dental perforation reversal in 115 healed teeth (follow-up was curtailed at 14 years post-treatment).

Predictors of reversal	**N (%) recurring**	**Univariate**		**Multiple**				
		HR	***(95% CI)***	***HR***	***(95% CI)***	***p-value***	***Bootstrap HR***	***(95% CI)***
Age								
≤50 years	43/101 (43)							
>50 years	5/14 (36)	0.9	(0.3-2.2)	0.9	(0.3-2.1)	0.77	0.8	(0.2-1.9)
Gender								
Male	25/61 (41)							
Female	23/54 (43)	1.1	(0.6-1.9)	0.9	(0.5-1.6)	0.70	1.0	(0.5-1.7)
Tooth Location								
Anterior and Premolar	8/29 (31)							
Molar	39/86 (45)	1.7	(0.9-3.8)	1.6	(0.7-3.7)	0.26	1.5	(0.7-3.7)
Probing								
Negative	21/74 (28)							
Positive	27/41 (66)	3.6	(2.0-6.4)	3.3	(1.8-6.0)	**<0.001**	2.5	(1.4-4.6)
Perforation site								
Coronal	25/58 (43)							
Middle third and Apical	23/57 (40)	0.90	(0.51-1.60)	1.0	(0.5-1.9)	0.96	1.1	(0.6-2.2)
Perforation size								
≤3mm	25/86 (29)							
>3mm	23/29 (79)	4.1	(2.3-7.3)	4.1	(2.3-7.4)	**<0.001**	3.2	(1.9-5.9)

Figure 1. Survival probability (95% CI), number of non-healing events and cumulative number of censoring.

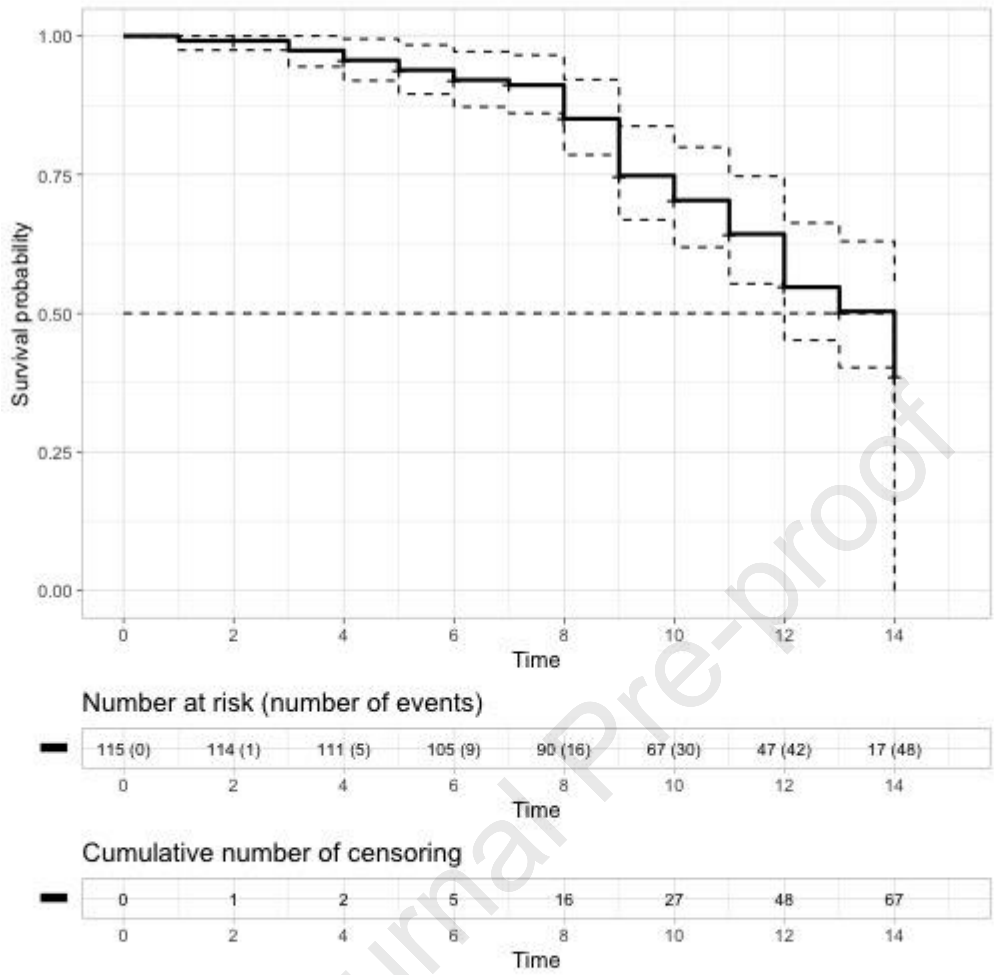

Figure 2. Reversal-free probability curves according to probing levels and perforation size. The corrected group prognosis method was adjusted for the fourteen-year follow-up (26).

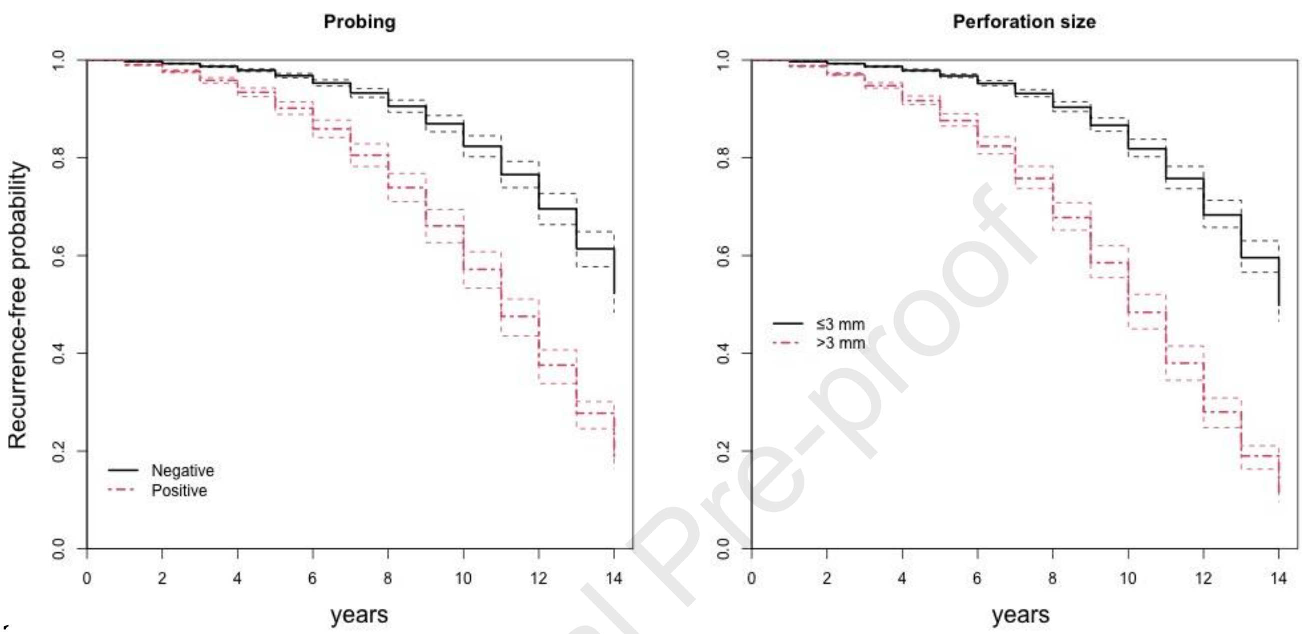

Figure 3. A first lower molar with a perforation in the coronal third has been sealed by MTA (a); in the x-ray at the follow-up after 2 years, it might be considered a favourable progression (b). On the contrary, the 8 years follow-up shows a clear failure (c) that was also assessed by cone-beam computed tomography (CBCT) (d).