Periodontal Regeneration Compared with Access Flap Surgery in Human Intrabony Defects 20-year Follow-up of a Randomized Clinical Trial: Tooth Retention, Periodontitis Recurrence and Costs.

Running Title: 20-Year follow-up of regeneration

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Key words: Intrabony defects, Periodontal Regeneration, Long term, Cost analysis

Conflict of Interest and Source of Funding Statement

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Abstract

Aim: compare the long-term outcomes and costs of 3 treatment modalities in intrabony defects.

Materials and Methods: 45 intrabony defects in 45 patients had been randomly allocated to receive: modified papilla preservation technique with titanium reinforced e-polytetrafluoroethylene (ePTFE) membranes (MPPT Tit, N=15); access flap with e-PTFE membranes (Flap-ePTFE, N=15); access flap alone (Flap, N=15). Supportive periodontal care (SPC) was provided monthly for 1 year, then every 3 months for 20 years. Periodontal therapy was delivered to sites showing recurrences.

Results: 41 patients complied with SPC. 4 subjects were lost to follow-up. Clinical attachment level differences between 1 and 20 years were -0.1±0.3mm (P=0.58) in the MPPT Tit; -0.5±0.1mm (P=0.003) in the Flap-ePTFE; -1.7±0.4mm (P<0.001) in the Flap. At 20-

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years, sites treated with Flap showed greater attachment loss compared to MPPT-Tit (1.4 ± 0.4 mm; \(P=0.008\)) and to Flap-ePTFE (1.1 ± 0.4 mm; \(P=0.03\)). Flap group lost 2 treated teeth. Five episodes of recurrences occurred in the MPPT-Tit, 6 in the Flap-ePTFE, 15 in the Flap group. Residual pocket depth at 1-year was significantly correlated with the number of recurrences (\(P=0.002\)). Sites treated with flap had greater OR for recurrences and higher costs of re-intervention than regenerated sites over a 20-year follow-up period with SPC.

**Conclusions:** Regeneration provided better long-term benefits than Flap: no tooth loss, less periodontitis progression, less expense from re-intervention over a 20-year period. These benefits need to be interpreted in the context of higher immediate costs associated with regenerative treatment. These initial observations need to be extended to larger groups and broader clinical settings.

**Clinical Relevance**

*Scientific rationale for the study*

Persistent deep pockets associated with intrabony defects entail high risk of recurrence and progression of periodontitis over time. Intrabony defects can be treated either with regenerative or flap surgery. This study evaluates the 20 year clinical stability of sites treated with regeneration compared to flap surgery alone

*Principal findings*

Sites treated with regeneration are clinically more stable, show less recurrences, no tooth-loss and lower costs associated with re-interventions than sites treated with access flap surgery alone
Practical implications

Clinicians should consider the long-term advantages of applying regenerative surgery when treating deep intrabony defects. The higher initial cost of regeneration needs to be taken into account.

Introduction

Teeth with deep periodontal pockets associated with deep intrabony defects have long been considered a clinical challenge. Various approaches, including scaling and root planing, flap surgery, osseous resective surgery, and periodontal regeneration have been proposed for the treatment of intrabony defects (Pagliaro et al. 2008). Periodontal regeneration is effective in the treatment of 1-2-3-wall intrabony defects or combination thereof, from very deep to shallow, from wide to narrow (Cortellini & Tonetti 2015). In this context, the ability to predictably obtain greater attachment level gains and shallower, maintainable pockets with respect to standard flap procedures are key elements for the clinical decision to treat intrabony defects with periodontal regeneration (Murphy & Gunsolley 2003, Needleman et al. 2006, Esposito et al. 2009). The persistence of deep pockets following active periodontal therapy has been associated with increased probability of tooth loss in patients attending supportive periodontal care programs (Matuliene et al. 2008). A growing amount of evidence indicates that results obtained with periodontal regeneration can be maintained over time resulting in long-term retention of teeth presenting at baseline with deep pockets associated with intrabony defects (Cortellini & Tonetti 2004, Sculean et al. 2008, Pretzl et al. 2009b, Nygaard-Østby et al. 2010). Long-term studies after periodontal regeneration report substantial stability of the outcomes over time in patients who do not smoke and comply with a regular periodontal supportive care program (Cortellini et al. 1994, 1996, 1999, Cortellini & Tonetti 2004, Eickholz et al 2007, Sculean et al. 2008, Pretzl et al. 2009, Nygaard-Østby et
These observations are in agreement with clinical studies emphasizing the importance of high oral hygiene standards to maintain teeth in healthy condition for long periods of time (Axelsson et al 2004, Lindhe & Nyman 1984, Huynh-Ba et al. 2009, Chambrone et al. 2010, Leininger et al. 2010, Bäumer et al. 2011, Ng et al. 2011). So far, no prospective controlled studies with observation periods above 10 years have compared the stability of outcomes obtained with regenerative and non-regenerative treatment modalities in intrabony defects.

Aim of this follow-up study was to evaluate and compare the clinical stability of treatment outcomes obtained with 2 different regenerative approaches and flap surgery in intrabony defects and to perform a recurrence analysis to evaluate costs of re-interventions required over a follow-up period of 20 years with regular supportive periodontal care.

Materials and Methods

Experimental Design
This 20-year follow-up of a randomized controlled clinical trial compares three treatment modalities in deep intrabony defects: i) the test group was treated with titanium reinforced e-PTFE membranes and the modified papilla preservation technique (MPPT Tit, Cortellini et al 1995a); ii) a barrier membrane group was treated with an access flap procedure and e-PTFE membranes (Flap e-PTFE, Cortellini et al 1993); iii) a third group was treated with an access flap procedure according to the Modified Widman Flap approach (Flap, Ramfjord & Nissle 1974). The design of the original trial has been reported along with the one year results (Cortellini et al 1995b). Clinical outcomes of the three groups were longitudinally followed for 20 years (Figure 1). The study protocol was approved in 1993 by the Ethic Committee of the Accademia Toscana di Ricerca Odontostomatologica (ATRO, Firenze Italy). All patients gave informed consent to participate into the clinical trial. Follow up data were recorded in
the context of routine clinical care in a private clinical setting, all subject gave informed consent for anonymized data extrapolation.

Subject population
Following completion of cause-related treatment consisting of scaling and root planing and oral hygiene instructions, 45 patients (21 males, 24 females) aged 25 to 61 years (mean age 42.8 ± 8.9) in good general health, were enrolled in the controlled clinical trial. In each subject a deep infrabony defect, located in the interproximal area, was identified. Defects did not extend into a furcation. The tooth population consisted of 17 incisors, 13 cuspids, 7 bicuspids and 8 molars. Thirty-six of these teeth were located in the maxillary arch (Table S1).

Clinical measurements
Full mouth plaque scores (FMPS) and full mouth bleeding scores (FMBS) were recorded, along with probing pocket depth (PPD) and clinical attachment level (CAL) by a single investigator masked with respect to treatment (Cortellini et al 1995b). Clinical measurements were made 1 week before the surgical procedure, at the 1 year follow-up, and every two years during the long-term supportive periodontal care (SPC). Intrasurgery measurements were obtained following debridement of the defects (Cortellini et al 1995b).

Randomization
Patients were randomized to the three treatment groups (15 subjects/group) using a randomized block approach. Blocking to control for the effects of the prognostic variables depth of the intrabony component of the defect and CAL was used to obtain comparable groups with small sample size (Tonetti et al 1993, Cortellini et al 1995b, Fleiss 1986).

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Surgical procedures
Fifteen defects in 15 patients were treated with titanium reinforced membranes and the modified papilla preservation technique (Cortellini et al 1995a). In the e-PTFE membrane group (15 patients / defects), a more conventional open flap surgical approach was applied, essentially as described elsewhere (Cortellini et al 1993, 1995b). In the flap alone group (15 patients / defects), the employed technique was an access flap alone, essentially as described by Ramfjord & Nissle (1974).

Post-surgical period
Patients were instructed to rinse twice daily with 0.2% chlorhexidine and to use modified oral hygiene procedures for 3 weeks (Flap group) or up to 2 weeks after the removal of the membranes (regeneration groups). In the first postoperative week, all patients were prescribed tetracycline HCl 250 mg four times per day. Professional tooth cleaning was performed weekly for the first 6 weeks in all groups. Membranes were removed at 6 weeks. Patients were re-instructed to rinse twice daily with 0.2% chlorhexidine. Professional tooth cleaning was performed weekly for 1 month. At that time full interproximal cleaning was allowed and chlorhexidine discontinued.

Long term supportive periodontal care
All patients were maintained by monthly supportive periodontal care (SPC) up to the 1 year examination. No attempt at probing or deep scaling was made before the 1 year follow-up. After the 1-year re-evaluation all patients were enrolled into a 3-month SPC in the original private practice setting. Periodontitis progression (disease recurrence) at the treated teeth was detected with a two step approach: i) an increase of PD ≥2mm with persistent BOP was
flagged by the attending hygienist during the routine SPC appointment (Lang et al 1986, Claffey et al 1990); ii) disease recurrence was then confirmed through the detection of a CAL loss ≥2mm by the calibrated examiner. These sites received adjunctive periodontal therapy consisting either in non-surgical root planing, flap surgery, or regenerative surgery, as indicated. Teeth with periodontitis progression and not responding to therapy were extracted when the residual periodontal support was incompatible with function and comfort and could not be improved with additional periodontal therapy.

Data analysis

Data were expressed as means ± standard deviation. All analyses were performed according to the Last Observation Carried Forward (LOCF) method to take into account the values of CAL and PPD in cases of tooth extraction. Comparisons between 1- and 20-year measurements were made by paired tests, to detect any changes in CAL and PPD for each study group. An analysis of covariance was used to compare the mean changes between groups, with the baseline value as a covariate. Pairwise differences between the three groups were investigated using Tukey HSD test for post-ANOVA for mean CAL and PPD changes between 1- and 20-years. A linear regression analysis was also conducted using the total number of recurrences requiring re-intervention as the outcome variable and residual PPD at 1 year after surgery and treatment as independent variables. Number of visits per patient requiring re-intervention between 1 and at 20 years on the total number of visits and the relative Odds Ratios of between-group differences were calculated by chi-squared test.

Recurrence analysis was then performed to obtain the mean cumulative costs (MCC, expressed in euro) for the number of periodontal recurrences requiring re-intervention per year. Recurrent event data involves the cumulative frequency or “cost” of repairs as units age. As costs have been used in the present analysis, the MCF is a mean cumulative cost per
unit as a function of age. Cost indicators are the reverse of censor indicators seen in life distribution or survival analyses. For the cost variable, average costs of procedures were based on the tariffs collected among 3 dental practices from north, 3 from centre and 3 from south of Italy and reported in Table S2. The 9 selected practices was a convenience sample of representative practices with more than 10 years of experience in providing periodontal care in Italy. The value of 0 indicated that the unit of analysis (patient) was no longer in the study (end of observational period, drop-out or tooth extraction). All statistical comparisons were conducted at the 0.05 level of significance.

**Results**

**Experimental Population**

At baseline, mean subject age in the MPPT Tit, Flap e-PTFE and Flap alone groups were 39.3 ± 6.4, 43.7 ± 9.6, and 45.4 ± 9.7 years, respectively. In the MPPT Tit group 10 patients were females, while in the Flap e-PTFE and Flap alone groups 6 and 8, respectively. Two subjects in each group were cigarette smokers (self reported, < 20/day).

**Baseline Oral Hygiene and Defect Characteristics.**

Baseline oral hygiene and defect characteristics are reported in a previous paper (Cortellini et al 1995b). No statistically significant differences were observed among the three groups in any of the considered clinical parameters. In brief, baseline CAL was 9.9 ± 3.2 mm in the MPPT Tit group, 10.3 ± 2.4 mm in the Flap e-PTFE group, and 9.5 ± 2.7 mm in the Flap group (P=0.73, NS). The depth of the infrabony component of the defects was 5.5 ± 2.9 mm, 5.8 ± 2.7 mm, and 5.3 ± 1.8 mm, respectively (P=0.86, NS).
Clinical Outcomes at 1 Year

At 1 year, CAL improved to 4.7 ± 1.8 mm in the MPPT Tit group, to 6.3 ± 1.9 mm in the Flap e-PTFE group, and to 7.1 ± 2.4 mm in the Flap group. Differences between baseline and 1 year CALs were clinically and statistically significant in all groups (P<0.0001). The largest amount of CAL gains (5.3 ± 2.2 mm, range 3-10 mm) was observed in the MPPT Tit group. CAL gains of 4.1 ± 1.9 mm (range 1-7 mm) were obtained in the Flap e-PTFE group, while the Flap group resulted in CAL gains of 2.5 ± 0.8 mm (range 1-4 mm). The differences among the 3 groups were statistically significant (P=0.0003, analysis of variance). Residual PPDs of 2.1 ± 0.5 mm were reported in the MPPT Tit group, 2.7 ± 1 mm in the Flap e-PTFE group, and 3.7 ± 1.3 mm in the Flap group. The differences among the three groups were statistically significant (P=0.001, analysis of variance).

Long-term clinical outcomes

The CONSORT flow chart accounting for patient disposition is in Figure 1. Four patients were lost to follow-up. The MPPT Tit group accounted for 1 drop-out (the patient moved to another country); the Flap e-PTFE group for 2 drop-outs (1 patient moved to another region, 1 patient could not follow a regular SPC due to severe illness), and the Flap group for 1 drop-out (the patient decided to discontinue SPC). These patients were not available for re-examination. All remaining patients complied with the 3-month SPC program in the original study setting. In particular, over 20 years subjects in the MPPT group attended an average of 77.4 ± 2.3 (range 73÷80) out of 80 SPC appointments, 77.2 ± 2.3 (range 74÷80) in the Flap e-PTFE group and 76.9 ± 2.5 (range 73÷80) in the Flap group. Full mouth plaque and bleeding scores remained stable over the 20 year follow up period (Table 1). Twenty years CAL and PPD changes and differences between 1 and 20 years are reported in Table 2. At 20 years, sites treated with Flap alone showed a statistically significant greater
attachment loss compared to MPPT-Tit (1.4 ± 0.4 mm; 95% CI [0.33;2.48] P=0.008) and to Flap e-PTFE group (1.1 ± 0.4 mm; 95% CI [0.11;2.12], P=0.029), while no differences were noted between the regenerative techniques (0.3 ± 0.4 mm, 95%CI [-0.72;1.33], P=0.756). No significant differences between-groups were observed for PPD changes (Table 2).

A total of 2 teeth were lost in 20 years, both from the Flap group, 11 and 15 years after baseline flap surgery. Overall, all the regenerated teeth were still in function 20 years after baseline treatment, while in the Flap group 85.7% of the teeth survived through time.

Disease recurrences occurred in the three groups. A total of 5 periodontal recurrences in 4 patients were observed in the MPPT Tit group. Six events in 5 patients were recorded in the Flap e-PTFE group. The Flap group accounted for 15 events in 8 patients. Details of recurrences can be found in the supplementary material (Table S2).

Figure 2 shows the average trend of clinical attachment changes from baseline, to 1 year re-evaluation and through 20 years SPC. A substantial CAL stability is evident after the significant 1-year CAL gain. The slight average CAL loss at different time-points in the three groups is associated with periodontal recurrences (Table S1). In particular, the CAL loss observed in years 2004 and 2006 in the Flap group is associated with severe CAL loss that resulted in the clinical decision to extract 2 teeth. CAL loss detected in 2008 in the Flap e-PTFE group was mainly determined by the severe recurrence of one experimental site that was treated again with periodontal regeneration resulting in a sizeable attachment gain. The resulting CAL gain is evident in the measurements taken 2 years afterwards.

Altogether, a total of 26 recurrences in the 3 groups required re-intervention in 20 years.

Figure 3 reports the n° of recurrences in each group stratified according to the 1-year residual PPD at each treated site. Sites presenting with 1-year residual PPD ≥ 5 mm showed the highest frequency of recurrences that required re-intervention. In the Flap group, 4 sites showed 1-year residual PPD ≥ 5 mm that accounted for 9 recurrences treated in the 20-year...
follow-up; in the Flap e-PTFE group one re-intervention was delivered to the only site with 1-year residual PPD ≥ 5 mm. Regression analysis showed that residual PPD at 1-year is significantly correlated with recurrences (P=0.0024, R^2=0.31, Root Mean Square Error = 0.75).

Number of visits per patient requiring any re-intervention (RPL, Surgery, Extraction) between 1 and at 20 years compared to the total number of visits and relative Odds Ratios of between-group differences are reported in Table 3. Flap group showed an OR = 3.4 (P=0.013) compared to MPPT Tit group, and OR = 2.6 (P=0.042) compared to Flap e-PTFE. No significant differences were detected between the two regenerative groups (P=0.675).

Average costs of initial interventions were higher for Flap e-PTFE and MPPT Tit (1183 $) than for Flap alone group (549 $) (Table S1). However, expected costs of recurrences (expressed as MCC) requiring re-intervention per group were generally higher for flap surgery compared to regenerative procedures at each estimated time-point. In particular, at 20 years MCC were 501.27 ± 210.54 (95% CI [88.61;913.93]) for Flap alone, compared to 159.00 ± 88.95 (95% CI [-15.33;333.33]) for Flap e-PTFE and to 99.79 ± 54.14 (95% CI [-6.33;205.90]) for MPPT Tit groups (Fig 4a).

Overall, expected costs of baseline surgeries and recurrences (expressed as MCC) requiring re-intervention per group are reported in Table S3 and presented in Fig 4b.

A further analysis was conducted to include costs of supportive periodontal therapy. Average costs of a 3-month recall programme were considered for each group in addition to expenses for baseline surgeries and re-interventions. At 20 years MCC were 3090.98 ± 210.66 (95% CI [2678.1;3503.86]) for Flap alone, compared to 3382 ± 88.95 (95% CI [3207.67;3356.33]) for Flap e-PTFE and to 3322.79 ± 54.14 (95% CI [3216.67;3428.90]) for MPPT Tit groups.
Discussion

The results of the present follow-up study confirm and extend to 20 years the superiority of regenerative techniques over access flap surgery in providing clinical conditions more favorable to be maintained during regular SPC; nonetheless half of the sites treated with flap alone remained stable over the 20-year observation period. In these analyses, observed long-term benefits of regeneration were based upon: i) greater short-term CAL gain and PPD reduction; ii) absence of tooth loss; iii) less periodontitis progression; and iv) less need and expense of reintervention over a 20-year period. The results reported in this trial likely represent a best case scenario and their external applicability to a wider population of clinicians is unknown.

The added short-term benefits of regeneration in terms of surrogate outcomes are well documented in systematic reviews and meta-analyses. Benefits related to harder outcomes such as periodontitis progression or tooth loss are not well documented in studies at low risk of bias. Available evidence suggests excellent stability and tooth retention after application of regenerative therapy in deep intrabony defects (Cortellini et al. 1999, Cortellini & Tonetti 2004, Eickholz et al 2007, Sculean et al. 2008, Pretzl et al. 2009, Nygaard-Østby et al. 2010). Long-term studies of secondary prevention of periodontitis indicate that such stability depends upon the application of appropriate SPC and risk factor control (Axelsson et al 2004, Chambrone et al. 2010). In discussing the external validity of this study, it is important to underline that the outcomes obtained are likely to represent a best case scenario of highly motivated, mostly non-smoking subjects treated in a private clinical setting providing high-standard of periodontal care.

Important confounders may play a role. On one side the nature of the histologic healing expected after access flap rather than regenerative surgery: repair with a long-junctional epithelium may be less stable. This has been clinically explored in a previous study from our
group (Cortellini et al 1996); in that study results indicated that patient - rather than treatment modality - factors are the major drivers of stability or recurrence after regenerative and conventional treatment in a given subject. The limited 3-year observation period of that study compared with the excellent outcomes noted in the present study during the first 10 years after access flap surgery question the significance of those observations: in subjects participating and compliant with the objectives of a good SPC program the choice of regenerative rather than access flap surgery does not seem to impact harder outcomes short to medium-term. The scenario may be different over a longer observation period.

Healing after access flap is not only expected to be histologically different from the one expected after regenerative surgery; but it is also expected that access flap will result in deeper residual pockets (Graziani et al 2012) and that these will be at higher risk of progression (Matuliene et al 2008). The association between residual PPD and progression/need for re-treatment observed in this study is consistent with the importance of this major ecological determinant on long-term stability, independent on other local and patient factors (Lang & Tonetti 1996, McGuire & Nunn 1996a, b, Kwok & Caton 2007). It is thus unclear whether the major benefit of regeneration was due to qualitatively (type of histological healing) or quantitatively better outcomes (extent of PPD reduction). This material does not allow further speculation into this aspect but allows better hypothesis generation for future studies. This group has completed long term studies with large number of patients that will allow insight into this aspect.

While in absolute terms regeneration of intrabony defects results in significantly better surrogate outcomes and perhaps better tooth retention, regenerative surgery is more costly than access flap. In many circumstances, therefore, the choice of regenerative therapy needs to also consider economic issues. Inserting cost-benefit elements into periodontal decision-making has received relatively little attention for a long time but recent research has been
taking this important aspect into consideration. Measures like willingness to pay for an additional mm of CAL gain/PPD reduction or for an extra year of (disability adjusted) tooth retention have added a valuable dimension to the comparison of different treatments (Listl & Birch 2013, Listl et al. 2010, 2015, Schwendicke et al. 2014, 2016). In this study actual costs for retaining compromised teeth over a 20-year period have been assessed and expressed as the mean cumulative sum of the costs of initial treatment and re-treatment over 20 years or cost of re-treatment alone. The cumulative cost analysis, that does not take into account all the dimensions of costs that are used in an economic analysis and in cost-benefit analyses, underlines that the initially higher costs of periodontal regeneration are partly offset by lower need and cost for retreatment. These initial data suggest that periodontal regeneration requires a higher initial cost but that as time passes the initial investment pays off in two ways: i) higher tooth retention and less periodontitis progression; and ii) lower investment to manage periodontitis progression and tooth loss. Of great interest is also the distribution of costs displayed in Figure 4a and b. Most of the cost for re-treatment was incurred in the second decade of observation and suggests that the added initial costs of regeneration may be even more justified for subjects with a long life expectancy.

The data presented in this long-term RCT are pilot in nature and will have to be confirmed in larger trials but some consideration should be made as they provide insight into the design of future trials and analyses of ongoing ones. Of great importance is the recognition that the standard of care control (access flap) performs well in terms of hard outcomes in the first decade of treatment in subjects participating in a secondary prevention program. Assessment of the benefits in terms of true outcomes of regenerative treatment are likely to require either longer follow-up periods than thus far hypothesized or more severe initial defects/high risk patients: in this trial tooth loss in the flap alone group was observed 11 and 15 years after
surgery and would have been missed in most previously published trials. Recurrence analysis may prove to be an interesting proxy of tooth retention in this field.

Several conclusions and considerations can be made at this time:

1) Teeth presenting with deep pockets associated with deep intrabony defects can be successfully treated with regeneration and flap surgery.

2) These teeth can be maintained for 20 years within a regular SPC program.

3) Regeneration provided better long-term benefits: no tooth loss and less periodontitis progression. Flap approach alone resulted in more persistent pockets at the end of active treatment and these were significantly associated with a greater probability to develop recurrences over time.

4) Tooth survival and stability of the clinical outcomes over time are predictably associated with the application of regenerative procedures.

5) Costs of re-intervention/tooth replacement becomes progressively higher for flap approach compared to regenerative procedures over a 20-year period. Greater costs for reinterventions and replacement of lost teeth need to be interpreted in the context of higher immediate costs associated with regenerative treatment.

6) These initial observations need to be extended to larger groups and different clinical settings.

References


related risk factors for tooth loss in aggressive periodontitis after active periodontal therapy.


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Table and Figure Legends

Table 1: Plaque control and gingival inflammation. Percentage of sites exhibiting detectable plaque or bleeding on probing at different time points

Table 2: Within-group changes in mm (paired t-test) between 1- and 20-years values for CAL and PPD and between-groups differences (analysis of variance).

Table 3: Number of visits per patient requiring any re-intervention (RPL, Surgery, Extraction) between 1 and 20 years over the total number of visits and relative Odds Ratios of between-group differences.

Figure 1: Study flow chart

Figure 2: Average clinical attachment changes through time in the 3 treatment groups.

Figure 3: Number of recurrences over 20-years requiring re-intervention grouped per sites of different residual probing pocket depth at 1-year after surgery.

Footstep: In red: number of residual PPD ≥ 5 mm; in blue: number of recurrences requiring re-interventions.

Figure 4a,b: Plot of expected costs of recurrences over time without (4a) and with (4b) costs of baseline surgeries.

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Table 1
Plaque control and gingival inflammation. Percentage of sites exhibiting detectable plaque or bleeding on probing at different time points

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<th>Baseline*</th>
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<td></td>
<td>Mean percentage ± STD (Range)</td>
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<td><strong>Control Group (access flap)</strong></td>
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<td>Full mouth plaque score FMPS</td>
<td>12.2±1.2 (9.6-15)</td>
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<td>10.2±2 (4.8-13)</td>
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* Baseline values refer to data collected after the cause related phase of treatment and before surgical intervention.
Table 2
Within-group changes in mm (paired t-test) between 1- and 20-years values for CAL and PPD and between-groups differences (analysis of variance).

<table>
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<td>20-years</td>
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<td>Mean±SE</td>
</tr>
<tr>
<td></td>
<td>4.9±2</td>
<td>6.7 ±2.1</td>
<td>8.9 ±3.2</td>
</tr>
<tr>
<td><strong>Within-group Change (CAL loss)</strong></td>
<td>-0.1±0.3</td>
<td>-0.5±0.1</td>
<td>-1.7±0.4</td>
</tr>
<tr>
<td></td>
<td>[-0.69;0.41]</td>
<td>[-0.85;-0.22]</td>
<td>[-2.54;-0.88]</td>
</tr>
<tr>
<td><strong>PPD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
</tr>
<tr>
<td></td>
<td>2.1±0.5</td>
<td>2.7±1</td>
<td>3.7±1.3</td>
</tr>
<tr>
<td>20-years</td>
<td>Mean±SE</td>
<td>Mean±SE</td>
<td>Mean±SE</td>
</tr>
<tr>
<td></td>
<td>3±0.9</td>
<td>3.6±1</td>
<td>5.5±2.7</td>
</tr>
<tr>
<td><strong>Within-group Change (PPD increase)</strong></td>
<td>0.9±0.2</td>
<td>1±0.2</td>
<td>1.9±0.6</td>
</tr>
<tr>
<td></td>
<td>[0.39;1.46]</td>
<td>[0.51;1.49]</td>
<td>[0.56;3.16]</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.0023*</td>
<td>0.0008*</td>
<td>0.0086*</td>
</tr>
<tr>
<td><strong>Between-groups difference</strong></td>
<td>B</td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>

*statistical significant difference; ** Pair-wise differences in mm between groups (post-ANOVA Tukey test) for linear regression (LOCF) model at 20-years: levels not connected by the same letter are statistically significantly different.
Table 3
Number of visits per patient requiring any re-intervention (RPL, Surgery, Extraction) between 1 and 20 years over the total number of visits and relative Odds Ratios of between-group differences.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flap (14/150) vs. MPPT Tit (5/156)</td>
<td>3.4</td>
<td>[1.28;10.71]</td>
<td>0.0130*</td>
</tr>
<tr>
<td>Flap (14/150) vs. Flap e-PTFE (6/147)</td>
<td>2.6</td>
<td>[1.04;7.57]</td>
<td>0.0416*</td>
</tr>
<tr>
<td>Flap e-PTFE (6/147) vs. MPPT Tit (5/156)</td>
<td>1.3</td>
<td>[0.38;4.58]</td>
<td>0.6745</td>
</tr>
</tbody>
</table>

*statistical significant difference; in brackets: number of visits per patient requiring re-intervention/total number of visits; OR=Odds Ratio