Influence of Donor Site and Harvesting Technique of Connective Tissue Graft on Root Coverage Outcomes of Single Gingival Recessions: Systematic Review and Meta-analyses

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Abstract

Objectives: To compare the outcomes of root coverage when the (1) donor site of connective tissue graft is the palate or tuberosity and (2) when connective tissue graft is harvested with intra- or extra-oral de-epithelization techniques.

Methods: The primary outcome was patient satisfaction. Secondary outcomes included complete root coverage, percentage of root coverage and keratinized tissue width. Searches were conducted until December 2019 in PubMed, EMBASE, Scopus and CENTRAL.

Results: 3275 studies were retrieved, but no randomized trials (randomized controlled trials) were found comparing tuberosity and palate. Data were extracted for one arm assessing any connective tissue graft technique from 56 randomized controlled trials to compare intra-oral de-epithelization and extra-oral de-epithelization outcomes. Among these studies, none have harvested connective tissue graft from tuberosity. Patient satisfaction for intra-oral de-epithelization and extra-oral de-epithelization ranged between 79% and 95%. Complete root coverage for intra-oral de-epithelization and extra-oral de-epithelization techniques was 55% (95%CI 46-65) and 70% (95%CI 63-77). Meta-regression analyzes demonstrated that free gingival graft presented 4.41 higher chance of CRC [odds ratio (OR)=4.41, p=0.001] compared to single incision technique, followed by Bruno's (OR=4.39) and double-blade (OR=3.85) techniques. There were no differences between de-epithelization techniques for percentage of root coverage and keratinized tissue width.

Conclusions: No evidence was found to support the use of connective tissue grafts from the tuberosity. If complete root coverage is the major clinical goal, extra-oral de-epithelization may be preferred over intra-oral de-epithelization techniques.

Keywords: Root coverage, connective tissue graft, systematic review

Introduction

Gingival recession is defined as an apical shift of the gingival margin which may be caused by different conditions/pathologies and may lead to impaired esthetics, higher dentine hypersensitivity and poorer quality of life (Jepsen *et al.*, 2018; Wagner *et al.*, 2016). There are a variety of periodontal plastic surgery procedures that can be used to cover root surfaces exposed due to gingival recession (Chambrone and Tatakis, 2015; Chambrone *et al.*, 2018). In this regard, the use of a connective tissue graft has been considered the gold-standard in most cases mainly because of the presence of a thin gingiva surrounding the exposed root (Chambrone *et al.*, 2008).

Traditionally, a connective tissue graft is harvested from the palate between the first molar and the canine. Different techniques have been proposed to harvest connective tissue aiming to obtain characteristics related to better root coverage outcomes, with low patient morbidity (Langer and Langer, 1985; Hurzeler and Weng,

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1999; Zuhr *et al.*, 2014). One of the major differences between techniques is the removal of the connective tissue graft with (Miller, 1985; Langer and Langer, 1985; Harris, 1992; Bruno, 1994) or without (Edel, 1998; Hurzeler and Weng, 1999; Liu and Weisgold, 2002) epithelial tissue, using extra- or intra-oral de-epithelization, respectively. There are many systematic reviews evaluating the outcomes of root coverage procedures (Chambrone *et al.*, 2010; Cairo *et al.*, 2011; Buti *et al.*, 2013; Tavelli *et al.*, 2019a) however, to the best of the authors' knowledge, none of them have focused on the comparison between harvesting techniques. Moreover, little is known about the clinical outcomes and patient's preferences when choosing one technique over another (Zucchelli *et al.*, 2010).

More recently, it has been proposed that connective tissue grafts may be harvested from the tuberosity (Studer *et al.*, 1997; Jung *et al.*, 2008). The choice for the tuberosity as a donor site relies on evidence indicating that there is a lower amount of adipose and glandular tissues and a greater proportion of connective tissue fibers (Sanz-Martin *et al.*, 2019). It has been also proposed that harvesting connective tissue graft from the tuberosity may lead to reduced pain (Amin *et al.*, 2018) decreasing patients' morbidity. Added to the limited risk of trans-surgical and post-operative complications, these characteristics of the tuberosity as a donor site resulted in a great popularity of the technique. Connective tissue grafts from the tuberosity have also been evaluated for the correction of soft tissue defects around implants with interesting results in terms of soft tissue convexity (Roccuzzo *et al.*, 2014). However, there is scant scientific information to help clinicians and patients to determine the real advantages of the tuberosity for root coverage (Tavelli *et al.*, 2019b).

The aim of this systematic review was to evaluate if different clinical and patient-centered outcomes of single root coverage are achieved when the donor site of connective tissue graft is the palate or tuberosity and when connective tissue graft is harvested with different techniques regarding the removal of the epithelium. The following PICO questions were addressed: (1) In patients with single Miller Class I and II or Cairo RT1 gingival recession defects, does the use of connective tissue graft harvested from the palate or tuberosity provide different root coverage outcomes? (2) Moreover, in patients with single Miller Class I and II or Cairo RT1 gingival recession defects, does intra- and extra-oral de-epithelization harvesting techniques of connective tissue graft provide different root coverage outcomes?

The following PICOT questions were formulated according to PRISMA recommendations (Moher *et al.*, 2009):
PICOT-1:
P- patients with single Miller Class I and II gingival recession defects; I- connective tissue graft harvested from the palate; C- connective tissue graft harvested from the tuberosity; O- patient satisfaction, percentage of root coverage, percentage of sites with complete root; coverage, and width of keratinized tissue; T- over at least 6 months.
PICOT-2
P- patients with single Miller Class I and II gingival recession defects; I- connective tissue graft de-epithelized intra-orally; C- connective tissue graft de-epithelized extra-orally; O- patient satisfaction, percentage of root coverage, percentage of sites with complete root coverage, and width of keratinized tissue; T- over at least 6 months.

Materials and methods

Inclusion criteria

The first *a priori* approach was to include exclusively randomized controlled trials of at least 6 months of follow-up applying the following two comparisons: connective tissue graft harvested from the tuberosity compared to that harvested from the palate for single recession defects; connective tissue graft harvested with extra-oral compared to intra-oral de-epithelization techniques for single recession defects.

It was detected that there were no randomized controlled trials published in the literature addressing the abovementioned comparisons. Consequently, the inclusion criteria were changed to allow indirect comparisons between donor sites (palate vs. tuberosity) and harvesting techniques (extra- versus intra-oral de-epithelization) from different study arms of randomized controlled trials. Accordingly, the following inclusion criteria were applied: randomized controlled trials of at least 6 months of follow-up that had at least one group comprised by connective tissue graft; Root coverage of single Miller Class I or II or Cairo RT1 gingival recession defects of at least 2mm; randomized controlled trials that included patients aged ≥18 years old.

For studies that compared two or more flap techniques, data from the coronally advanced flap technique was retrieved and included in the review.

The following exclusion criteria of studies were adopted: absence of data regarding the outcomes of interest of this review; inclusion of multiple recession defects; Inclusion of cases with non-cervical carious lesions; data obtained from the same sample from previous published articles.

Search strategy

Searches were conducted in MEDLINE via Pubmed, EMBASE, Scopus and CENTRAL in December 2019. The following search strategy was applied and adapted according to specific tools from each database: #1

Patients: Gingival recession[Mesh Terms] OR Gingival recession[Text word] OR root coverage[Text word] OR recession defect[Text word] OR recession-type[Text word] OR root exposure[Text word] OR Miller Class I[Text word] OR Miller Class II[Text word] OR Miller I[Text word] OR Miller II[Text word] OR muco-gingival surgery[Text word] OR mucogingival surgery[Text word] OR soft tissue augmentation[Text word] OR periodontal plastic procedure[Text word]#2 Intervention and comparison: connective tissue graft[Text word] OR connective tissue[Mesh Terms] OR connective tissue[Text word] OR autografts[Mesh Terms] OR autograft[Text word] OR autografts[Text word] OR grafting[Text word]; #3: #1 and #2.

Selection of studies

Screening of all titles and abstracts was independently performed by two reviewers (WK and CCO). Afterwards, the full text reading was performed on every study selected by the two reviewers. This process was conducted by three reviewers (WK, FWMGM, and CO), which verified if the studies fulfilled the abovementioned inclusion criteria. In case of any doubts or discrepancies, another reviewer (ANH) confirmed the inclusion of the study.

Data extraction

One reviewer (WK) independently extracted data from the studies in a prepared sheet specifically developed for this study. Another reviewer (ANH) checked if all the information extracted were accurate. In this sheet, the following variables were collected: authors, year of publication, country, time of follow-up, techniques used to harvest the grafts and the donor area, number of participants in the study arm, and estimates of each of outcomes of interest.

Risk of bias

Two authors independently performed the assessment of risk of bias for each study using Review Manager (RevMan). Studies were categorized as having low, unclear and high risk of bias applying the 7 criteria of the tool developed by the Cochrane Collaboration (Higgins *et al*., 2011). Low risk of bias was attributed when no bias was found or bias was unlikely to alter the results. Unclear risk of bias was defined when the information provided in the study did not allow clear evaluation and raised any doubt about the results. High risk of bias was determined when the bias found could alter the results seriously in one or more of the 7 domains.

Outcomes

The primary outcome of this review was patient satisfaction. Secondary outcomes were percentage of root coverage, percentage of sites with complete root coverage, and keratinized tissue width.

Data synthesis

Results for patient centered outcomes were expressed only by qualitative description because reported data did not allow meta-analyses to be carried out. Meta-analyses were performed for complete root coverage , percentage of root coverage and keratinized tissue width in Stata software (STATA version 14 for Macintosh) applying random effects models due to high heterogeneity determined by the I^2 statistic (Q test).

The number of sites with complete root coverage were analyzed as a proportion. Proportions of each study arm were pooled using the *metrapop* command (Nyaga *et al*., 2014), and weighted proportions with 95% confidence interval (95%CI) were reported in forest plots according to IO and EO techniques.

The percentage of root coverage and final keratinized tissue width were analyzed as continuous outcomes. Means and standard deviations (SD) reported at the end of each study arm were used to estimate the weighted mean and its 95%CI using the *metan* command (DerSimonian and Laird method). Means were also reported in forest plots according to IO and EO techniques.

Meta-regression

Meta-regression models were fitted to assess the contribution of each de-epithelization technique on the observed heterogeneity and to provide estimates of the clinical relevance of each of them for the three clinical outcomes assessed (complete root coverage, percentage of root coverage, keratinized tissue width). The use of antibiotics (yes/no), country or region of the study center (Europe, USA, Brazil, Asia), follow-up period (6 months vs >6 months) and publication year (<2006; ≥2006) were also evaluated and included in meta-regression models. Variables in meta-regression were introduced one after another according to their p-value, starting with the lowest (forward stepwise), and maintained in final model if $p<0.15$. The heterogeneity parameter (tau2) was calculated using the method of moment.

For complete root coverage, binomial meta-regression was fitted, and odds ratios (OR) were estimated and reported together with their 95% confidence interval (95%CI). For percentage of root coverage and keratinized tissue width, linear meta-regression was applied and weighted absolute differences were estimated. No study provided more than one group, therefore effect size for comparisons were estimated across studies and not within studies.

Results

The initial search retrieved 4,303 articles (Figure 1). After the analysis of titles and abstracts, 156 studies remained eligible. Among them, 45 citations were related to trials' registrations, resulting in 111 remaining citations for full paper analysis. Thereafter, 56 studies were included after the full text evaluation. Reasons for exclusion of studies from the review are reported in the supplemental material.

In regards to the comparison between donor sites, all included studies have harvested connective tissue graft from the palate and no studies have harvested it from the tuberosity. Noteworthy, one randomized controlled trial was found comparing palatal and tuberosity donor sites, but included Class III recession defects and was not included in the review (Amin *et al.*, 2018).

In regards to the comparison between harvesting techniques, two randomized controlled trials were found comparing directly intra-oral and extra-oral de-epithelization but were not included in this review because included patients with multiple recession defects (Zucchelli *et al.*, 2010; Pandit *et al.*, 2016).

Among the studies included for comparison of study arms, 36 applied intra-oral de-epithelization (Table 1). The trap door technique was the most frequently (22 studies) studied harvesting technique. Six studies stated that the graft was harvested without the epithelium but did not describe which technique was used. The vast majority of the studies had follow-up periods of 6 months. In total, 20 studies applied extra-oral de-epithelization (Table 2). Eight studies applied a double blade to remove the graft, whereas only 3 studies used the free gingival graft technique.

Very few studies evaluated patient satisfaction. Four studies that evaluated intra-oral de-epithelization collected some data about patient satisfaction (Table 1). The method applied to assess patient satisfaction varied across studies. Three of them used a VAS scale (Fernandes-Dias *et al.*, 2015; Jenabian *et al.*, 2017;

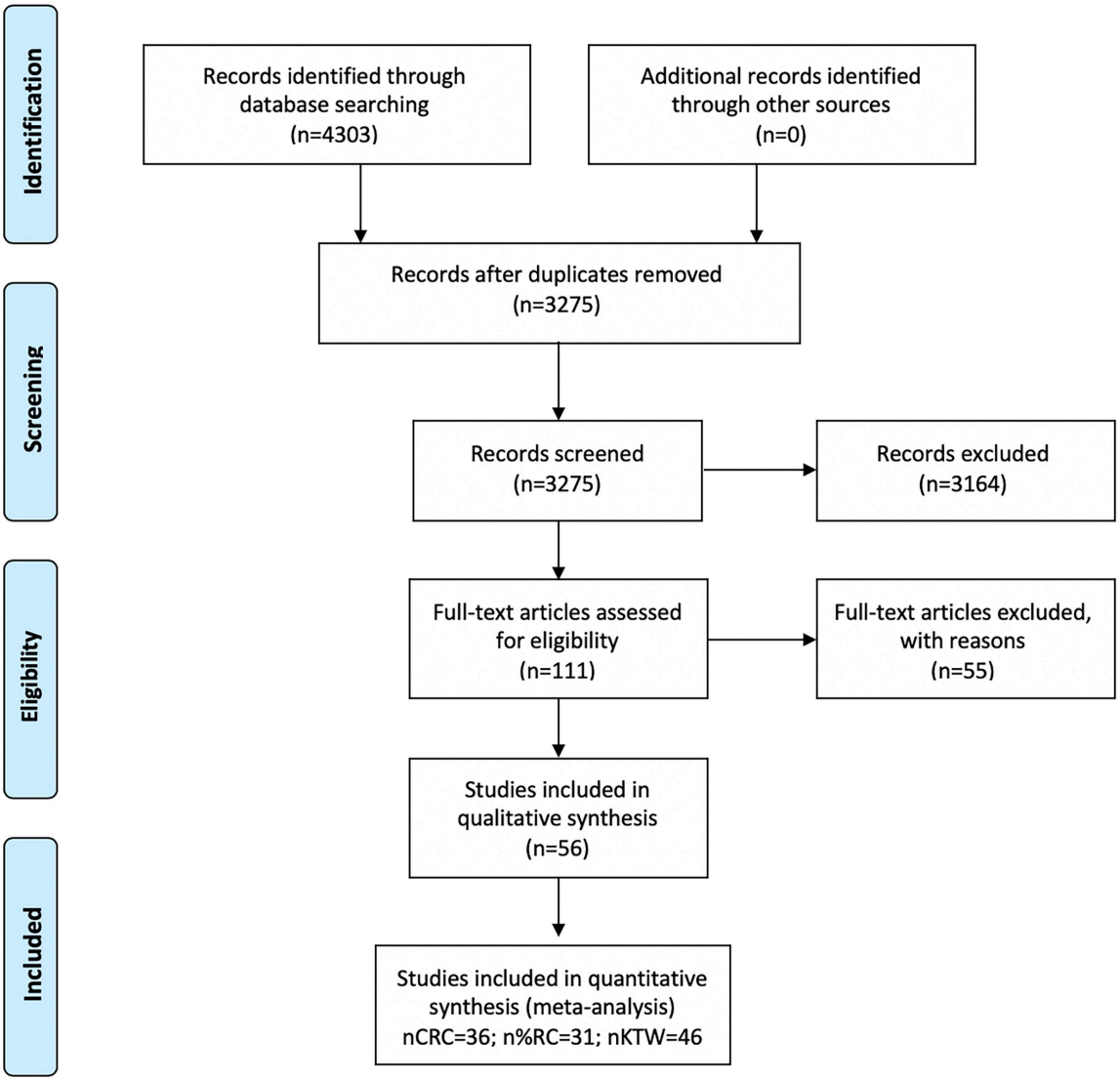

Figure 1. Flowchart of study selection.

Table 1. Characteristics and main findings of studies that evaluated intra-oral de-epithelization techniques.

Study	Donor area technique	Sample size	Follow-up	Baseline GR (mean)	Final GR (mean)	% sites with complete RC	Patient satisfaction
(Jahnke *et al.*, 1993)	Trap door	9	6 months	2.8	0.6	55.5	NR
(Borghetti *et al.*, 1999)	Trap door	14	6 months	3.85	0.96	28.6	NR
(Novaes *et al.*, 2001)	Single incision	15	6 months	2.97	1.13	NR	NR
(Romagna-Genon, 2001)	Trap door	20	6 months	3.76	0.57	NR	95%
(Cetiner *et al.*, 2003)	NR	20	1 year	3.8	0.6	NR	NR
(McGuire and Nunn, 2003)	Trap door	17	1 year	4.25	0.24	79	NR
(da Silva *et al.*, 2004)	Trap door	11	6 months	4.2	1.04	18.2	NR
(Burkhardt and Lang, 2005)	Single incision	8	1 year	4.06	NR	25	NR
(Tozum *et al.*, 2005)	Trap door	17	6 months	3.47	0.97	NR	NR
(Rahmani and Lades, 2006)	Trap door	10	6 months	3.7	1.1	NR	NR
(Joly *et al.*, 2007)	L-shaped incision	10	6 months	4.4	0.9	NR	NR
(Keceli *et al.*, 2008)	Single incision	19	1 year	3.0	0.5	40	NR
(McGuire *et al.*, 2009)	Trap door	30	6 months	3.4	0.1	NR	NR
(McGuire and Scheyer, 2010)	NR	25	6 months	3.2	0.1	NR	NR
(Jhaveri *et al.*, 2010)	Single incision	10	6 months	2.8	0.5	60	NR
(Dilsiz *et al.*, 2010)	Trap door	12	6 months	3.0	0.46	66.7	NR
(Rasperini *et al.*, 2011)	NR	30	1 year	4.7	1.1	47	NR
(Shori *et al.*, 2013)	Trap door	10	6 months	4.1	NR	60	NR
(Mahajan *et al.*, 2012)	Trap door	10	1 year	3.3	0.5	70	NR
(McGuire *et al.*, 2012)	Trap door	9	10 years	4.0	NR	77.8	NR
(Sayar *et al.*, 2013)	NR	20	6 months	3.0	1.17	NR	NR
(Kuis *et al.*, 2013)	Trap door	57	5 years	2.63	0.19	82.5	NR
(Kumar and Murthy, 2013)	Trap door	12	1 year	2.75	0.54	NR	NR
(Thomas *et al.*, 2013)	Trap door	10	6 months	3.3	0.1	90	NR
(Trivedi *et al.*, 2014)	Trap door	30	6 months	2.17	0.33	NR	NR
(Pendor *et al.*, 2014)	Trap door	10	6 months	4.1	0.76	84.7	NR
(Fernandes-Dias *et al.*, 2015)	NR	20	6 months	3.33	0.21	35	8.6 (VAS)
(Deliberador *et al.*, 2015)	L-shaped incision	12	6 months	3.25	1.08	50	NR
(Keceli *et al.*, 2015)	Single incision	20	6 months	3.2	0.65	35	NR
(Dulani *et al.*, 2015)	Trap door	30	6 months	4.67	0.46	66.3	NR
(Gilbert *et al.*, 2015)	Trap door	20	6 months	4.4	1.15	NR	NR
(Taiyeb Ali *et al.*, 2015)	L-shaped incision	4	6 months	3.0	1.38	NR	NR
(Yogini *et al.*, 2016)	Trap door	10	6 months	NR	NR	80	NR
(Santamaria *et al.*, 2017)	NR	17	2 years	3.33	0.26	76	9.7 (VAS)
(Jenabian *et al.*, 2017)	Single incision	7	6 months	1.71	0.43	NR	7.1
(Kumar *et al.*, 2017)	Trap door	15	6 months	2.2	0.93	20	NR

Table 2. Characteristics and main findings of studies that evaluated extra-oral de-epithelization techniques.

Study	Donor area technique	Sample size	Follow-up	Baseline GR (mean)	Final GR (mean)	% sites with complete RC	Patient satisfaction
(Jepsen *et al.*, 1998)	Double blade	15	1 year	3.6	0.5	NR	NR
(Trombelli *et al.*, 1998)	Double blade	12	6 months	3.0	0.5	50.0	NR
(Zucchelli *et al.*, 1998)	Double blade	18	1 year	5.6	NR	NR	NR
(Rosetti *et al.*, 2000)	Bruno's technique	12	1.5 years	4.2	0.2	NR	NR
(Tatakis and Trombelli, 2000)	Free gingival graft	6	6 months	2.5	0.1	83.0	NR
(Wang *et al.*, 2001)	Langer & Langer	16	6 months	3.4	0.7	43.8	NR
(Aichelmann-Reidy *et al.*, 2001)	Langer & Langer	22	6 months	3.0	0.8	63.63	NR
(Paolantonio *et al.*, 2002)	Double blade	15	1 year	4.8	0.53	44.6	NR
(Bittencourt *et al.*, 2006)	Double blade	17	6 months	2.15	0.1	76.4	NR
(Bittencourt *et al.*, 2009)	Double blade	17	2.5 years	2.15	0.07	88.2	82.3%
(Sadat Mansouri *et al.*, 2010)	Langer & Langer	9	6 months	2.66	0.44	55.55	NR
(Babu *et al.*, 2011)	Bruno's technique	10	6 months	4.0	0.6	NR	NR
(Cardaropoli *et al.*, 2012)	Bruno's technique	11	1 year	3.05	0.09	81.0	NR
(Bittencourt *et al.*, 2012)	Double blade	24	1 year	2.53	0.29	58.3	79.1%
(Rosetti *et al.*, 2013)	Bruno's technique	12	2.5 years	4.2	0.3	NR	NR
(Eren and Atilla, 2014)	Double blade	22	6 months	2.61	0.16	77.3	NR
(Goyal *et al.*, 2014)	Langer & Langer	15	6 months	4.33	1.43	NR	16.9
(Zucchelli *et al.*, 2014	Free gingival graft	30	1 year	3.93	0.17	80.0	NR
(Lafzi *et al.*, 2016)	Free gingival graft	15	6 months	3.43	0.8	66.6	NR
(Santamaria *et al.*, 2017)	Bruno's technique	21	6 months	3.2	0.4	71.4	8.9 (VAS)

GR: gingival recession; RC: root coverage; NR: not reported;

Santamaria *et al.*, 2017) and found final average scores ranging from 7.1 to 9.7. Also, Romagna-Genon (2001) evaluated patient satisfaction with a binary response (patient satisfied or not) and obtained a final percentage of satisfied patients of 95%.

Four studies that evaluated extra-oral de-epithelizations have assessed data for patient satisfaction. Goyal *et al.,* (2014) evaluated patient satisfaction about root coverage, color, shape and contour, surgical procedure, post-surgical phase and cost effectiveness in a scale of 19 points at total and found a final mean score of 16.9 points. Santamaria *et al.* (2017) applied VAS and found a final mean score of 8.9. The other two studies from a same research group assessed questions regarding esthetics, root sensitivity (before and after surgery) and the postoperative period, finding complete satisfaction for 79.1% (Bittencourt *et al.*, 2012) and 82.4% (Bittencourt *et al.*, 2009).

The overall proportion of sites with complete root coverage for intra- and extra-oral de-epithelization techniques was 55% (95%CI 46-65) and 70% (95%CI 63-77), respectively (Figure 2). A significant heterogeneity between the two techniques was observed (p=0.01) and the overall heterogeneity was high (I^2=61.9). Among the intra-oral de-epithelization techniques (Figure 2 supplemental material), the trap door technique provided the best estimate reaching 61%, whereas the single incision technique resulted in 40% of complete root coverage . The FGG and Bruno's techniques resulted in 78% and 75% of complete root coverage , respectively. The double-blade and Langer & Langer techniques reached 68% and 55% of complete root coverage. Again, significant heterogeneity between the techniques was observed (p=0.003).

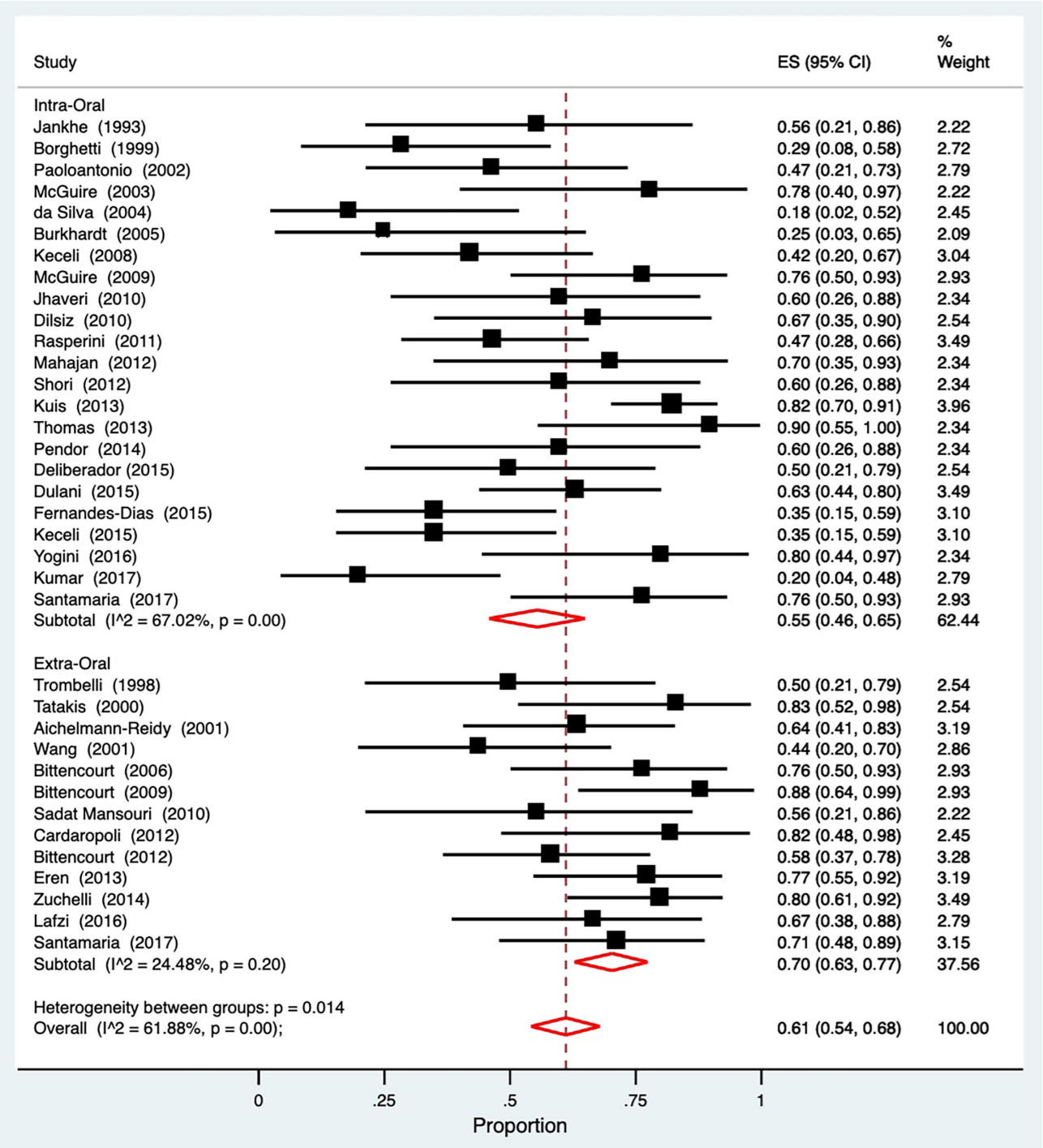

Figure 2. Forest plot of the proportion of sites with complete root coverage for all intra- and extra-oral de-epithelization techniques.

Table 3 presents results of binomial meta-regression of complete root coverage. The single incision technique was considered the reference category since it presented the worse clinical outcomes, and, compared to it, the free gingival graft presented the best outcome with 4.41 higher chance of resulting in complete root coverage (OR=4.41, p=0.001), followed by Bruno's (OR=4.39) and double-blade (OR=3.85) techniques. The trap door technique was the only intra-oral de-epithelization technique better (OR=2.77) than the single incision technique. Studies with follow-up >6 months, published after 2006 and conducted in the USA also had higher chances of complete root coverage.

The percentage of root coverage was 97.3% and 94.3% for the intra- and extra-oral de-epithelization techniques (Figure 3) without significant heterogeneity. Studies that used the Bruno's technique reached percentage of root coverage of 96.1% (Figure 3 supplemental material). Only one study applying the FGG technique provided data for percentage of root coverage and found 75.5%, whereas double-blade reached 92.3% of root coverage. There were no significant differences

Table 3. Results of binomial meta-regression of complete root coverage.

	N studies (patients)	Crude Weighted CRC (95%CI)	Adjusted OR	95%CI	p	p*
De-epithelization technique						
Single incision	4 (57)	40 (27 – 54)	Ref.			
Bruno	2 (32)	75 (58 – 89)	4.39	1.54 – 12.59	0.01	
Double blade	6 (107)	68 (54 – 80)	3.85	1.82 – 8.12	<0.001	
FGG	3 (57)	78 (65 – 88)	4.41	1.87 – 10.38	0.001	
Langer & Langer	3 (47)	55 (40 – 70)	2.17	0.80 – 5.89	0.13	
L-shaped incision	1 (12)	50 (21 – 79)	1.78	0.44 – 7.02	0.41	
Trap door	14 (224)	61 (48 – 74)	2.77	1.44 – 6.50	<0.001	
IO Not Specified	3 (67)	52 (30 – 74)	1.22	0.55 – 2.71	0.62	0.0002
Antibiotics						
No	23 (443)	62 (53 – 77)				
Yes	13 (160)	61 (50 – 73)				
Follow-up						
6 months	24 (356)	58 (50 – 65)	Ref.			
>6 months	12 (247)	67 (55 – 77)	1.63	1.05 – 2.42	0.03	
Publication year						
<2006	10 (128)	50 (36 – 63)	Ref.			
≥2006	26 (475)	65 (57 – 72)	3.63	2.02 – 6.51	<0.001	
Country/region						
Europe	12 (250)	57 (44 – 76)	Ref.			
Asia	10 (129)	62 (50 – 74)	0.90	0.49 – 1.65	0.73	
Brazil	8 (139)	61 (45 – 76)	0.87	0.50 – 1.53	0.65	
USA	6 (85)	67 (54 – 78)	3.20	1.42 – 7.22	0.01	0.02

*Overall p value for dummy variables.
Ref.: reference category; FGG: free gingival graft; IO: intra-oral technique; N: number; CRC: complete root coverage; OR: odds ratio; 95%CI: 95% confidence interval.

between techniques in regards to percentage of root coverage (Table 4).

The final keratinized tissue width for intra-oral and extra-oral de-epithelization study arms was 3.65mm and 3.47mm, respectively (Figure 4), with a significant heterogeneity. The highest keratinized tissue width weighted mean was observed for the L-shaped incision technique (4.00mm), but only including two studies. The lowest mean keratinized tissue width was observed for the FGG technique (2.50mm) with three studies (Figure 4 supplemental material). However, there were no significant differences between techniques regarding the final keratinized tissue width (Table 5).

Findings of the assessment of risk of bias are summarized in the supplemental material. Overall, 20 (35%) among all the included studies scored low risk of bias. 34 (59.7%) were classified as having unclear bias, and only 3 (5.3%) were at high risk of bias.

Discussion

This systematic review did not find any randomized controlled trials comparing connective tissue graft removed from the palate and from the tuberosity regarding outcomes of root coverage procedures for single gingival recession defects. In regards to harvesting techniques, 56 arms of randomized controlled trials could be included allowing meta-analyses and meta-regressions to be carried out to estimate comparisons. There were statistically significant and clinically relevant differences between intra-oral de-epithelization and

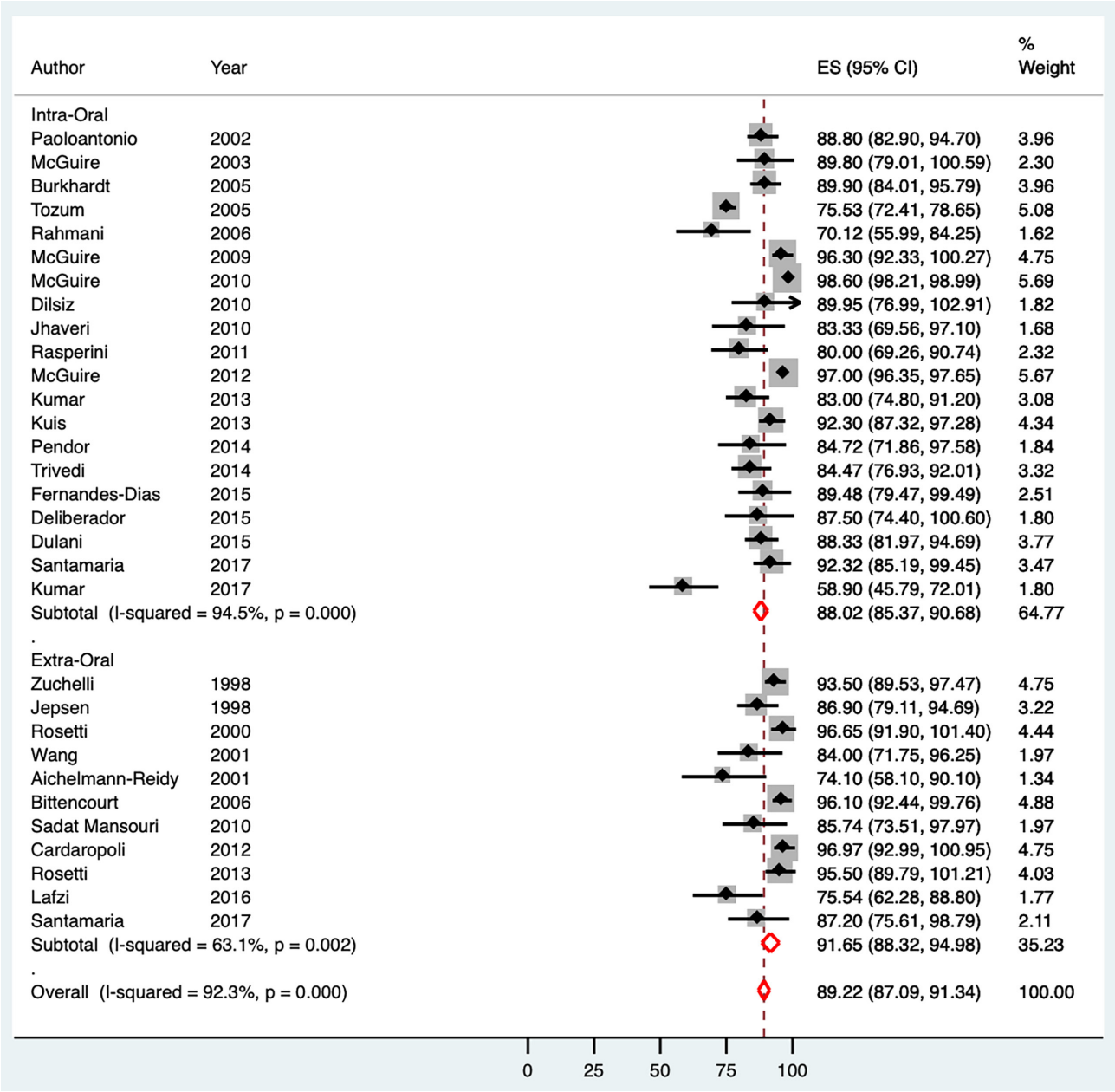

Figure 3. Forest plot of the percentage of root coverage for all intra- and extra-oral de-epithelization techniques.

extra-oral de-epithelization techniques for complete root coverage outcomes, but not for percentage of root coverage and keratinized tissue width.

One important consideration regarding the extrapolation of the findings of this review is that it included only studies treating single recession defects. The inclusion of multiple and single recession defects in a same randomized controlled trial input analytical bias if the cluster of more than one recession per patient is not accomplished in the analytical models, for example by applying multilevel analyses. This bias may also be present in systematic reviews including such randomized controlled trials. This is the reason we chose to exclude randomized controlled trials that evaluated both multiple and single recession defects, or exclusively multiple recession defects, to avoid such bias.

This systematic review indicated that very few studies have assessed patient centered outcomes. The findings of this review suggest that patients were satisfied after root coverage, with rates of satisfaction ranging between 79% and 95% for both epithelized and de-epithelized grafts harvested from the palate. Although it may be argued that the removal of connective tissue graft with epithelial tissue may lead to higher pain and adverse events due to the ulceration left in the palate, it was demonstrated in this review that no patients' specific preference may be expected comparing harvesting techniques. One randomized controlled trial designed specifically to compare connective tissue graft harvested with the trap door and the free gingival graft techniques to treat multiple recession defects showed no significant differences in various patient morbidity outcomes, but

Table 4. Results of linear meta-regression of percentage of root coverage.

	N studies (patients)	Crude Weighted %RC (95%CI)	Adjusted %RC difference	95%CI	p	p*
De-epithelization technique						
Single incision	2 (18)	88.9 (83.5 – 94.3)	Ref.			
Bruno	4 (56)	96.1 (93.4 – 98.7)	3.5	-11.6 – 18.6	0.64	
Double blade	4 (65)	92.2 (88.4 – 96.1)	2.3	-11.4 – 16.1	0.73	
FGG	1 (15)	75.5 (62.2 – 88.8)	-9.3	-32.9 – 14.1	0.42	
Langer & Langer	3 (47)	82.4 (74.8 – 90.1)	-10.2	-27.7 – 7.2	0.24	
L-shaped incision	1 (12)	87.5 (74.4 – 100.0)	-2.6	-27.1 – 21.8	0.82	
Trap door	12 (249)	84.9 (78.5 – 91.5)	-3.9	-16.6 – 8.83	0.53	
IO Not Specified	4 (92)	91.3 (83.4 – 99.1)	-1.3	-15.9 – 13.4	0.86	0.56
Antibiotics						
No	17 (340)	91.9 (89.5 – 94.3)				
Yes	14 (214)	83.4 (75.9 – 90.9)				
Follow-up						
6 months	18 (321)	84.6 (79.1 – 90.2)	Ref.			
>6 months	13 (233)	92.2 (89.7 – 94.8)	3.1	-3.8 – 9.9	0.36	
Publication year						
<2006	9 (140)	87.1 (80.8 – 93.6)				
≥2006	22 (414)	91.5 (89.5 – 93.4)				
Country/region						
Europe	9 (183)	88.3 (82.2 – 94.4)	Ref			
Asia	9 (141)	80.4 (74.8 – 86.0)	-1.2	-10.9 – 8.6	0.80	
Brazil	7 (111)	94.8 (92.5 – 97.1)	4.1	-5.3 – 13.4	0.38	
USA	6 (119)	96.8 (94.9 – 98.6)	10.5	1.3 – 19.8	0.03	0.04

Adjusted R square = 43.62%
*Overall p value for dummy variables.
Ref.: reference category; FGG: free gingival graft; IO: intra-oral technique; N: number; %RC: percentage root coverage; 95%CI: 95% confidence interval.

they did not evaluate patient satisfaction (Zucchelli *et al.*, 2010). Considering that single recession defects need smaller grafts than multiple recession defects, it may be expected that patient morbidity and preferences would not differ between epithelized and de-epithelized grafts, but randomized controlled trials are needed to confirm this.

Overall, meta-analyses of study arms demonstrated that the difference between intra- and extra-oral de-epithelization techniques in complete root coverage was 15% in favor of the latest. These findings may be compared to two randomized controlled trials that conducted direct comparisons between de-epithelization techniques and were excluded from this review because evaluated multiple gingival recession defects (Zucchelli *et al.*, 2010; Pandit *et al.*, 2016). Pandit *et al.* (2016) compared a trap door technique performed with a specific knife (intra-oral de-epithelization) to the Langer and Langer technique (extra-oral de-epithelization) in 30 recession defects from 16 patients. There were no significant differences between groups in regards to pain in the donor area, and percentage of root coverage was 54% and 68% (p=0.4) for the intra-oral de-epithelization and extra-oral de-epithelization groups respectively (diff=14%). Zucchelli *et al.* (2010) compared the trap door and the free gingival graft techniques and

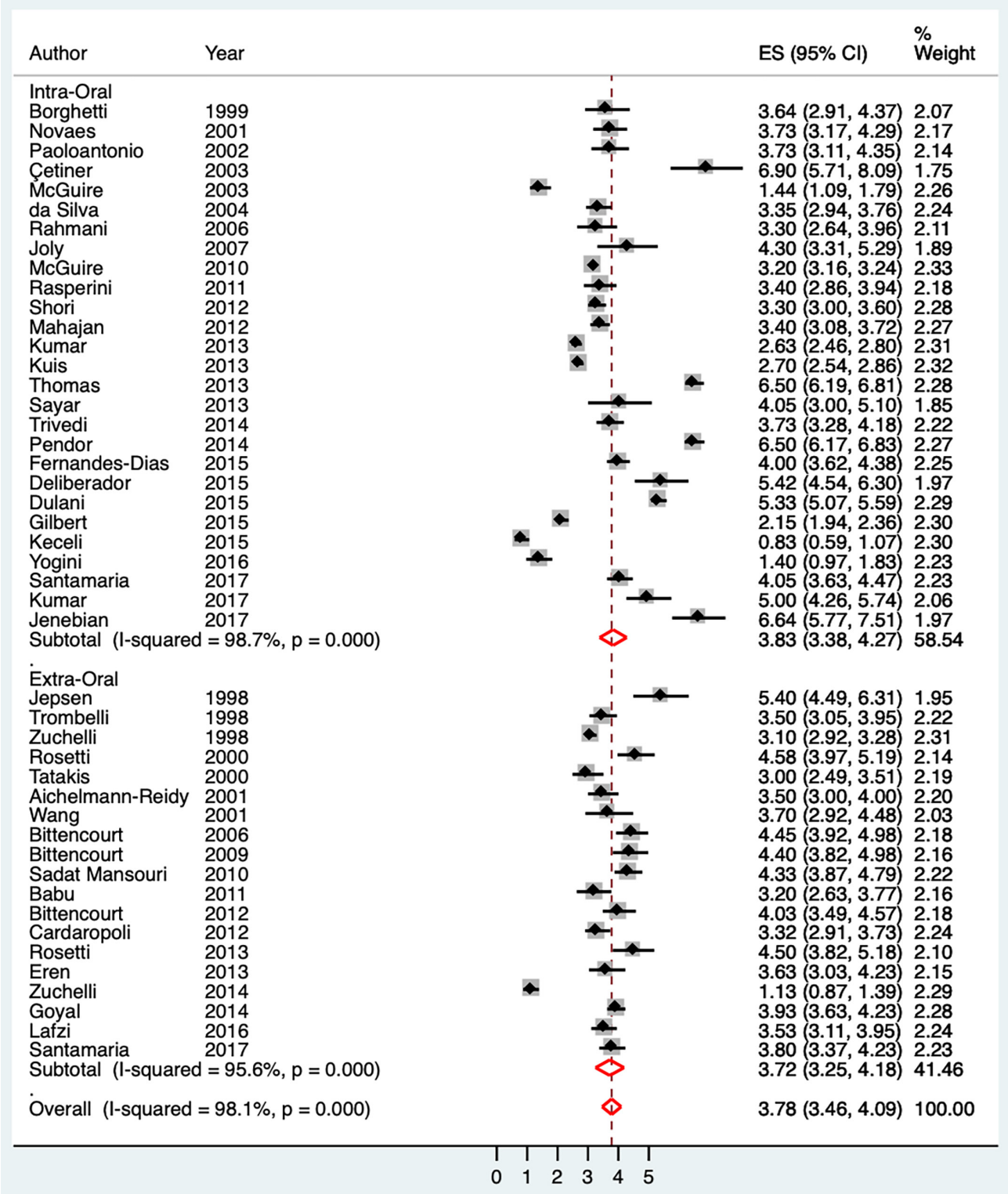

Figure 4. Forest plot of final keratinized tissue width for all intra- and extra-oral de-epithelization techniques.

found complete root coverage equal to 72% and 84% (diff=12%), respectively, without significant difference. Taking into consideration all these data, a difference in favor to extra-oral de-epithelization techniques of 12-15% in complete root coverage may be expected. In some cases, such magnitude may be of clinical relevance for esthetic and functional outcomes.

The other two clinical outcomes evaluated in this review (percentage of root coverage and keratinized tissue width) did not differ between intra-oral de-epithelization and extra-oral de-epithelization. Taking this into consideration, clinician's choice between one approach and another should be made considering not only the evidence herein scrutinized. For instance, this choice may be also determined by clinical experience and for techniques that provide characteristics of the graft that should be targeted to lead to better clinical results of root coverage such as graft thickness and size

Table 5. Results of linear meta-regression of final keratinized tissue width (millimeters).

	N studies (patients)	Crude Weighted KTW (95%CI)	Adjusted KTW difference	95%CI	p	p*
De-epithelization technique						
Single incision	3 (42)	3.71 (0.57 – 6.85)	Ref.			
Bruno	5 (66)	3.85 (3.33 – 4.37)	0.37	-1.55 – 2.31	0.69	
Double blade	8 (140)	3.97 (3.47 – 4.47)	0.72	-1.07 – 2.53	0.41	
FGG	3 (57)	2.55 (0.89 – 4.19)	-0.71	-2.90 – 1.49	0.51	
Langer & Langer	4 (62)	3.90 (3.56 – 4.23)	0.22	-1.96 – 2.40	0.83	
L-shaped incision	2 (22)	4.88 (3.78 – 5.98)	1.59	-0.99 – 4.18	0.21	
Trap door	15 (266)	3.62 (2.84 – 4.40)	-0.35	-2.08 – 1.38	0.68	
IO Not Specified	6 (132)	4.09 (3.46 – 4.72)	1.09	-0.81 – 3.00	0.25	0.43
Antibiotics						
No	30 (548)	3.76 (3.24 – 4.28)				
Yes	16 (239)	3.95 (3.43 – 4.47)				
Follow-up						
6 months	30 (470)	3.88 (3.43 – 4.33)				
>6 months	16 (317)	3.57 (3.10 – 4.04)				
Publication year						
<2006	13 (199)	3.72 (3.19 – 4.25)	Ref.			
≥2006	33 (588)	3.79 (3.40 – 4.18)	-0.98	-2.11 – 1.38	0.08	
Country/region						
Europe	12 (264)	3.35 (2.68 – 4.01)	Ref.			
Asia	17 (243)	4.05 (3.29 – 4.79)	1.70	0.33 – 3.07	0.02	
Brazil	12 (188)	4.14 (3.87 – 4.41)	0.77	-0.39 – 1.94	0.18	
USA	5 (92)	2.94 (2.16 – 3.72)	-0.43	-2.09 – 1.23	0.61	0.04

Adjusted R square=7.45%
**Overall p value for dummy variables.
Ref.: reference category; FGG: free gingival graft; IO: intra-oral technique; N: number; KTW: keratinized tissue width; 95%CI: 95% confidence interval.

and amount of adipose tissue (Zucchelli and Mounssif, 2015; Chambrone *et al.*, 2018).

No studies were found comparing palate and tuberosity as donor sites of connective tissue graft for root coverage of single recession defects. Moreover, all included arms of randomized controlled trials harvested connective tissue graft from the palate. Consequently, no data exist regarding these two donor sites for treating Miller Classes I and II single gingival recession defects. Of note was one randomized controlled trial that compared palatal and tuberosity donor sites in a split-mouth design including Miller Class III recession defects (Amin *et al.*, 2018). The two surgical approaches were conducted in the same appointment, which limits the evaluation of pain in the patient perspective. Nevertheless, pain (0-10 scale) after 2 weeks was significantly higher in the palate (5.9±2.7) than in the tuberosity (2.6±2.2) site. Mean percentage of root coverage after 2 months did not differ between recession defects receiving tuberosity (67±12%) and palate (62±13%) grafts. At the present moment, there is no evidence to support the use of connective tissue graft from the tuberosity for root coverage of single recession defects.

One limitation of this review relates to the evidence summarized. Meta-analysis comparisons were performed between studies and not within studies, since there were no randomized controlled trials comparing intra-oral de-epithelization and extra-oral de-epithelization directly. Thus, this review is similar to those from cohort studies, and not randomized controlled trials. Consequently, there may be differences between patients from one study and another in terms of predictors of root coverage and prognosis. However, this is probably not the case since there was a clear difference between

all extra-oral de-epithelization compared to intra-oral de-epithelization techniques. This indicates that the outcomes from this review were found not because one technique in one study performed better, but because of a consistent better performance of extra-oral de-epithelization than intra-oral de-epithelization across studies in regards to complete root coverage .

In conclusion, this systematic review has shown that there is no scientific evidence available to support the use of connective tissue graft from the tuberosity for root coverage of single recession defects. Consequently, connective tissue graft harvested from the palate should still be preferred until well-designed RCT are conducted evaluating tuberosity as a donor site. In regards to the de-epithelization technique, indirect comparisons from study arms of randomized controlled trials indicate that extra-oral techniques provide better outcomes in terms of complete root coverage than intra-oral techniques as a whole. The free gingival graft, Bruno's and double-blade techniques performed better than the single incision technique. No differences were found between intra-oral de-epithelization and extra-oral de-epithelization in regards to percentage of root coverage and keratinized tissue width.

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Supplemental material

Excluded articles

Among the 50 articles excluded after reading the full text, the reasons for exclusion are:

Author	Reasons for exclusion
Lafzi *et al*. (2007, 2012); Maheshwari *et al*. (2015); Han *et al*. (2008)	Follow-up of only 3 months.
Borghetti and Louise (1994); Amin *et al*. (2018)	Patients with class III recession.
Azaripour *et al*. (2016); Bouchard *et al*. (1994); Lops *et al*. (2015); Mazzocco *et al*. (2011); Cairo *et al*. (2012, 2015); Cheung *et al*. (2004); Cieslik-Wegemund *et al*. (2016); Culhaoglu; Taner and Guler (2018); Ghahroudi *et al*. (2013); Gobbato *et al*. (2016); Isler *et al*. (2018); Haghighati *et al*. (2009); Molesmi *et al*. (2011); Rebele *et al*. (2014); Jindal *et al*. (2015); Roman *et al*. (2013); Salhi *et al*. (2014); Tal *et al*. (2002); Zucchelli *et al*. (2010, 2014); Zuhr *et al*. (2014); Jankovic *et al*. (2012); Pandit *et al*. (2016); Cordioli *et al*. (2001); Cortellini *et al*. (2009); Demante *et al*. (2019)	Patients with multiple recession.
Baghele and Pol (2012); Moses *et al*. (2006); Nemcovsky *et al*. (2004); Souza *et al*. (2008)	Non-randomized control trials.
Barros *et al*. (2004); McGuire *et al*. (2014); Pendey *et al*. (2013)	No group with SCTG.
Cordioli *et al*. (2001); Santamaria *et al*. (2009, 2013, 2016, 2018)	Patients with cervical lesions and/or restorations.
Gholami *et al*. (2013)	Recession average values were not reported.
McGuire *et al*. (2016)	Gingival recession was induced.
Sanz *et al*. (2009)	Only evaluated gingival volume increase.
Wilson; McGuire and Nunn (2005); Aydinyurt *et al*. (2019); Matoh *et al*. (2019)	SCTG extraction technique not reported.
Zucchelli *et al*. (2003)	Used 2 SCTG extraction techniques in the same group.
Ozcelik *et al*. (2016)	De-epthelization performed with diode-laser.
De Resende *et al* (2018)	Mandibular recession included

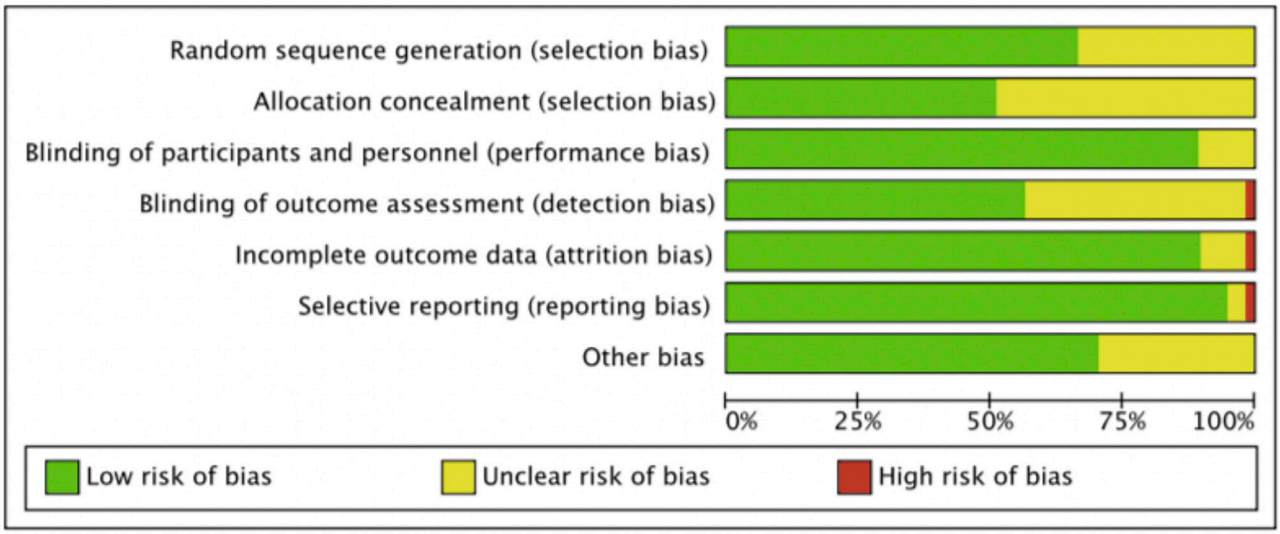

Figure 1 supplemental material. Risk of bias of included studies.

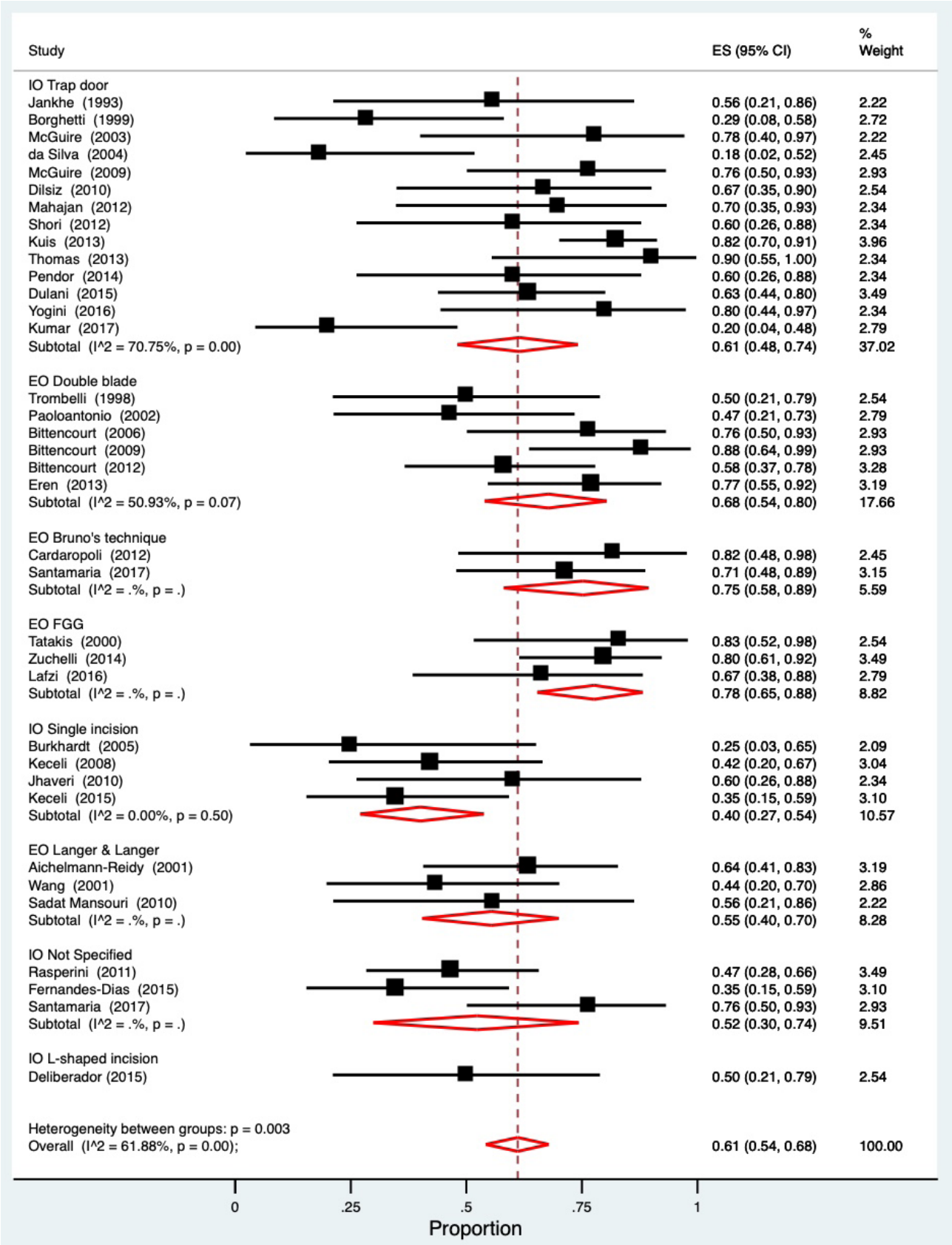

Figure 2 supplemental material. Forest plot of proportion of sites with complete root coverage for each de-epithelization techniques.

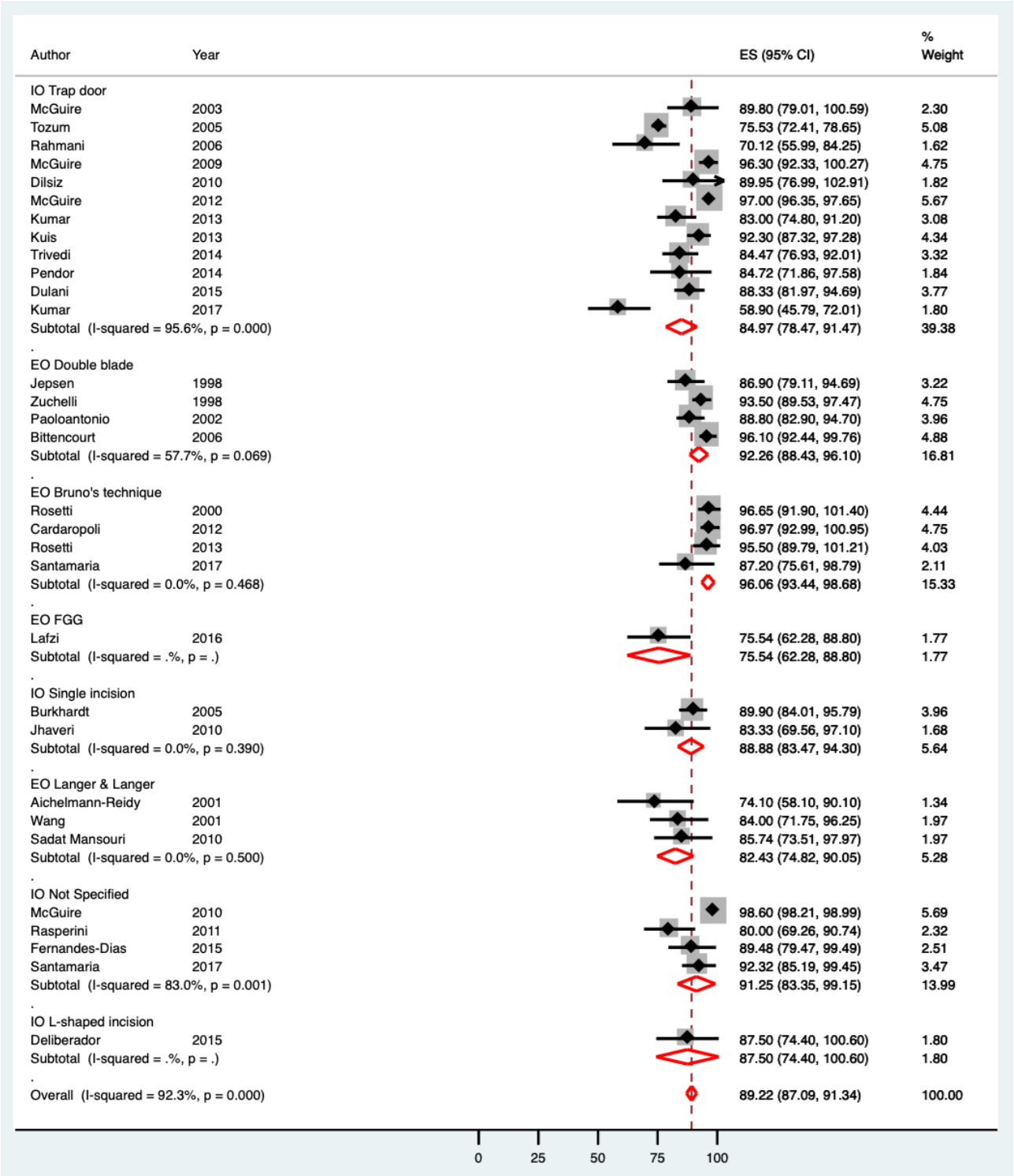

Figure 3 supplemental material. Forest plot of proportion of sites with complete root coverage for each de-epithelization techniques.

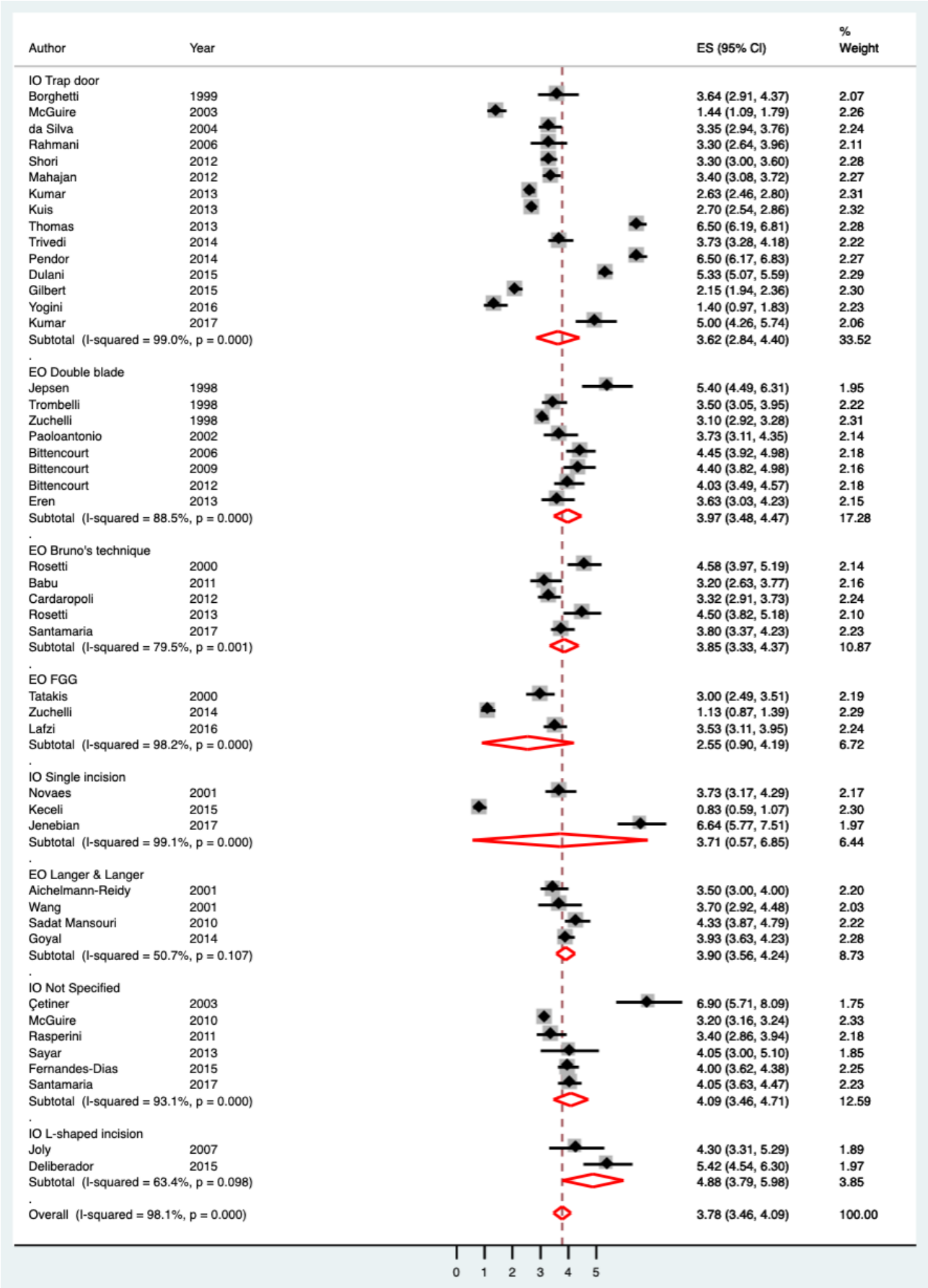

Figure 4 supplemental material. Forest plot of final keratinized tissue width for each de-epithelization techniques.