



A biofeedback-guided programme or pelvic floor muscle electric stimulation can improve early recovery of urinary continence after radical prostatectomy: A meta-analysis and systematic review

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Abstract

Purpose: Urinary incontinence (UI) after radical prostatectomy (RP) is an early side effect after catheter removal. This systematic review and meta-analysis were conducted to compare different forms of non-invasive treatments for post-RP UI and to analyse whether the addition of biofeedback (BF) and/or pelvic floor muscle electric stimulation (PFES) to PF muscle exercise (PFME) alone can improve results in terms of continence recovery rate.

Materials and Methods: A literature search was performed following the PRISMA guidelines. We performed a cumulative meta-analysis to explore the trend in the effect sizes across subgroups during a 12-months follow-up.

Results: Twenty-six articles were selected. At baseline after RP and catheter removal, mean pad weight varied extremely. At 1- and 3-months intervals, mean difference in pad weight recovery from baseline was significantly higher using guided programs (BF, PFES or both) than using PFME alone (3-months: PFME 111.09 g (95%CI 77.59-144.59), BF 213.81 g (95%CI -80.51-508.13), PFES 306.88 g (95%CI 158.11-455.66), BF + PFES 266.31 g (95%CI 22.69-302.93); $P < .01$), while at 6- and 12-months differences were similar ($P > .04$). At 1- and 3-months intervals, event rate (ER) of continence recovery was significantly higher using guided programs than using PFME alone (3-months: PFME 0.40 (95%CI 0.30-0.49), BF 0.49 (95%CI 0.31-0.67), PFES 0.57 (95%CI 0.46-0.69), BF + PFES 0.75 (95%CI 0.60-0.91); $P < .01$), while at 6- and 12-months ERs were similar.

Conclusions: Regarding non-invasive treatment of UI secondary to RP, the addition of guided programs using BF or/and PFES demonstrated to improve continence

All authors listed gave a substantive contribution to this study and to this original article.

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recovery rate, particularly in the first 3-month interval, when compared with the use of PFME alone.

1 | INTRODUCTION

Although advancements of surgical techniques in recent years consistently reduced morbidity after radical prostatectomy (RP) for prostate cancer (PC), RP remains one of the most relevant causes of iatrogenic incontinence in men. Reported rates of urinary incontinence (UI) after RP vary from 5% to more than 40%, depending on the definition of UI and on the methods of evaluation.¹⁻³ UI after RP is mainly an early side effect, starting at catheter removal and is more significant in the first 6 months, affecting patient health-related quality of life. The most common causes of UI after RP are urethral sphincter deficiency, as well as bladder dysfunction.¹ In clinical practice, non-invasive and non-surgical therapies are usually attempted first. For instance, pelvic floor muscle exercises (PFME) can be to improve function of the pelvic floor by accomplishing urethral stability after RP.¹ Several forms of PFME are currently available, can be self-administered, or guided by a physiotherapist. As stated by European Association of Urology (EAU) guidelines, post-RP PFME does not cure UI, but may speed the recovery of continence. For a correct contraction of PF muscles, a specific biofeedback (BF)-guided program (under visual, tactile, or auditory stimuli) can be used.⁴ An alternative non-invasive treatment is a functional pelvic floor electrical stimulation (PFES).^{1,2,5} PFES artificially stimulates the pudendal nerve and its branches to cause direct and reflex responses of the urethral and periurethral striated muscles.⁵ Methods of delivery of ES vary considerably, and ES can also be combined with other conservative therapies, eg, PFME and BF.

There are several randomised prospective clinical trials evaluating the role of these non-invasive methods in managing post-RP UI. However, as stated by Cochrane reviews^{6,7} and EAU guidelines,¹ the data are still controversial, and the level of evidence remains uncertain. Therefore, we performed a systematic review and meta-analysis on the role of non-invasive treatments, such as PFME without and with BF and PFES in patients with post-RP UI.

2 | MATERIALS AND METHODS

2.1 | Objective

The primary *aim* of this systemic review and meta-analysis is to analyse and compare a PFME (without BF) program with other non-invasive treatments, such as specific PFME using a BF-guided program, PFES, or their combinations in patients with post-RP UI. We analysed the effect of these procedures in terms of UI improvement (pad weight) and continence recovery (pad-free status) at different post-operative intervals, therefore to determine also a possible time-related effect.

2.2 | Search strategy

A literature search using electronic databases, such as PubMed, Medline, Web of Science, Scopus and the Cochrane library was performed without time limits. The search process was performed on a combination of the items (“urinary incontinence” and “radical prostatectomy” and “pelvic floor muscle exercise” and/or “biofeedback” and/or “pelvic floor electrical stimulation”) without language restrictions and following the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines. Original and review articles were included and critically considered. We have not included abstracts or reports from meetings.

2.3 | Selection of the studies and inclusion criteria

Entry into the analysis was restricted to data collected from original studies on clinical prospective trials including patients submitted to RP with post-surgical UI. Two authors (AS, AA) independently screened titles and abstracts of all articles using predefined inclusion criteria. The full-text articles were independently examined by three authors (AS, MM, PV) to determine whether or not they met the inclusion criteria. Then two authors (FDG, PV) extracted data from the selected articles. Final inclusion was determined by discussion of all investigators' evaluation.

Studies selected for inclusion met the following criteria: (a) UI after RP; (b) at least one post-operative non-invasive treatment among PFME, BF-guided program, PFES, or their combination; (c) prospective analysis with a follow-up from 1 to 12 months; (d) evaluation using at least one of the following methods: questionnaires on urinary symptoms and voiding diaries, pad testing, continence recovery rate (pad-free rate).

Articles were excluded if (a) multiple reports were published on the same population; (b) data provided were insufficient for the outcomes described in the aim section; (c) failed to meet inclusion criteria.

2.4 | Statistical analysis

Risk of bias (RoB) for all included studies was evaluated using the Review Manager (RevMan) (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) tool for the assessment of the methodological quality of trials (Figure S1). The two reviewing authors independently assessed the methodological quality based on sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, intention-to-treat analysis, and additional sources of bias.

Furthermore, publication bias was tested both by visual assessment of the Deeks' funnel plot and calculation of *P* value using the Deeks' asymmetry test. The Egger's regression test was implemented to explore the relative importance of small-study effect.

According to predetermined endpoints, we compared the available treatment arms using Standardised Mean Difference (SMD) and Event Rate (ER) with 95% confidence interval (CI) for mean pad weight (grams, g) and percentage of pad-free patients, respectively, at 1-, 3-, 6- and 12-months following baseline evaluation. Sensitivity analyses was performed to assess the contribution of each study to the pooled subgroup estimate by excluding individual trials one at a time and recalculating the pooled estimates for the remaining studies. Evaluation for presence of heterogeneity was done using⁸ the following: (a) Cochran's Q-test with $P < .05$ signifying heterogeneity; (b) Higgins I^2 test with inconsistency index (I^2) = 0%-40%, heterogeneity might not be important; 30%-60%, moderate heterogeneity; 50%-90%, substantial heterogeneity; and 75%-100%, considerable heterogeneity.

The pooled SMD and ER estimate for each group of treatment was calculated using a random effects model. Our results are graphically displayed as forest plots, with pooled SMDs and ERs indicating overall mean pad weight and pad-free rate for each study arm. A recovery regimen for post-RP UI based on the sub-group comparison of PFME versus any other non-invasive interventions, and the multiple comparison of each single non-invasive rehabilitative program (ie, PFME versus BF versus PFES) was implemented.

Meta-regression analyses were performed using available continuous variables retrieved among the studies to assess potential source of heterogeneity, including year of publication, mean age of participants, sample size and mean baseline pad weight. The point estimates of the SMDs and ERs were obtained and plotted with the area of the circles proportional to the inverse of the squared standard errors of the studies included.

Furthermore, with regard to mean pad weight difference outcome, we performed a cumulative meta-analysis to explore the trend in effect sizes across subgroups as a function of mean baseline pad weight within the studies included, and at each follow-up visit assessed. Calculations were accomplished using Stata version 16.1 (Stata Corporation) with all tests being two sided, and statistical significance set at <0.05 .

3 | RESULTS

3.1 | Studies included in the meta-analysis

Database searches initially yielded 237 article references. Of these, 156 were subsequently removed because of either duplication or failure to meet the inclusion criteria. Full-text articles were then re-evaluated and critically analysed for the remaining 81 references. Of these, 55 did not meet the inclusion criteria. The remaining 26 articles were considered for our critical review and meta-analysis (Figure S2, Table 1).

3.2 | Quality of studies and sample size

Of the 26 articles selected for the review,^{4,5,9-32} all studies were prospective mono or multicentre clinical trials, and 24 were randomised with at least two treatment arms.^{4,5,9-16,18-24,26-32} In some randomised studies, one of the two treatment arms did not meet our inclusion criteria in terms of treatment procedure, and therefore that specific arm was not included in our analysis.

Sample size of post-RP UI ranged from 30 to 205 patients across the 26 studies. None of these studies accurately defined the patient population, in terms of either pre-operative characteristics (pre-operative lower urinary tract symptoms, prostate volume, PC stage, related diseases or treatments), or surgical techniques, that may influence post-operative UI. Therefore, it was not possible to stratify our results on the basis of these pre-operative and intra-operative variables. Follow-up during treatment ranged from 3 to 12 months.

3.3 | Assessment of continence improvement

At baseline and during follow-up, post-RP continence status was mainly assessed using urinary symptom questionnaires, voiding diary, pad test results and rate of pad-free patients. In particular, an extreme heterogeneity of questionnaires was used among the different studies, so that we were not able to perform a comparison of results according to this parameter. Moreover, parameters reported in terms of voiding diary varied heterogeneously in number of incontinence episodes, number or volume of voids and number of pads used. Homogeneously, 16 studies^{4,5,9-11,14,15,17-20,22-24,30,32} reported results in terms of 24-hour pad test and pad weight (in grams). In 21 studies,^{4,10-23,25,26,28,30-32} continence was objectively defined as no pad use (pad-free status) or <2 g at 24-hours pad test. Only two studies reported some results in terms of urodynamic test.

3.4 | Baseline characteristics of populations

In the 26 studies, mean age of populations ranged from 50.0 to 69.4 years. Baseline parameters were considered at different intervals after catheter removal, ranging from 1 to 30 d. At baseline, after RP and catheter removal, mean pad weight varied extremely from 7.0 ± 56.3 g to 738.5 ± 380.6 g. In particular, baseline mean pad weight was <200 , 200-400 g and >400 g in seven,^{4,9,10,18,24,30,32} five^{11,15,17,19,23} and four^{5,14,20,22} studies, respectively.

3.5 | PFME, BF and PFES regimens

None of the studies included evaluated non-invasive or non-surgical therapies prior before surgery. The different treatment arms included PFME (without BF) in 24,^{4,5,9-13,15,16,18-32} PFME guided with BF in eight,^{4,10-14,16,29} PFES in seven,^{5,9,14,18-20,22} and PFME guided with BF + PFES in three^{17,21,23} studies. Treatments started at

TABLE 1 Main data from the 26 studies considered in the meta-analysis

Study author	Year	Study design	Treatments analysed	Patients for treatment group, n	Outcomes measurements	Follow-up (months)	Time between catheter removal and treatment (days)	Time for treatment session (minutes)	Sessions per week, n	Treatment period (weeks)
Laurienzo et al ⁹	2018	RCT	- PFME not assisted - PFES	- 41 - 42	IPSS, Pad test	3, 6	- 30 - 30	- NR - NR	- NR - 2	- 24 - 24
Mathewson-Chapman et al ¹⁰	1997	RCT	- BF - PFME not assisted	- 27 - 24	Bladder diary, Pad test	1, 3	- 21 - NR	- NR - NR	- 3 - NR	- 12 - 12
Moore et al ¹¹	2008	RCT	- PFME not assisted - BF	- 77 - 89	IPSS, Pad test	3, 6, 12	- 28 - 28	- NR - 30	- NR - NR	- 54 - 24
Ribeiro et al ¹²	2010	RCT	- BF - PFME not assisted	- 26 - 28	ICSI, ICST, Pad test	1, 3, 6, 12	- NR - NR	- 30 - NR	- 1 - NR	- 12 - 12
Tienforti et al ¹³	2012	RCT	- BF - PFME not assisted	- 16 - 16	ICIQ-UI, IPSS-QoL, Pad test	1, 3, 6	- 15 - 15	- 20 - 15	- NR - NR	- NR - NR
Van Kampen et al ¹⁴	2000	RCT	- BF - PFES	- 48 - 50	Pad test	1, 3, 6, 12	- NR - NR	- NR - NR	- NR - NR	- 54 - 54
Dubbelman et al ¹⁵	2010	RCT	- PFME assisted - PFME not assisted	- 33 - 33	Pad test	6	- NR - NR	- NR - NR	- NR - NR	- 26 - 26
Floratos et al ⁴	2002	RCT	- BF - PFME not assisted	- 28 - 14	Pad test	1, 3, 6	- 7 - 7	- 30 - 10	- 3 - 7	- 24 - 24
Franke et al ¹⁶	2000	RCT	- BF - PFME not assisted	- 15 - 15	Pad test	1, 3, 6	- NR - NR	- 45 - NR	- NR - NR	- 24 - 24
Mariotti et al ¹⁷	2015	Prospective	BF + PFES	60	ICS-male, Pad test	1, 3, 6	14	35	2	6
Gomes et al ¹⁸	2018	RCT	- PFME assisted - PFES	- 34 - 35	Pad test	3	- NR - NR	- 45 - 20	- NR - NR	- 10 - 10
Moore et al ⁵	1999	RCT	- PFME assisted - PFES	- 18 - 19	Pad test	3, 6	- NR - NR	- 30 - 30	- 2 - 2	- 12 - 12
Pedriali et al ¹⁹	2016	RCT	- PFME assisted - PFES	- 26 - 28	Pad test	3	- NR - NR	- 45 - 20	- 1 - 1	- 10 - 10
Yokoyama et al [20]	2004	RCT	- PFES - PFME not assisted	- 12 - 12	Pad test	1, 3, 6	- NR - NR	- 15 - NR	- 7 - NR	- 4 - 4
Wille et al ²¹	2003	RCT	- PFME assisted - PFES - PFES + BF	- 47 - 46 - 46	Pad test	3, 12	- 1 - 1 - 1	- 20-30 - 15 - 15	- 14 - NR - 14	- 12 - 12 - 12
Yamanishi et al ²²	2007	RCT	- PFES - PFME not assisted	- 26 - 30	Pad test	1, 3, 6, 12	- NR - NR	- 30 - NR	- NR - NR	- 8 - 8
Mariotti et al ²³	2009	RCT	- BF + PFES - PFME not assisted	- 30 - 30	Pad test	1, 3, 6	- 7 - NR	- 35 - NR	- 2 - NR	- 6 - 6

TABLE 1 (Continued)

Study author	Year	Study design	Treatments analysed	Patients for treatment group, n	Outcomes measurements	Follow-up (months)	Time between catheter removal and treatment (days)	Time for treatment session (minutes)	Sessions per week, n	Treatment period (weeks)
Tantawy et al ²⁴	2019	RCT	- PFME not assisted ^a - PFMS not assisted + whole body vibrations	- 31 - 30	ICIQ-UI, Pad test	1, 3	NR	5	3	12
Pan et al ²⁵	2019	Prospective	PFME not assisted	43	UISRP	1, 3	7	NR	NR	12
Manassero et al ²⁶	2007	RCT	- PFME not assisted ^a - Life style advices	- 54 - 54	Pad test	1, 3, 6, 12	NR	NR	NR	48
Nilssen et al ²⁷	2012	RCT	- PFME assisted ^a - PFME not assisted	- 42 - 43	UCLA-PCI, Pad test	3, 6, 12	1	45	1	48
Glazener et al ²⁸	2011	RCT	- PFME assisted ^a - Life style advices	- 205 - 206	ICIQ-UI SF, Pad test	3, 6, 9, 12	NR	NR	NR	NR
Simeit et al ²⁹	2010	RCT	- PFME assisted - BF	- 87 - 72	SGUIS	1, 3, 6	- 14 - 14	- NR - NR	- 5 - 5	NR
Park et al ³⁰	2012	RCT	- PFME not assisted ^a - PFME not assisted ^b	- 33 - 33	Pad test	3	21	60	2	12
Filocamo et al ³¹	2005	RCT	- PFME not assisted ^a - control group	- 150 - 150	ICS, Pad test	1, 3, 6, 12	1	NR	7	24
Overgård et al ³²	2008	RCT	- PFME assisted ^a - PFME not assisted	- 42 - 43	Pad Test	1, 3, 6, 12	1	45	1	48

Abbreviations: BF, biofeedback; ICIQ-UI SF, International Consultation on Incontinence-Urinary Incontinence Short Form; ICS, International Continence Society; ICSI, Interstitial Cystitis Symptom Index; IPSS, International Prostate Symptom Score; NR, not reported; PFES, pelvic floor electrical stimulation; PFME, pelvic floor muscle exercises; QoL, quality of life; RCT, randomised controlled trial; SGUIS, St George Urinary Incontinence Score.; UCLA-PCI, UCLA Prostate Cancer Index; UISRP, Urinary Incontinence Scale after Radical Prostatectomy.

^aOnly the first arm was considered in the analysis

^bdifferent types at comparison.

different intervals after catheter removal, ranging from 1 to 30 d. Different methods were used for each treatment regimen among studies, with different lengths, times and characteristics. PFME (without BF) was self-administered in 16^{4,9-13,15,16,20,22-27,31} and physiotherapist guided in nine^{5,18,19,21,27-30,32} studies. Time PFME sessions varied from 5 to 60 minutes with intervals from all days per week to just once per week.

PFME guided with a BF program were always performed under the assistance of a physiotherapist and varied regarding apparatus used and exercises performed. Time of BF sessions varied from 15 to 45 minutes, with intervals ranging from five to just once per week.

All studies with PFES treatments were performed with the assistance of a physiotherapist. In different studies, PFES was developed using different apparatus and pulsed from 4 to 50 Hz square waves at a pulse duration from 300 to 1000 μ s and a maximum output current from 24 to 70 mA. Time of PFES session varied from 15 to 30 minutes, with intervals from ranging twice to just once per week.

The combination of BF + PFES treatment was obtained starting with BF for the first 15 minutes followed by ES for the next 20 minutes, twice a week.

3.6 | Outcome results in terms of pad weight

According to previously declared random effect model, we first compared results between PFME alone and guided programs using BF, PFES, or both within 16 eligible studies.^{4,5,9-11,14,15,17-20,22-24,30,32}

At 1-month interval after RP,^{4,10,14,17,20,22-24,32} pooled SMD for pad weight recovery from baseline was significantly different with 59.6 (95%CI 30.7-88.6) and 271.0 (95%CI 147.1-394.9) for PFME alone and all guided programs together (BF, PFES or both), respectively (I^2 85.7% and 99.4%, respectively; $Q - P < .01$). Stratifying results according to the different guided treatment programs, 1-month SMD from baseline varied significantly with 136.9 (95%CI 110.2-384.1), 457.3 (95%CI 218-696.6) and 215 (95%CI 174.5-255.4) for BF, PFES and BF + PFES, respectively (Test of group differences $P < .01$) (Figure 1A).

Similarly, at 3-month interval after RP^{4,5,9,11,14,17-20,22-24,30,32} pad weight mean difference from baseline was 111.1 (95%CI 77.6-144.6) and 275.7 (95%CI 167.4-384.0), respectively for PFME alone and all guided programs together (BF, PFES or both) (I^2 97.5% and 99.8%, respectively; $Q - P < .01$). Stratifying results according to the different guided treatment programs, at 3-month SMD from baseline varied significantly with 213.8 (95%CI 80.5-508.3), 306.9 (95%CI 158.1-455.7) and 266.3 (95%CI 229.7-302.9), respectively for BF, PFES and BF + PFES (Test of group differences $P < .01$) (Figure 1B).

Differently, at 6- and 12-months of follow-up,^{4,5,9,11,14,15,17,20,22,23,32} SMDs from baseline were similar between PFME alone and guided programs using BF, PFES, or both (6-months: PFME 262.2, 95%CI 170.7-353.8 and guided programs 340.5, 95%CI 195.7-485.3, $P = .37$; 12-months: PFME 303.2, 95%CI 161-445.5 and guided programs 423.0, 95%CI 382.8-463.2, $P = .11$; Figure 1C,D).

Deeks' funnel plots, as well as results from the Egger's regression test for each single follow-up evaluation, are displayed in Figure S3.

Meta-regression plots and analysis are presented in Figure S4. Notably, we found a constantly positive association between the higher baseline mean pad weight and the subsequent improved SMD recovery over the follow-up. This moderator was therefore explored as the possible cause for the consistent heterogeneity retrieved among the studies and a subgroup analysis stratifying for the quartiles baseline pad weight distribution has been performed and shown in Figure S5. This resulted in a significant reduction in the heterogeneity findings per each single follow-up interval, corroborating the role of initial incontinence variability as a critical predictor among the included studies. For this reason, we explored in a cumulative meta-analysis the relative effect size variation as function of the increasing initial incontinence burden confirming that as the number of initial mean pad weight increased, the overall SMD and its significance (P -value) increased with a similar trend observed per each subgroup analysis and follow-up interval (Figure 2).

3.7 | Outcome results in terms of continence rate recovery

A meta-analysis was implemented in order to examine the rate of a complete continence recovery (pad-free rate or pad weight < 2 g) with 95%CI obtained at the different follow-up intervals (1-, 3-, 6-, 12-months) among the groups of treatment. Considering a random effect model among 21 eligible studies,^{4,10-23,25,26,28,30-32} we first compared results between simple PFME without BF and guided programs using BF, PFES, or both.

At 1-month interval after RP,^{11-15,17,22,23,25,26,31} ER of continence recovery was 0.16 (95%CI 0.10-0.22) and 0.41 (95%CI 0.27-0.55), respectively for PFME alone and all guided programs together (BF, PFES, or both) (I^2 53.6% and 74.7%, respectively; $Q - P < .01$). Stratifying results by the different guided treatment programs, at 1-month ER of continence recovery varied significantly with 0.38 (95%CI 0.18-0.58), 0.24 (95%CI 0.11-0.36) and 0.66 (95%CI 0.48-0.83) for BF, PFES and BF + PFES, respectively (Test of group differences $P = .03$) (Figure 3A).

Similarly, at 3-month interval after RP,^{10-19,21-26,30-32} ER of continence recovery was 0.40 (95%CI 0.30-0.49) and 0.59 (95%CI 0.47-0.71), for PFME alone and all guided programs together, respectively (I^2 68.6% and 65.3%, respectively; $Q - P = .00$). Stratifying results by the different guided treatment programs at 3-months ER of continence recovery varied significantly with 0.54 (95%CI 0.32-0.75), 0.57 (95%CI 0.46-0.69) and 0.75 (95%CI 0.60-0.91), for BF, PFES and BF + PFES, respectively (Test of group differences $P = .00$) (Figure 3B).

On the contrary, at 6- and 12-month intervals, ERs of continence recovery^{4,11-17,20-23,26,28,31,32} were similar between PFME alone and guided programs using BF, PFES, or both (6-months: PFME 0.59, 95%CI 0.42-0.76 and guided programs 0.80, 95%CI 0.66-0.94, Test of group differences $P = .07$; 12-months: PFME 0.76, 95%CI

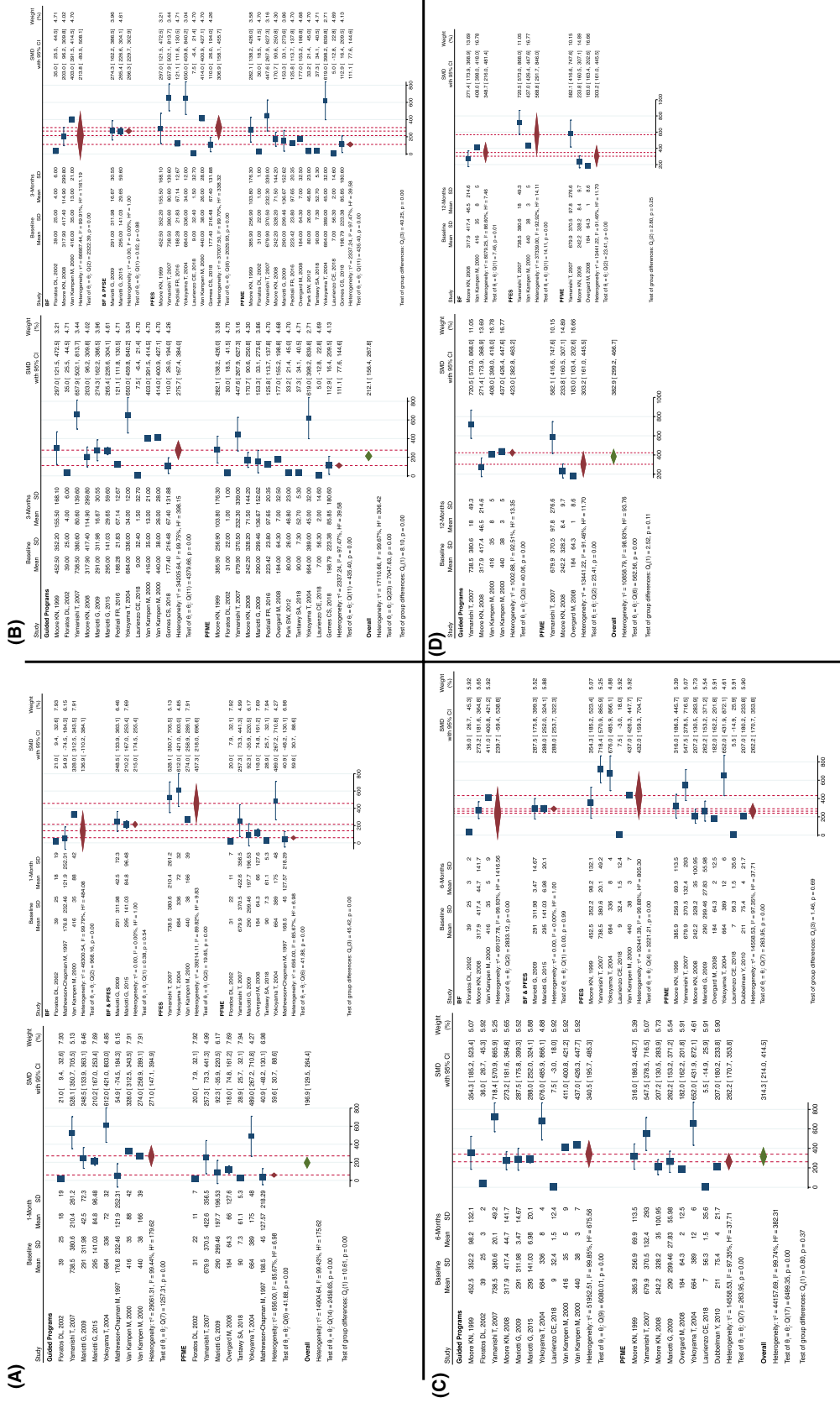


FIGURE 1 Forrest plot assessing Standardised Mean Difference (SMD) for Pad Weight recovery at 1-(A), 3-(B), 6-(C) and 12-Months (D) follow-up within all guided programmes versus PFME, and according to each single recovery programme implemented within the studies included for analysis. BF, biofeedback; CI, confidence interval; PFES, pelvic floor electric stimulation; PFME, pelvic floor muscle exercise; SD, standard deviation

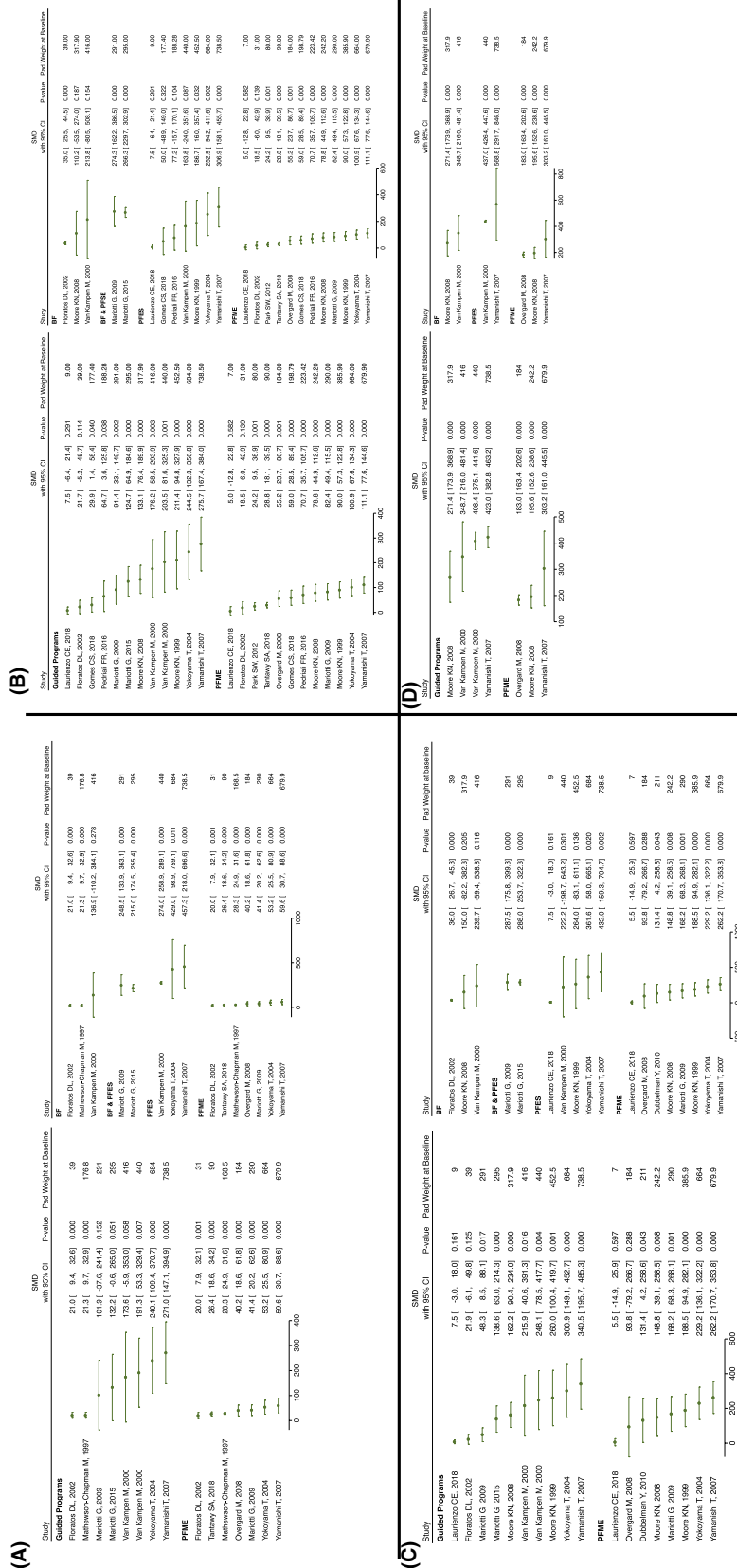


FIGURE 2 Cumulative meta-analysis for Pad Weight recovery at 1-(A), 3-(B), 6-(C), and 12-(D) months within all guided programmes versus PFME and according to each single recovery programme implemented within the studies included for analysis stratified by Pad Weight at baseline. BF, biofeedback; CI, confidence interval; PFES, pelvic floor electric stimulation; PFME, pelvic floor muscle exercise; SD, standard deviation

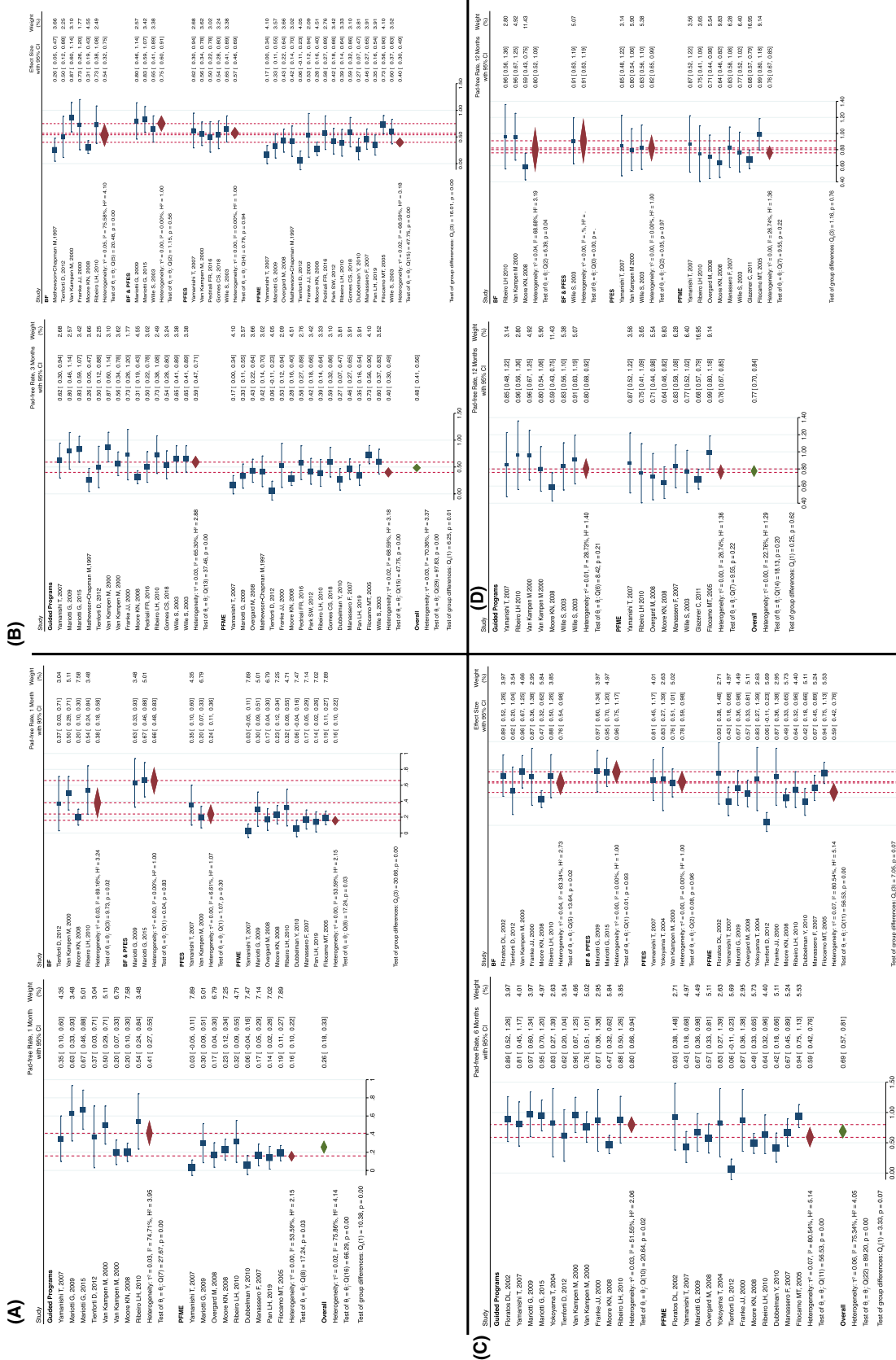


FIGURE 3 Forrest plot assessing Pad-free Rate at 1-(A), 3-(B), 6-(C) and 12-months (D) follow-up within all guided programmes versus PFME, and according to each single-recovery programme implemented within the studies included for analysis. BF, biofeedback; CI, confidence interval; PFES, pelvic floor electric stimulation; PFME, pelvic floor muscle exercise; SD, standard deviation

0.67-0.85 and guided programs 0.80, 95%CI 0.68-0.92, Test of group differences $P = .62$) (Figure 3C,D).

Deeks' funnel plots, as well as results from the Trim and Fill method and Egger's regression test for each single follow-up evaluation, are displayed in Figure S5 and suggest absence of any consistent heterogeneity among the studies for the aim of interest, while highlighting the existence of significant small-study effect over the follow-up.

Meta-regression plots and analysis are presented in Figure S6. Notably, at 1-month follow-up visit, we found an inversely negative association between mean age of participants and the higher pad-free rate (Figure S7). This trend was not further confirmed at subsequent follow-up visits, suggesting the relative influence of age on early continence recovery only within the weeks following RP.

3.8 | Strengths and limitations

Strengths: (a) the present meta-analysis considered objectives and included results different from previous studies; (b) all studies included are prospective and most are randomised; (c) the two parameters considered (ie, 24-h pad weigh and ER of continence recovery) are objectively and homogeneously defined in the different studies.

Limitations: (a) a high level of heterogeneity in mean difference in pad weight is present among studies; (b) a high level of heterogeneity in the baseline post-RP pad weight among studies is present; (c) studies did not accurately define pre-operative and intra-operative characteristics of the population.

4 | DISCUSSION

To our knowledge, this is the first meta-analysis evaluating non-invasive treatments for post-RP UI and comparing results among post-operative PFME and other specific programs guided by BF or using PFES. EAU guidelines summarise that PFME does not cure UI in men post-RP, yet it appears to speed the recovery of continence following surgery.¹ A 2015 Cochrane review stated that the benefits of conservative treatment in men with post-RP UI remain uncertain, and PFME does not produce significant benefit.³³ Moreover, the EAU guidelines underlined that there is conflicting evidence on whether the addition of BF increases the effectiveness of PFME alone and that PFES may add benefit in the short-term.¹

In the present meta-analysis, we analysed studies only including post-operative non-invasive programs for the treatment of post-RP UI, trying to define whether the use of guided programs using BF or PFES may improve results obtained with only PFME.

Our study found a significant heterogeneity of results in terms of mean difference in pad weight ($I^2 > 80\%$). As demonstrated within other uro-oncologic surgically resected disease series varying from kidney to bladder cancer,^{34,35} postoperative functional and/or survival outcomes can be influenced by a wide variable list of socio-demographic, racial, diagnostic, biochemical, procedural,

and patients-related features together with pre-, intra and/or early postoperative surgical confounders.^{36,37} Similarly, in the RP setting for PC, several well-established patient disease-specific, psychological as well as pathological features may condition UI after RP.^{38,39} Unfortunately, these variables were not addressed or not adequately classified by all the selected studies as data regarding pre-operative conditions, co-morbidities, prostate volume and surgical techniques used to reduce the incidence of post-RP UI are incomplete. All these variables likely conditioned the heterogeneity of UI levels detected in terms of pad weight at baseline after catheter removal. Therefore, in our meta-analysis we stratified results based on post-operative baseline pad weight instead of pre-operative or intraoperative variables.

At baseline after RP and catheter removal, mean pad weight extremely varied from 7.0 ± 56.3 to 738.5 ± 380.6 g. Baseline pad weight is a variable able to condition the heterogeneity of results in terms of mean difference of pad weight improvement at different follow-up intervals. We found a consistently positive association between higher baseline mean pad weight and subsequent improved SMD recovery over the follow-up. A subgroup analysis stratifying for the quartiles of baseline pad weight distribution resulted in a significant reduction in the heterogeneity findings for each single follow-up interval, corroborating the role of initial incontinence variability as a critical predictor among the studies included. This effect was similar in the different treatment groups with a similar trend observed per each subgroup analysis and follow-up interval. The same analysis performed for the outcome ER of continence recovery suggested the absence of any consistent heterogeneity among the studies for this item.

Variability of results could be also conditioned by different treatment programs in terms of interval from catheter removal, time length of each session and of the entire treatment. Treatments started at different intervals after catheter removal ranging from 1 to 30 d. In particular, PFME programmes (without BF) were self-administered in 16 and guided by physiotherapists in nine studies. Time of PFME session varied from 5 to 60 minutes, with intervals from 7 days to just once per week. On the contrary, PFME guided with a BF programme and PFES treatments were more homogeneously performed under the assistance of a physiotherapist and less variability in time of session and week intervals was present.

Our meta-analysis suggests that a specific BF-guided program or the addition of PFES to PFME significantly ($P < .01$) improve short-term (1- and 3-month intervals) results, either in terms of pad weight reduction or continent rate (pad-free) recovery, when compared with the use of post-operative simple PFME assisted or without a physiotherapist. On the contrary, this advantage is not significant ($P > .1$) in long-term (6- and 12-months) follow-up, though results continue to be better adding BF and/or PFES to PFME. Notably, ER of continence recovery significantly increased up to 66% and 75%, at 1- and 3-month intervals, respectively when a PFES was added to PFME and BF, compared with an ER of 16% and 40% at 1- and 3-month interval, respectively when using PFME alone. At 6- and 12-month intervals, ER of continence recovery, although differences

were not statistically significant ($P > .1$), reached 96% and 91%, respectively adding a PFES and BF programme compared with 59% and 76%, respectively using PFME alone.

Some limitations associated to the present meta-analysis must be underlined. Populations considered from the different studies significantly varied in terms of baseline level of UI, as demonstrated by the post-surgical mean pad weight. As previously stated, patient characteristics significantly varied in terms of pre-operative and intra-operative variables were not accurately defined by the studies and, therefore, were not considered in our meta-analysis. However, the quality of the studies included in our analysis was high considering that all studies were prospective and most were randomised trials. The two parameters considered, pad weight and ER of continence recovery, are objectively and homogeneously defined in the different studies. We excluded parameters such as questionnaires or number of pads used as a result of the extremely heterogeneous data among the studies.

5 | CONCLUSIONS

The use of non-invasive therapies such as guided incontinence programmes (BF or/and PFES) in the management UI following RP for PC demonstrate improved incontinence recovery rate within the first 3 months following RP compared with PFME alone. While we would readily advise the need for a more comprehensive and standardised reporting approach in terms of clinical and perioperative variables (such as ICS Standards for incontinence or Dindo's Classification for the complications) in the studies analysing UI post-RP, future research should also better consider and stratify results according to pre-operative conditions and post-operative pad weight differences able to influence results among the different non-invasive treatment strategies.

DISCLOSURES

The Authors declare that they have no conflict to disclose.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. Alessandro Sciarra, Alessandro Arditi, Pietro Viscuso did conceptualisation. Ettore De Berardinis, Francesco Del Giudice, Alessandro Gentilucci performed methodology; Gian Maria Busetto, Benjamin I. Chung, Vittorio Canale, Gianna Mariotti did formal analysis and investigation; Alessandro Sciarra, Martina Maggi, Fernandino Vilson did writing - original draft preparation; Stefano Salciccia, Michael L. Eisenberg, Giovanni Battista Di Pierro did writing - review and editing; Francesco Del Giudice and Matteo Ferro performed statistical analysis. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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