Elsevier Editorial System(tm) for European Urology
Manuscript Draft

Manuscript Number: EURUROL-D-12-01782R2

Title: Influence of pre- and post- versus postoperative pelvic floor muscle training on urinary incontinence after radical prostatectomy: a randomized controlled trial.

Article Type: Original Article

Section/Category: Incontinence (INC)

Keywords: urinary incontinence; radical prostatectomy; pelvic floor muscle training

Corresponding Author: Mrs. Inge Geraerts,

Corresponding Author's Institution: KU Leuven

First Author: Inge Geraerts

Order of Authors: Inge Geraerts; Hein Van Poppel, Prof. Dr.; Nele Devoogdt, Dr.; Steven Joniau, Dr.; Ben Van Cleynenbreugel, Dr.; An De Groef; Marijke Van Kampen, Prof. Dr.

EUROPEAN UROLOGY Authorship Responsibility, Financial Disclosure, and Acknowledgment form.

By completing and signing this form, the corresponding author acknowledges and accepts full responsibility on behalf of all contributing authors, if any, regarding the statements on Authorship Responsibility, Financial Disclosure and Funding Support. Any box or line left empty will result in an incomplete submission and the manuscript will be returned to the author immediately.

Title	Mrs.	
First Name	Inge	
Middle Name		
Last Name	Geraerts	
Degree	Dra.	(Ph.D., M.D., Jr., etc.)
Primary Phone	003216329120	(including country code)
Fax Number	003216329197	(including country code)
E-mail Address	inge.geraerts@faber.kuleuven.be	

Authorship Responsibility

By signing this form and clicking the appropriate boxes, the corresponding author certifies that each author has met all criteria below (A, B, C, and D) and hereunder indicates each author's general and specific contributions by listing his or her name next to the relevant section.

☒ A. This corresponding author certifies that:

• the manuscript represents original and valid work and that neither this manuscript nor one with substantially similar content under my authorship has been published or is being considered for publication elsewhere, except as described in an attachment, and copies of closely related manuscripts are provided; and
• if requested, this corresponding author will provide the data or will cooperate fully in obtaining and providing the data on which the manuscript is based for examination by the editors or their assignees;
• every author has agreed to allow the corresponding author to serve as the primary correspondent with the editorial office, to review the edited typescript and proof.

☒ B. Each author has given final approval of the submitted manuscript.

☒ C. Each author has participated sufficiently in the work to take public responsibility for all of the content.

☒ D. Each author qualifies for authorship by listing his or her name on the appropriate line of the categories of contributions listed below.

The authors listed below have made substantial contributions to the intellectual content of the paper in the various sections described below.

(list appropriate author next to each section – each author must be listed in at least 1 field. More than 1 author can be listed in each field.)

_ conception and design	I Geraerts, M Van Kampen, H Van Poppel
_ acquisition of data	I Geraerts, A De Groef, H Van Poppel, S Joniau, B Van Cleynenbreugel
_ analysis and interpretation of data	I Geraerts, M Van Kampen, A De Groef
_ drafting of the manuscript	I Geraerts, M Van Kampen, A De Groef
_ critical revision of the manuscript for important intellectual content	M Van Kampen, H Van Poppel, N Devoogdt, S Joniau, B Van Cleynenbreugel
_ statistical analysis	I Geraerts, A De Groef
_ obtaining funding	I Geraerts, M Van Kampen, N Devoogdt
_ administrative, technical, or material support	I Geraerts, M van Kampen
_ supervision	I Geraerts, M Van Kampen, H Van Poppel
_ other (specify)	

Financial Disclosure

☒ None of the contributing authors have any conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

OR

☐ I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: (please list all conflict of interest with the relevant author's name):

Funding Support and Role of the Sponsor

☒ I certify that all funding, other financial support, and material support for this research and/or work are clearly identified in the manuscript.

The name of the organization or organizations which had a role in sponsoring the data and material in the study are also listed below:

Agency for Innovation by Science and Technology (Applied Biomedical Research): Governmental grant

All funding or other financial support, and material support for this research and/or work, if any, are clearly identified hereunder:

The specific role of the funding organization or sponsor is as follows:

☐ Design and conduct of the study
☐ Collection of the data
☐ Management of the data
☐ Analysis
☐ Interpretation of the data
☐ Preparation
☐ Review
☐ Approval of the manuscript

OR

☐ No funding or other financial support was received.

Acknowledgment Statement

This corresponding author certifies that:
• all persons who have made substantial contributions to the work reported in this manuscript (eg, data collection, analysis, or writing or editing assistance) but who do not fulfill the authorship criteria are named with their specific contributions in an Acknowledgment in the manuscript.
• all persons named in the Acknowledgment have provided written permission to be named.
• if an Acknowledgment section is not included, no other persons have made substantial contributions to this manuscript.
H. Lemkens, K Sterckx, A Gielen

After completing all the required fields above, this form must be uploaded with the manuscript and other required fields at the time of electronic submission.

INFLUENCE OF PRE- AND POST- VERSUS POSTOPERATIVE PELVIC FLOOR MUSCLE TRAINING ON URINARY INCONTINENCE AFTER RADICAL PROSTATECTOMY: A RANDOMIZED CONTROLLED TRIAL.

Inge Geraerts *Dra. in biomedical science*[a], Hendrik Van Poppel P*rofessor, M.D., Ph. D.*[b], Nele Devoogdt Ph.D.[a], Steven Joniau *M.D., Ph.D.*[b], Ben Van Cleynenbreugel *M.D.*[b], An De Groef *research fellow*[a], Marijke Van Kampen *Professor, Ph.D.*[a]

[a] KU Leuven, Department of Rehabilitation Science

[b] UZ Leuven, Department of Urology

Corresponding author:

Inge Geraerts

KU Leuven

Department of Rehabilitation Science

Tervuursevest 101

Postoffice box 1501

3000 Leuven

Tel.: 0032 16 329120

Fax.: 0032 16 329197

Email: inge.geraerts@faber.kuleuven.be

Keywords: urinary incontinence, pelvic floor muscle training, radical prostatectomy

Word count text: 2713 words, word count abstract: 287 words

Abstract

Background: Efficacy of preoperative pelvic floor muscle training (PFMT) for urinary incontinence (UI) after open (ORP) and robot-assisted laparoscopic (RALP) radical prostatectomy is still unclear.

Objective: To determine whether patients with additional preoperative PFMT regain urinary continence earlier than patients with only postoperative PFMT after ORP and RALP.

Design, setting and participants: A randomized controlled trial enrolled men (n=180) planned for ORP/RALP.

Intervention: The experimental group (E, n=91) started PFMT 3 weeks before surgery and continued after surgery, the control group (C, n=89) started PFMT after catheter removal.

Outcome measurements and statistical analysis: Primary endpoint was time to continence. Patients measured urine loss daily (24hpad test) until total continence (3 consecutive days of 0 gram) was achieved. Secondary endpoints were 1hpad test, visual analogue scale (VAS), international prostate symptom score (IPSS), quality of life (King's health questionnaire (KHQ)). Kaplan-Meier analysis and Cox regression with correction for 2 strata (age, type of surgery) compared time to continence. Fisher's exact test was applied for 1hpad test and VAS, Mann-Whitney-U test for IPSS and KHQ.

Results and limitation: Patients, with additional preoperative PFMT, had no shorter duration of postoperative UI compared to patients with only postoperative PFMT (p=0.878). Median

time to continence was 30 and 31 days and median amount of first day incontinence was 108 gram and 124 gram for (E) and (C), respectively. Cox regression neither indicated a significant difference between (E) and (C) (p= 0. 773, HR 1.047 (0.768-1.425)). The 1hpad test, VAS and IPSS were comparable between both groups. However 'incontinence impact' (KHQ) was in favor of (E) at 3 and 6 months after surgery.

Conclusions: Three preoperative sessions of PFMT did not improve postoperative duration of incontinence.

Trial registration Netherlands Trial Register No NTR 1953

Introduction

Urinary incontinence (UI) remains a common postoperative consequence after open (ORP) and robot-assisted laparoscopic (RALP) radical prostatectomy [1-4].

UI has a spontaneous recovery in most men, but it may take up to 1 to 2 years after radical prostatectomy (RP) [5]. Different investigators proved that continence can be achieved faster with pelvic floor muscle training (PFMT) [1, 2, 6]. Additionally, 6 studies attempted to investigate the effect of pre-operative PFMT on the duration and severity of UI after RP [3, 7-11]. Five studies found positive results of preoperative PFMT [3, 7, 8, 10, 11]. However, due to the multitude of existing bias, results must be interpreted with caution. Parekh et al, Burgio et al and Tienforti et al altered both pre- and postoperative treatment, which made defining the effect of preoperative PFMT impossible [3, 8, 11]. Bales et al compared the effect of two different preoperative treatments and Sueppel et al compared only one preoperative session with a control group who completed PFMT 6 weeks after surgery and only included 16 patients. [7, 9]. Furthermore, follow-up was usually only 3 or 6 months [3, 9-11] Finally, a wide range of continence criteria was used among studies, which made it difficult to compare results.

The aim of this study was to determine whether patients who performed PFMT before and after surgery, regained urinary continence earlier than patients who only performed PFMT after catheter removal.

Methods

Patients

Inclusion criteria were men planned for ORP or RALP in the University Hospitals Leuven, who accepted ambulatory visits once a week until total continence was achieved and agreed to perform measurements preoperatively, at 1, 3, 6 and 12 months after surgery. Patients were excluded if they had cognitive problems, were non-Dutch speaking, simultaneously planned for other pelvic surgery or a salvage procedure, had transport problems, lack of time, psychosocial or other medical problems, did not want to participate, insisted on preoperative PFMT, were not approachable or when there was not enough time between diagnosis and date of planned surgery.

Procedure

Before surgery, patients were randomized into the experimental group, starting PFMT 3 weeks before RP and continuing after surgery, or the control group, starting PFMT after catheter removal. Patients were recruited on the outpatient clinic of urology. PFMT could only start 3 weeks before surgery, because the waiting list for surgery was only 3 weeks. Randomization was performed within each stratum by using permuted blocks (size=4). Strata were age (<65 vs. ≥65) and surgical technique (ORP vs. RALP), because these 2 factors are important risk factors for UI [12-16]. Allocation to the treatment groups was concealed. A computer program carried out the randomization. The sequence of randomization was determined by the patient's presence on the outpatient clinic of urology. Choice of surgical technique depended on tumor characteristics, choice of the patient and medical history. Three experienced surgeons each specialized in ORP and/or RALP and blinded to randomization completed all operations.

Interventions

The PFMT program, consisted of exercises of the pelvic floor manually controlled by the therapist and supplied with EMG-biofeedback. Every patient received individual treatment on an outpatient basis once a week. The experimental group started exercising 3 weeks before RP. They received one session of 30 minutes of guided PFMT per week until surgery. Additionally patients performed a home program of 60 contractions/ day and were instructed on contracting the pelvic floor muscles while coughing and sitting down/ getting up from a chair. The fourth day after surgery, with the urinary catheter in situ, patients were encouraged to restart PFMT. The control group started exercising the day of catheter removal. Postoperatively all patients came to the hospital once a week to discuss the bladder diary and to perform an individual guided exercise session with digital or EMG-biofeedback control. Further specific exercises and advice were given on how to use the pelvic floor muscles to prevent urine loss in particular functional activities indicated by the patient. In both groups PFMT was continued as long as any degree of UI persisted.
All patients in the experimental group were preoperatively treated by the same therapist (different from the therapist who performed the postoperative treatments and from the assessor). After catheter removal all patients were treated by another therapist. Both therapists had several years of experience in treatment of UI. Patients were controlled for adherence to the home exercises. When they performed the prescribed 60 contractions per day, they had to color 3 squares in their diary (each square equaled 20 contractions).

Assessments

After catheter withdrawal urine loss per 24 hours was recorded. Patients continued this at home until continence was achieved. Continence was defined as three consecutive days of 0

gram urine loss on the 24hpad test. Double-check of the auto-measurements of the patients happened on a regular base by weighing the pad they wore, when they came to therapy. Furthermore, from time to time, patients had to collect all diapers from 24h in a plastic bag and bring it to the hospital for a second measurement. No difference was made in analysis between types of incontinence (stress, urge).

All patients were prospectively assessed before and 1, 3, 6 and 12 months after RP in the physiotherapy department. Patients had to perform a 1hpad test, fill in a VAS concerning their subjective feeling about UI and the international prostate symptom score (IPSS) [17], a questionnaire to assess voiding symptoms. Additionally the King's health questionnaire (KHQ), to evaluate the impact of UI on quality of life was completed [18]. Strength and endurance were also measured. Preoperatively all patients performed a 24hpad test during 3 days. One blinded and well trained assessor performed the measurements. Patients were explicitly asked not to mention their group allocation to the assessor. No urodynamic measurements were performed in the first postoperative year. Anticholinergics were not prescribed in the initial postoperative period.

Primary outcome parameters were cumulative incidence of continence and time to continence (24hpad test). Secondary outcomes were the point prevalence of continence, measured with the 1hpad test and the VAS at 1, 3, 6 and 12 months after surgery. At the same time points, IPSS and KHQ were assessed.

Sample size and statistical analysis

Sample size was calculated to detect a difference between the control and the treatment group in time until continence based on a two-sided log-rank test (α=0.05). An exponential distribution was assumed for the event times, yielding 60% and 40% of patients being continent after 6 months, in treatment and control group, respectively. Note that the scenario for the difference after 6 months was derived from Burgio et al [3]. The assumed distribution and difference after 6 months corresponded to a median time until continence of 4.5 months and 8.1 months, in treatment and control group, respectively. Further, it implied 84% (treatment) and 64% (control) of the subjects being continent after 1 year, the time at which the comparison was made. In total 166 subjects were needed to have 90% power to detect the assumed difference between both survival curves. Drop outs taken into account, 180 patients had to be included.

We compared patient's characteristics between excluded and included patients to analyse if both groups were comparable.

Data were analysed according the intention to treat principle. Kaplan-Meier analyses with log rank test were used to compare the time to continence between both groups. Drop outs were censored at moment of last follow-up. Afterwards a Cox regression was applied to compare the different groups concerning the time to continence with correction for the two strata. Fisher's exact test was used to compare objective and subjective point prevalence of urinary continence, defined as 0 or ≤ 1 gram on the 1hpad test and the VAS, measured at 1, 3, 6 and 12 months after surgery. For comparison of voiding symptom severity and quality of life at 1, 3, 6 and 12 months after surgery, the Mann-Whitney-U test was used, because data were not normally distributed. All data were analyzed with SPSS 19.0.

The procedures of the study received ethical approval from the commission medical ethics of the University Hospitals Leuven responsible for human/animal experimentation (ML5470). This trial was registered in the Netherlands Trial Register No NTR 1953.

Results

Between September 2009 and July 2011, 275 patients with localized or locally advanced prostate cancer were scheduled for ORP or RALP in the University Hospitals Leuven. Finally 180 patients met the inclusion criteria (Figure 1: trial profile) and signed written informed consent. Patients who did not want to participate for several reasons (n= 81) were asked to report their date of continence.

Compared to non-participating (excluded) patients, included patients had less ORP and more RALP surgery (p= 0.001), had more patients with an intermediate and less patients with a high D'Amico risk group (p< 0.001), less patients had non-nerve sparing surgery and more patients had bilateral nerve sparing surgery (p=0.001). Other characteristics like age and surgical margin status were comparable between both groups (data not shown).

One hundred eighty patients were included, 91 patients were randomized to the intervention group and 89 patients to the control group. Ten patients were lost to follow-up. Figure 1 shows the flow of patients and reasons for drop out (Figure 1). Patients were very strictly towards their appointments with the physiotherapist and the performance of exercises.

All characteristics of both groups were comparable (Table 1). Median time to continence was 30 and 31 days for control and experimental group, respectively (p= 0.878). Median amount of first day UI was 108 gram and 124 gram for experimental and control group, respectively (p= 0.880).

Primary outcomes

Figure 2 shows the Kaplan-Meier analyses for time to continence (24hpad test). Time to continence was comparable between experimental and control group during the first year after surgery (p= 0.878). Additionally, Cox regression with correction for the two strata (age and type of surgery) gave comparable results (p= 0.773, HR 1.047 (0.768-1.425)) (Table 2).

Four patients in the control group and two in the experimental group remained incontinent 12 months after surgery. Compared to controls, patients in the intervention group had comparable cumulative incidence rates for continence and average amount of urine loss (24hpad test), at all-time points (Table 3).

Secondary outcomes

The point prevalence of urinary continence, defined as 0 or ≤1 gram on the 1hpad test and the VAS was comparable for both groups at 1, 3, 6 and 12 months after RP (Table 4). Voiding symptoms (IPSS) did not differ at any time point between experimental and control group. Only one aspect of the KHQ, namely 'incontinence impact' was in favor of the experimental group at 3 and 6 months after surgery (p= 0.008 and p= 0.024, respectively).

Strength and endurance did not significantly differ between both groups at any time point. However patients with stronger pelvic floor muscles needed less time to become continent (p= 0.015).

Furthermore, 23 patients of 180 (13%) received additional radiotherapy. In all patients, except three, radiotherapy was only started after continence was achieved. In these three patients, mean urine loss at the start of radiotherapy measured 7, 8 and 64 gram per day, respectively.

Sixty-five percent of patients were completely continent during 3 days in the preoperative period. Thirty percent had a small amount of urine loss (range 1-10 gram per day). However, Kaplan-Meier analyses for time to continence indicated that patients without preoperative urine loss achieved continence significantly faster than preoperatively incontinent patients ($p=0.01$).

Duration of incontinence, based on the patient-reported date of continence, did not differ between included and excluded patients ($p= 0.121$).

Discussion

Patients, who performed PFMT before and after surgery, had no shorter duration of postoperative UI than patients who only performed PFMT after catheter removal. Only six patients remained incontinent after one year (range 6-167 gram/day). Four patients opted for a male sling procedure and were continent afterwards. Two patients refused surgical treatment (minimal incontinence rate (6 gram/day) (n=1), other comorbidities (130 gram/day) (n=1)). Secondary analyses revealed that the 1hpad test and the VAS did not significantly differ between both groups. The median time to urinary continence and the median amount of first day UI was approximately the same for both groups. Voiding symptoms were comparable between both groups. Quality of life was in favor of the experimental group at 3 and 6 months after surgery, concerning the impact of incontinence. Although both groups recovered to the same extent of continence, we cannot explain why the experimental group had better quality of life scores. Furthermore, preoperative urine loss had a significant effect on duration of postoperative UI.

Our study had several strengths. Firstly, this was a prospective study offering the same postoperative treatment to both groups and only 3 sessions of preoperative PFMT to the experimental group. This makes comparison possible. All patients were followed for 12 months and evaluated at regular time intervals. Furthermore all patients measured urine loss daily during 24 hours by weighing pads accurately to 1 gram. Additionally, patients performed a 1hpad test, VAS, IPSS and KHQ at 1, 3, 6 and 12 months postoperative. Patients were assessed by a blinded independent assessor and treated by another blinded independent therapist. Patients were operated by three experienced surgeons, using highly standardized surgical procedures. Finally, our sample size was sufficiently large and based on a priori power analysis. Limitations were, firstly, the number of patients after ORP and RALP

being unequal (116 vs. 54 patients). Secondly, the short waiting list made only 3 preoperative sessions possible. Every therapy that shortens duration of incontinence is valuable, but patients maybe would have benefited from a longer preoperative exercise period to enhance strength and endurance. It can be assumed that 3 PFMT sessions only train awareness of the pelvic floor muscles. Additionally, it would have been interesting to administer the 1hpad test the day of catheter removal to have a second objective incontinence parameter. Patients were encouraged not to stay in bed during the whole day. However we noticed that several patients tended to be rather inactive to minimalize urine loss. This might have underestimated the first day UI. Finally, it would have been interesting to add a group without PFMT, but since evidence of PFMT exists, this was not allowed [1, 2, 19].

Twelve months after surgery, 80-97% of patients have regained continence [13, 14, 20-23]. Although we did not hypothesize on the number of patients with persistent incontinence at one year, results were in line with previous research [1, 13, 14, 23]. A recent review [24] supported the EAU guidelines [25] about UI that 'men undergoing some form of PFMT, before or after RP achieved continence more quickly than non-treated men'. However Campbell et al indicated that findings should be treated with caution, as most trials were of poor to moderate quality [24]. In general conservative management is advised as the main approach to UI after RP. Several studies consistently demonstrated that PFMT speeded the recovery of UI [2, 19, 26]. According to the EAU guidelines, approximately 10 trials compared the preventive effect of PFMT prior to RP. However, analyzing these studies very strictly, only five attempted to investigate the evidence of preoperative PFMT [3, 7-10]. Similar to our results, Bales et al did not find a significant effect of preoperative PFMT, although these authors only gave one preoperative session [9]. In other studies positive results of

preoperative training were mentioned [3, 7, 8, 10, 11], although a multitude of existing bias was cited. In our study, both groups recovered to the same extent of continence, when continence was defined as 3 consecutive days of 0 gram urine loss (24hpad test). Additionally, analysis based on a definition of <2 gram of urine loss, made no difference in time to continence between both groups (p=0.815). This was also confirmed by the 1hpad test. However, we cannot explain why the experimental group had better quality of life scores than the control group.

All patients of the experimental group expressed their satisfaction to receive PFMT before surgery. Patients in the control group were in general rather disappointed in not having had preoperative treatment. Three preoperative sessions of PFMT did not improve postoperative duration of incontinence.

Conclusions

In conclusion, standard postoperative continence rehabilitation using a strict pelvic floor reeducation scheme could not be improved by adding 3 preoperative sessions of PFMT. Incontinence impact on quality of life however was less in the experimental group.

Reference list

[1] Van Kampen M, de Weerdt W, Van Poppel H, De Ridder D, Feys H, Baert L. Effect of pelvic-floor re-education on duration and degree of incontinence after radical prostatectomy: a randomised controlled trial. The Lancet. 2000;355(9198):98-102.

[2] Manassero F, Traversi C, Ales V, et al. Contribution of early intensive prolonged pelvic floor exercises on urinary continence recovery after bladder neck-sparing radical prostatectomy: Results of a prospective controlled randomized trial. Neurourology and Urodynamics. 2007;26(7):985-9.

[3] Burgio KL, Goode PS, Urban DA, et al. Preoperative Biofeedback Assisted Behavioral Training to Decrease Post-Prostatectomy Incontinence: A Randomized, Controlled Trial. The Journal of Urology. 2006;175(1):196-201.

[4] Ficarra V, Novara G, Rosen RC, et al. Systematic Review and Meta-analysis of Studies Reporting Urinary Continence Recovery After Robot-assisted Radical Prostatectomy. Eur Urol. 2012;62(3):405-17.

[5] Sanda MG, Dunn RL, Michalski J, et al. Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors. New England Journal of Medicine. 2008;358(12):1250-61.

[6] Filocamo MT, Li Marzi V, Popolo GD, et al. Effectiveness of Early Pelvic Floor Rehabilitation Treatment for Post-Prostatectomy Incontinence. European Urology. 2005;48(5):734-8.

[7] Sueppel C, Kreder K, See W. Improved continence outcomes with preoperative pelvic floor muscle strengthening exercises. Urol Nurs. 2001;21(3):201-10.

[8] Parekh AR, Feng MI, Kirages D, Bremner H, Kaswick J, Aboseif S. The Role of Pelvic Floor Exercises on Post-Prostatectomy Incontinence. The Journal of Urology. 2003;170(1):130-3.

[9] Bales GT, Gerber GS, Minor TX, et al. Effect of preoperative biofeedback/pelvic floor training on continence in men undergoing radical prostatectomy. Urology. 2000;56(4):627-30.

[10] Centemero A, Rigatti L, Giraudo D, et al. Preoperative Pelvic Floor Muscle Exercise for Early Continence After Radical Prostatectomy: A Randomised Controlled Study. European Urology. 2010;57(6):1039-44.

[11] Tienforti D, Sacco E, Marangi F, et al. Efficacy of an assisted low-intensity programme of perioperative pelvic floor muscle training in improving the recovery of continence after radical prostatectomy: a randomized controlled trial. BJU International. 2012;110(7):1004-10.

[12] Tewari A, Srivasatava A, Menon M, members of the VIPT. A prospective comparison of radical retropubic and robot-assisted prostatectomy: experience in one institution. BJU International. 2003;92(3):205-10.

[13] Ficarra V, Novara G, Fracalanza S, et al. A prospective, non-randomized trial comparing robot-assisted laparoscopic and retropubic radical prostatectomy in one European institution. BJU International. 2009;104(4):534-9.

[14] Rocco B, Matei D-V, Melegari S, et al. Robotic vs open prostatectomy in a laparoscopically naive centre: a matched-pair analysis. BJU International. 2009;104(7):991-5.

[15] Kim SC, Song C, Kim W, et al. Factors Determining Functional Outcomes After Radical Prostatectomy: Robot-Assisted Versus Retropubic. European Urology. 2011;60(3):413-9.

[16] Khoder WY, Trottmann M, Stuber A, Stief CG, Becker AJ. Early incontinence after radical prostatectomy: A community based retrospective analysis in 911 men and implications for preoperative counseling. Urologic Oncology: Seminars and Original Investigations. (0).

[17] Barry MJ, Fowler FJ, Jr., O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992;148(5):1549-57; discussion 64.

[18] Okamura K, Nojiri Y, Osuga Y. Reliability and validity of the King's Health Questionnaire for lower urinary tract symptoms in both genders. BJU International. 2009;103(12):1673-8.

[19] Ribeiro LH, Prota C, Gomes CM, et al. Long-term effect of early postoperative pelvic floor biofeedback on continence in men undergoing radical prostatectomy: a prospective, randomized, controlled trial. J Urol. 2010;184(3):1034-9.

[20] Menon M, Shrivastava A, Kaul S, et al. Vattikuti Institute Prostatectomy: Contemporary Technique and Analysis of Results. European Urology. 2007;51(3):648-58.

[21] Di Pierro GB, Baumeister P, Stucki P, Beatrice J, Danuser H, Mattei A. A Prospective Trial Comparing Consecutive Series of Open Retropubic and Robot-Assisted Laparoscopic Radical Prostatectomy in a Centre with a Limited Caseload. European Urology. 2011;59(1):1-6.

[22] Lepor H, Kaci L, Xue X. Continence Following Radical Retropubic Prostatectomy Using Self-Reporting Instruments. The Journal of Urology. 2004;171(3):1212-5.

[23] Krambeck AE, DiMarco DS, Rangel LJ, et al. Radical prostatectomy for prostatic adenocarcinoma: a matched comparison of open retropubic and robot-assisted techniques. BJU International. 2009;103(4):448-53.

[24] Campbell SE, Glazener CM, Hunter KF, Cody JD, Moore KN. Conservative management for postprostatectomy urinary incontinence. Cochrane Database Syst Rev. 2012;1(1):CD001843.

[25] Lucas MG BJ, Cruz FR et al. Guidelines on urinary incontinence. European association of urology; 2012.

[26] Marchiori D, Bertaccini A, Manferrari F, Ferri C, Martorana G. Pelvic floor rehabilitation for continence recovery after radical prostatectomy: role of a personal training re-educational program. Anticancer Research. 2010;30(2):553-6.

REVISION NOTES

Comments reviewer 1: No

Comments reviewer #2: The authors have done a complete revision of the manuscript answering adequately to the constructive points suggested by reviewer and the manuscript has been greatly improved in this version.
1. Just one question remains: the strength of 4 or 5 on the Oxford scale preoperatively and postoperatively means that the preoperative strength was already very high and was not improved by training only the endurance was improved. However, the strength decreased (preop 67/70%, postop. 61/64%). Do you have an explanation for the decrease? In addition, was there a difference in time to continence in patients with a weak strength?

Indeed, preoperative strength was already high in most men, with 67% of patients in the control group and 70% of patients in the experimental group having strength of 4 or 5 on the Oxford scale.

Median time to continence was approximately 30 days for both groups. At each follow-up measurement, men were counseled to continue their pelvic floor muscle exercises although continence often was already achieved. However, most men admitted that they performed less exercises as time continued. In our opinion, the most important reason strength was decreased at 12 months is because patients did not exercise anymore. Additionally, we must take into account that patients underwent surgery in the pelvic region and age increased another year.

Although the Oxford scale is a reliable and valid scale to measure strength and endurance of the pelvic floor muscles, the measurement of strength by anal pressure (cm H_20) as a continuous measurement however gives more detailed information.

Patients with a preoperative strength between 0 and 3 on the Oxford scale needed more time to become continent than patients with a higher preoperative strength (4-5) (p= 0.015).

We added following sentence to the results section (line 181-182)*: However patients with stronger pelvic floor muscles needed less time to become continent (p= 0.015).*

Reviewer #3: Very good rebuttal.
The paper has been clearly improved, and all the questions clearly answered.

Reviewer #4:

1. If the authors claim that the 3 sessions of PFM are training awareness instead of muscle strength and endurance, this should be stated in the manuscript and discussed in the discussion section.

We acknowledge the comment of the reviewer and we added following sentence to the discussion section (line 238-239)*: It can be assumed that 3 PFMT sessions only train awareness of the pelvic floor muscles.*

2. Even if the scenario for the difference between the groups was derived from a publication from Burgio et al, the surgical results in their group were less good than in your group. I severely doubt that your sample size, based on the differences in outcome, is adequately designed to find the hypothesized difference.

As mentioned in the previous revision, sample size was calculated to detect a difference between the control group and the treatment group in time until continence based on a two-sided log-rank test (α=0.05). An exponential distribution was assumed for the event times, yielding 60% and 40% of patients being continent after 6 months, in treatment and control group, respectively. This scenario for the difference at 6 months was

indeed derived from Burgio et al [3]. The assumed distribution and difference after 6 months corresponded to a median time until continence of 4.5 months and 8.1 months, in treatment and control group, respectively. Further, it implied 84% (treatment) and 64% (control) of the subjects being continent after 1 year, the time at which the comparison was made.

We chose to indicate a power of 90% to detect the assumed difference between both survival curves instead of 80% like most studies. This resulted in a sample size calculation of 166 patients. With 80% power (which is already rather high) we would have needed only 124 patients. Furthermore we took into account a drop-out rate of 8% (14/180), although we only had a drop-out rate of 5.5%.

Additionally, no other study investigating the effect of preoperative pelvic floor muscle exercises included so many subjects as we did. (Bales et al (N=100), Burgio et al (N=125), Centemero et al (N=118), Parekh et al (N=38), Sueppel et al (N=16), Tienforti et al (N=32))

Take home message

Standard postoperative continence rehabilitation using a strict pelvic floor reeducation scheme could not be improved by adding 3 preoperative sessions of PFMT.

Figure 1

Figure 1: Trial profile

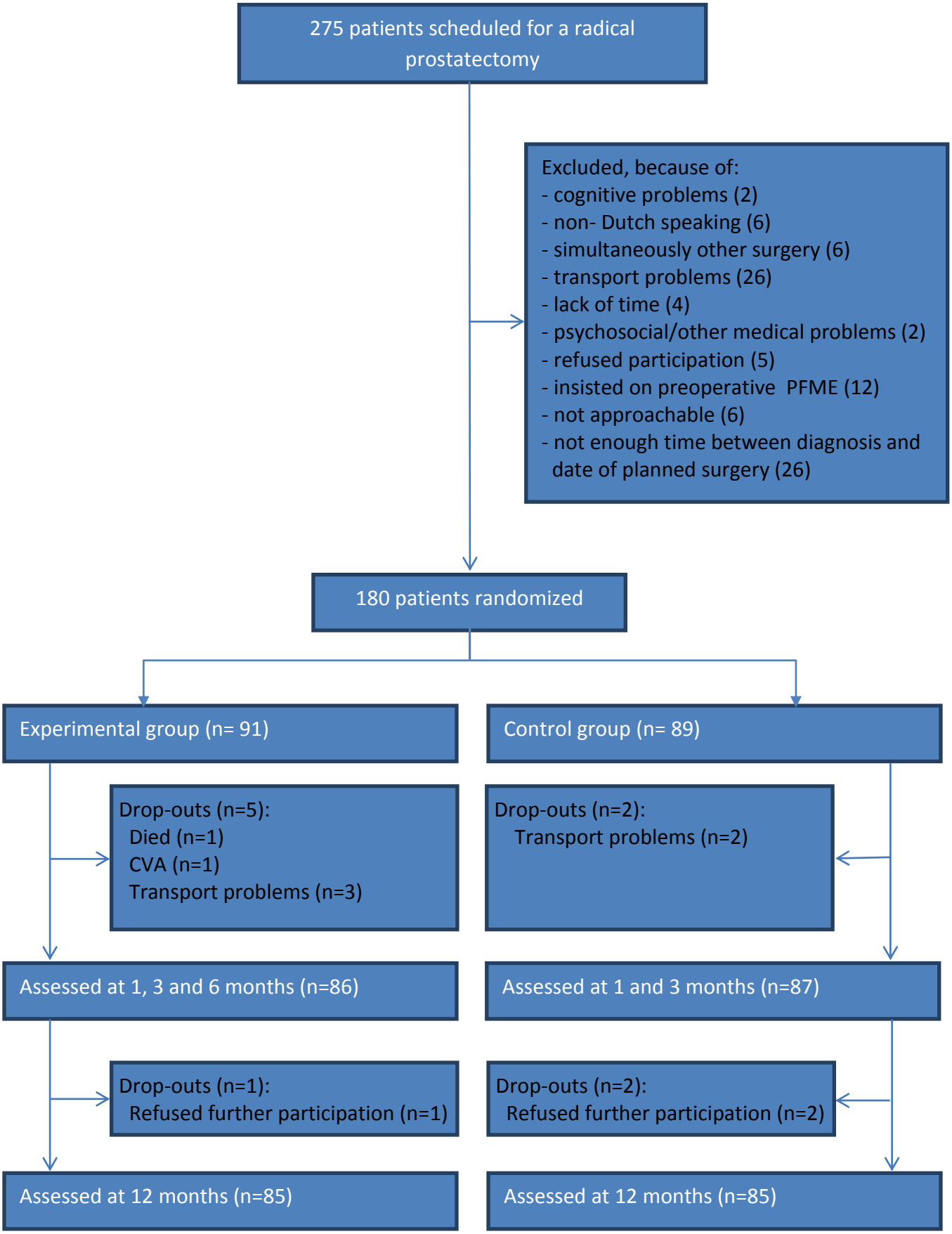

Figure 2

Figure 2: Time to urinary continence according to type of treatment

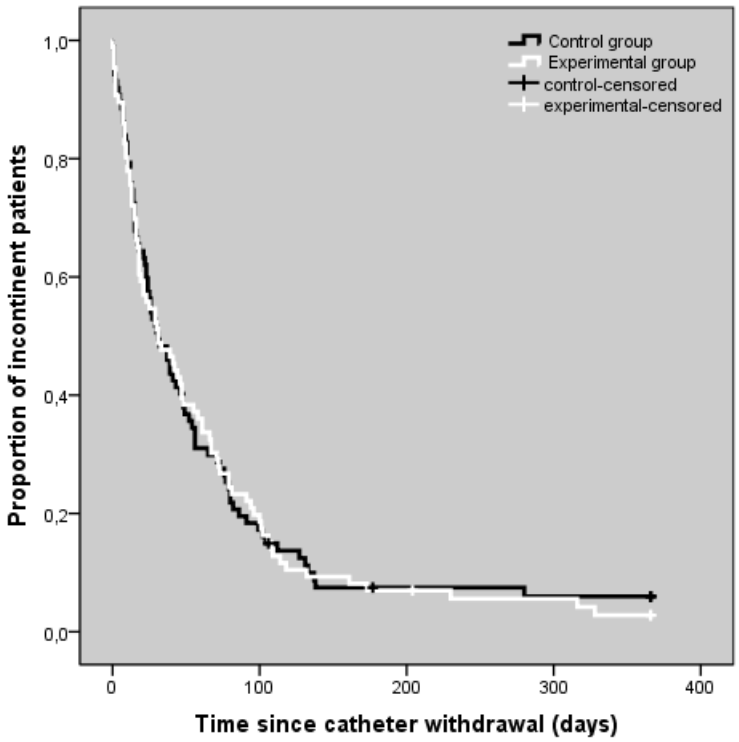

Table 1

Table 1: Characteristics of patients according to treatment group. Figures are numbers (percentages) of patients unless specified otherwise

	Experimental Group n= 91	Control Group n= 89
Mean (SD) (range) age (years)	61,88 (5,90) (44-73)	62,04 (6,33) (41-76)
Type of surgery		
ORP	60 (66)	56 (63)
RALP	31 (34)	33 (37)
D'Amico Risk Group		
I	13 (14)	9 (10)
II	45 (49)	48 (54)
III	32 (35)	32 (36)
Missing	1 (1)	0 (0)
Nerve sparing		
Non-nerve sparing	13 (14)	11 (12)
Unilateral-nerve	22 (24)	22 (25)
Bilateral-nerve sparing	56 (62)	56 (63)
Missing	0 (0)	0 (0)
Surgical Margin status		
Negative	73 (80)	63 (71)
Positive/doubtful	17 (19)	26 (29)
Missing	1 (1)	0 (0)
Preoperative continence status		
Continent	63 (69)	53 (59)
Incontinent	25 (28)	30 34)
Missing	3 (3)	6 (7)
Body Mass Index (kg/m²)		
<25.0	30 (33)	24 (27)
25.1-30.0	51 (56)	48 (54)
>30.0	10 (11)	17 (19)

Table 2 : Cox regression for the time to urinary continence according to type of treatment

	B	SE	Wald	df	p-value	HR	CI (95%)	
							Lower	Upper
Treatment Group	,046	,158	,083	1	,773	1,047	,768	1,425
Type of surgery	,430	,164	6,850	1	,009	1,537	1,114	2,122
Age	-,519	,173	9,035	1	,003	,595	,424	,835

B= B-coefficient; SE= standard error; df= degrees of freedom; HR= hazard ratio; CI= confidence interval

Table 3: Cumulative incidence of continence and average urine loss of patients at 1, 3, 6 and 12 months after radical prostatectomy (based on the 24hpad test).

Time since catheter removal	Number (%) of continent patients		Average urine loss (gram)	
	Experimental Group (n=85)	Control Group (n=85)	Experimental Group (n=85)	Control Group (n=85)
1 month	44 (52%)	44 (52%)	90	85
3 months	67 (79%)	71 (84%)	17	13
6 months	80 (94%)	80 (94%)	12	3
12 months	83 (98%)	81 (95%)	2	3

Table 4: Comparison of the point prevalence of continence after radical prostatectomy at 1, 3, 6 and 12 months after surgery, according to treatment group

	Experimental Group	Control Group	Odds Ratio (95% CI)	P value*
Point prevalence of continence, VAS-scale defined as ≤1/10				
At 1 month (89/88)	35 (39.3%)	38 (43.2%)	0.853 (0.469-1.552)	0.648
At 3 months (88/87)	64 (70.7%)	52 (59.8%)	1.795 (0.951-3.388)	0.080
At 6 months (88/86)	73 (82.9%)	65 (75.6%)	1.572 (0.749-3.302)	0.264
At 12 months (84/84)	72 (85.7%)	62 (73.8%)	2.129 (0.975-4.649)	0.083
Point prevalence of continence, 1h-pad test, defined as 0 gram				
At 1 month (85/86)	42 (49.4%)	41 (47.7%)	1.072 (0.588-1.953)	0.879
At 3 months (86/86)	63 (73.3%)	61 (70.9%)	1.123 (0.576-2.187)	0.865
At 6 months (86/85)	76 (88.4%)	73 (85.9%)	1.249 (0.509-3.068)	0.655
At 12 months (81/83)	68 (83.9%)	73 (87.9%)	0.717 (0.295-1.742)	0.506
Point prevalence of continence, 1h-pad test, defined as ≤ 1 gram				
At 1 month (85/86)	48 (56.5%)	51 (59.3%)	0.890 (0.485-1.634)	0.758
At 3 months (86/86)	71 (82.6%)	71 (82.6%)	1.000 (0.455-2.198)	1.000
At 6 months (86/85)	78 (90.7%)	80 (94.1%)	0.609 (0.191-1.944)	0.566
At 12 months (81/83)	74 (91.4%)	76 (91.6%)	0.974 (0.326-2.912)	1.000

*Fisher's exact test; statistical significance was defined as p<0,05