

Detailing sexual outcomes after focal therapy for localised prostate cancer: a systematic review and meta-analysis

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Abstract

Context: Focal therapy has emerged as a promising option to treat well-selected men with localised prostate cancer while preserving healthy prostate tissue and key structures, such as the urethral sphincter and neurovascular bundles. However, how this tissue preservation may translate into improved outcomes, particularly into improved sexual outcomes, is still an active research field.

Objective: We conducted a systematic review and meta-analysis of the literature to summarise the existing evidence in order to provide patients with updated data on what to

expect after treatment, and help identify gaps in current knowledge that may warrant future research.

Evidence acquisition: A systematic literature search was done on Medline, EMBASE, Scopus and Web of Science. The search strategy was defined using the 'litsearchr' function in R based on a preliminary "naïve" search using the following terms on Medline: (("focal therapy" OR "focal treatment") AND ("prostate cancer") AND ("sexual function" OR "erectile function")). A total of 42 studies, comprising 3117 patients treated and 2352 with available sexual outcomes were included in the qualitative data synthesis, and 26 in a random-effect meta-analysis.

Evidence synthesis: The 5 item International Index of Erectile Function (IIEF-5) was the most frequently used questionnaire (30/42 studies), with completion rates ranging from 24-100% at 18-24 months. A decrease was noted at 3 months (IIEF-5 decrease estimate -3.70 [95%CI $-4.43, -2.96$]) with an improvement at 6 (-2.18 [$-2.91, -1.46$]) and 12 months (-2.14 [$-2.96, -1.32$]). Studies in which patients had an altered baseline sexual function were more likely to report a significant and durable postoperative decrease in erectile function scores. The patient-reported outcomes questionnaires used were not designed for a diverse population. Functional outcomes were not the primary endpoint and have not been reported consistently in most studies considered.

Conclusions: Focal therapy led to changes in erectile function in most cases under the significance threshold of the patient-reported outcomes questionnaires used. However, patients should be counselled according to their baseline erectile function. More research is warranted to detail aspects other than erectile function, such as ejaculation or orgasm. The early post-operative period appears key to study sexual changes after focal therapy, while only a moderate decrease is expected at 12 months.

Patient summary: We reviewed the published literature detailing the sexual consequences of focal therapy for localised prostate cancer using patient-reported outcomes questionnaires. Patients were likely to describe a significant decrease in their erectile function at 3 months, with an improvement noted at 6 and 12 months. The results obtained may not be reproducible in a more diverse population and further research is warranted to better study aspects other than erectile function, such as ejaculation or orgasm.

Introduction

Focal therapy has emerged as a promising option to treat well-selected men with localised prostate cancer while preserving adjacent healthy prostate tissue and key structures, such as the urethral sphincter and neurovascular bundles. However, how this tissue preservation may translate into improved outcomes, particularly into improved sexual outcomes, is still an active research field. Early results with excellent potency preservation rates were often physician-reported. The patient-led EUPROMS study has recently shown us that there could be a significant gap between our physician-based idea of a good outcome and patient-reported outcomes (PROs) [1]. A large survey study including 934 men treated for localised prostate cancer found that significant sexual function bother was reported by 39% of men and strongly associated with treatment decision regret [2]. Another study linking PROs and decision regret confirmed that regret about the treatment choice (reported by 23% of patients) was more likely among patients with significant and enduring treatment-related symptoms [3]. How well we are able to inform patients on the possible post-operative outcomes has been shown of paramount importance to mitigate this treatment decision regret [4]. An international multidisciplinary consensus recently concluded that functional outcome assessment was a key component of focal therapy surveillance, but provided little guidance on how this endpoint should be achieved [5]. We conducted a systematic review and meta-analysis of the literature to analyse how tissue preservation with focal therapy with various energy sources translates into sexual outcomes.

Evidence acquisition

Systematic literature search

A systematic literature search was conducted on Medline, EMBASE, Scopus and Web of Science. The search strategy was defined using the 'litsearchr' function in R software (R foundation, version 3.6.1) based on a preliminary "naïve" search using the following terms on Medline: (("focal therapy" OR "focal treatment") AND ("prostate cancer") AND ("sexual function" OR "erectile function")). The detailed Boolean search is available as **Supplementary material 1**. Articles written in English only were considered, and no time limit was set. Reviews

were excluded but their references were manually searched for additional references. The review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines and registered on PROSPERO (CRD42020165763).

Study methodology

Population, Intervention, comparator and Outcomes (PICO) are available as **Supplementary Material 2**. Study selection was performed using the 'revtools' function in R, allowing for title and abstract screening. Study selection and data extraction were divided between a team of 4 (GF, AC, NRP, CP) to allow for double reading and checking of articles and data. Disagreements were solved by consensus and discussion with a fifth author (TY).

Risk of bias assessment

The following domains were assessed for risk of bias, using a modified Institute of Health Economics (IHE) quality appraisal checklist: study objective, study design, study population, intervention and co-interventions, outcome measures, statistical analyses, follow-up and adverse events reporting, competing interests and sources of support [6]. It was chosen because it allowed for the evaluation of all studies using the same tool, considering all potential sources of bias in before-after case series. Each domain was rated at low, unclear or high risk of bias. Each study was independently assessed by 2 reviewers and disagreements solved by consensus. The risk of bias was rated as high for domains 5 (characteristics of the patients included) and 9 (additional interventions) if baseline erectile function (number of pre-operatively potent patients) and co-administration of erectile dysfunction medications (e.g., PDE5 inhibitors) were not clearly stated. Funnel plots were drawn to assess publication bias at each time point.

Data synthesis

The year of publication, design, number of patients treated, patients' characteristics (age, baseline sexual function, cancer characteristics), treatment energy type and volume, primary endpoint of the study, PRO tool used, completion rate and sexual function evolution, co-interventions (erectile dysfunction medication), urinary outcome and need for radical treatment were extracted for each study included. We used 4 points as the minimal clinically

important (significant) difference for IIEF-5 and IIEF-15-Erectile Function scores [7], and 12 points for EPIC-sexual domain scores [8]. IIEF-5 scores obtained from prospective single-arm studies or prospective registries with protocol-driven PRO collection at predefined time points were combined into a meta-analysis of postoperative erectile function at 3 months, 6 months and 12 months when mean/median scores and a dispersion measure (IQR, standard deviation or range) were available. Medians and IQRs were transformed into medians and SDs. Between-study heterogeneity was assessed using I² statistic, with considerable heterogeneity defined as I²>75%. Sensitivity analyses were done to assess the impact of removing outliers, without a clear impact on the results, therefore presented with all studies included. R software (R Foundation for Statistical Computing, Vienna, Austria) Version 3.6.1 was used for the meta-analysis using a random-effect model with significance set at p<0.05.

Results

Literature search results

The literature search was first performed on 6/03/2020 and renewed on 6/06/2021. Overall, 955 records were identified from database search, and 18 through the manual search of the references included in literature reviews. After title and abstract screening, 185 full-texts were assessed for eligibility and 42 studies, comprising 3117 patients treated, among whom 2353 (75%) had available sexual outcomes and were included in the data synthesis (**Figure 1**).

Population and studies overview

Among the 42 studies included, 27 were prospective single-arm cohort studies, and 7 were based on a retrospective analysis of prospective registries collecting PROs at various time points defined prior to the conduction of the registry . Eight studies were retrospective. Median number of patients with detailed sexual outcomes in each study was 30 (19-60). Median age varied from 56.5 to 71. Five studies provided data on patients' ethnicity, including a total of 336 treated patients, among whom 283 (84%) were white, 38 (11%) black, 7 (2%) Hispanic and 3 (1%) of Asian origin [9–13]. No details on ethnicity or sexuality were given for patients who answered PRO questionnaires. One study mentioned the use of questionnaires translated in a language other than English [14].

Median PSA ranged from 3.5 to 10.4 ng/ml. Out of the 2367 patients with available Gleason grade data, 1199 (50%) had Gleason grade group (ISUP) 1 disease and 1143 (48%) Gleason grade group 2 or 3 (Gleason grade group 2 n=895; Gleason grade group 3 n=210; not detailed n=38). Median maximum cancer core length ranged from 1mm [15] to 8mm [16].

Self-reported scores at baseline defining baseline potency were clearly stated in 21/42 studies (50%) comprising 1317 patients. Using the threshold defined by each study, 917/1317 patients were pre-operatively potent with erections sufficient for penetration (70%). The risk of bias of the individual studies included is presented in the **Supplementary Figure 1**. Data extracted for each study are summarised in **Table 1**.

Types of focal energy and data available

The various types of energies used, number of patients included and analysed are also detailed in **Table 1**. HIFU/focused ultrasound (n= 1069, 45%) and cryotherapy (n=502, 21%) accounted for the highest number of patients analysed, while vascular targeted photodynamic therapy (VTP, n=168, 7%) and irreversible electroporation (n=187, 8%) were the least studied techniques. The most frequent treatment templates were a hemiablation (n=953), and focal ablation (n=1039) with a mean/median treatment volume available in 12 studies and ranging from 2.2cc [17] to 23cc [18].

Types of PRO questionnaires and details collected

Of the 42 studies included, 30 used the 5 item International Index of Erectile Function (IIEF-5), otherwise known as the Sexual Health Inventory for Men (SHIM). Six used the 15 item International index of Erectile Function (IIEF-15), and 2 used the 6 item International Index of Erectile Function (IIEF-6), also known as the Erectile Function Domain which consists of questions 1-5 and 15 of the IIEF-15 (IIEF-15-EFD). Five studies used the Expanded Prostate Cancer Index Composite sexual domain (EPIC) [12,19–22]. One study used the Prostate Quality of Life Survey, a web-based tool based on the IIEF-6 for the evaluation of sexual function [23].

Of the six studies using IIEF-15, 3 presented results for the overall score and erectile function domain [16,24,25]. Two studies also reported detailed results on orgasmic function, intercourse satisfaction, sexual desire and overall satisfaction [26,27].

Acceptability of sexual follow-up

The proportion of patients completing PRO questionnaires dedicated to their sexual function at baseline ranged from 47.5% [27] to 100% [24,28–30]. During follow-up, ranges evolved from 17%-92% at 6 months, 43-100% at 12 months and 24-100% at 18-24 months.

Overall, between 0% and 76% [31] of study populations did not complete all questionnaires. Most causes of dropout were not stated or simply described as "lost to follow-up". Reasons stated when reported included oncological unfavourable evolution (n=2) [14], PDE5 inhibitors use (n=11) [16,30], withdrawn consent (n=19) [11,14,21] and death due to unrelated causes [32].

Early and late erectile function evolution

All studies but one (n=41) [12] provided the detailed results of PRO questionnaires before and after treatment at various time points, ranging from 3 to 48 months.

Patient-reported sexual function using IIEF-5 was analysed for each focal therapy energy and in combination through a meta-analysis of the mean difference in IIEF-5 scores between baseline and 3 months (**Figure 2**), 6 months (**Figure 3**) and 12 months (**Figure 4**). A decrease was noted at 3 months (IIEF-5 decrease estimate -3.70 [95%CI -4.43, -2.96]) with an improvement at 6 (-2.18 [-2.91, -1.46]) and 12 months (-2.14 [-2.96, -1.32]). No statistically significant difference was found between different energy types at 6 and 12 months ($p=0.36$ and 0.69 , respectively). Interestingly, one study using a larger, hockey-stick ablation template, displayed worst outcomes at 3 and 6 months (IIEF-5 decrease -12.80 [-18.98, -6.62] and -11.95 [-18.13, -5.77]), but the difference was no longer significant at 12 months (-5.10 [-11.83, 1.63]) [33]. No major asymmetry was noted on the funnel plots drawn (**Supplementary Figure 2**), in favour of low publication bias.

The evolution of PRO scores in the five studies using IIEF-15 scores [16,24–27], and the 4 studies reporting EPIC-sexual function scores [19–22] are presented graphically in **Figure 5**.

Among the 8 studies reporting erectile function of patients with a mean/median baseline IIEF-5 score ≥ 22 or IIEF-6 (IIEF-15-EFD) ≥ 26 , comprising a total of 290 patients, two studies with 43 patients (15%) treated by focal VTP or hockey-stick cryotherapy showed a ≥ 4 point-decrease in patient-reported erectile function (median IIEF-5 decrease from 23 to 13 and 29 to 23 at last follow-up) [33,34].

Twenty-one studies included a total of 1111 patients with mean/median IIEF-5 score between 17 and 21 or IIEF-6/IIEF-15-EFD between 18 and 25. Among these, scores showed a significant decrease (≥ 4 points) in 8 studies representing 477 patients (43%), including one prospective study using HDR brachytherapy and reporting a 13-point IIEF-5 score decrease among the 30 patients enrolled [40].

PDE5 inhibitors use before and after treatment was reported in 6/42 and 12/42 studies, respectively. At baseline, the proportion of patients treated with PDE5 inhibitors ranged from 7% [29] to 14% [14]. After treatment, the proportion increased in all studies but one [23], PDE5 inhibitors being used by 12.5% [25] to 47% [12] of patients .

Secondary outcomes: continence and need for radical treatment

Twenty-nine studies provided data regarding post-operative continence. Using a definition of continence as no pad use, 19 studies reported no post-operative incontinence among the treated patients. Eight individual studies described post-operative incontinence rates ranging at last follow-up from 2% [22] to 12.5% [35].

The proportion of patients requiring radical treatment was available for 25 studies, and the mean/median follow-up was detailed in 12/25. The mean/median follow-up ranged between 3.7 [36] and 55 months [37]. For studies with follow-up > 12 months, radical treatment rates ranged from 0% [33] to 20.8% [35].

Discussion

The evidence displayed by this systematic review reveals several interesting aspects. Firstly, focal therapy led to changes in erectile function in most cases under the significance threshold of the patient-reported outcomes questionnaires used.

Secondly, most treatment effect on erectile function seems to appear shortly after treatment, in the 3 months post-treatment period, and the late recovery, after 12 months, appears to be modest. This is an important finding as it may help define future study protocols: an early time point (3 months) being key to analysing in-depth sexual consequences, while a 12-month time point can be used to assess recovery and erectile function preservation.

Thirdly, we need more evidence from studies looking at sexual function as a primary endpoint, as most studies focused and provided very detailed results on oncological outcomes, and by design did not consider confounding factors such as baseline potency and treatment by PDE5 inhibitors, while the results of PRO questionnaires were often found in the supplementary materials and proved more difficult to access.

Unsurprisingly, the IIEF-5 was the most widespread PRO questionnaire, and this allowed for a meta-analysis of the score reported after treatment with various energy sources. Of note, the IIEF-5 has originally been designed and validated in a population of men with erectile dysfunction engaged in a stable relationship with a female partner for at least 6 months [7], questioning its use among sexual minorities, and its measurement properties were recently questioned [38]. It also solely focuses on erectile function, and omits orgasmic, ejaculatory function, sexual desire or other masculinity/virility issues. Most of these domains are taken into account in the more thorough IIEF-15 questionnaire, used by 5 studies in this review. Unfortunately, the amount of patient-gathered data collected did not translate into more detailed study findings as the overall score and erectile-function domain were the only reported scores in all studies but two. Even more frustratingly, the details obtained in one of the latter appeared to be irrelevant because of very low baseline scores [27]. A previous study conducted by Li et al. had shown that it was possible to gather more in-depth descriptive results on sensitive issues such as penile length among patients treated by whole-gland HIFU and cryotherapy [39].

Although we weren't able to precisely gather the causes of dropout rates in each individual study, this review provides insight on the acceptability of such sexual follow-up on the short,

medium and long-term. Depending on study design (clinical trial, prospective registry, retrospective), population size, length of follow-up and possibly other factors such as oncological and urinary outcomes, the rate of patients failing to complete all questionnaires was up to 76%. This is an important finding as it underlines the difficulties of conducting such a study on a large scale, but also possible issues with the PRO tools used and their perception by users. Guidelines are being issued to include a more diverse population into the design of new PRO tools and their validation, as well as new means of applying these tools, using for instance online questionnaires that the patient can fill outside the setting of a hospital/clinic visit.

Our results reveal a significant gap in knowledge on this highly topical subject, as previously highlighted for sexual outcomes after prostate cancer treatment in general [40]. Results obtained were collected from studies with good level of evidence, mostly of prospective design or clinical trials, but confounding factors such as baseline potency rate and PDE5 inhibitors use were often not reported. Although the small number of patients in many studies allowed for a thorough collection of outcomes, including PROs, it also exposes to a higher risk of selection bias. Individual studies often used oncological outcomes or safety as their primary endpoint and were not powered to detect differences in postoperative erectile function. Many studies were development studies, implying that some degree of learning curve, either in the surgical technique or patient selection/treatment extent, has to be taken into account. The results obtained must be put in perspective with the profile of patients and cancers treated. Indeed, half of the patients had low-risk disease and would now probably be oriented towards active surveillance.

This review is not devoid of limitations. We chose to focus on sexual outcomes with the initial aim of reporting less frequently reported effects such as orgasmic and ejaculatory consequences, masculinity and virility issues, but the lack of published literature on these domains led us to present patient-reported sexual outcomes instead. When registering this review, we believed that we would gather a variety of outcomes, preventing us from combining the results obtained, and chose to deviate from our protocol in view of the number of studies reporting erectile function using the IIEF-5 score. Studies using PRO tools other than IIEF-5 were not considered in the meta-analysis. Focal therapy regroups a variety of techniques, administered using a spectrum of tissue preservation templates not always detailed or comparable, to preferentially treat different parts of the gland with various

degrees of nerve sparing. Subsequently, patients treated form a heterogeneous group, as shown by the between-studies heterogeneity in the meta-analysis for a minority of time points and energy types, making it more hazardous to draw definite conclusions and generalise the results obtained. Reassuringly though, previous work showed that the treatment template did not significantly impact post-operative erectile function as long as at least one neurovascular bundle was preserved, which was the case in all techniques involved in this review [24].

Conclusion

Focal therapy led to changes in erectile function in most cases under the significance threshold of the patient-reported outcomes questionnaires used. More research is warranted to detail aspects other than erectile function. The early post-operative period appears of interest to study detailed effects of focal therapy on aspects other than erectile function, while a 12-month time point is probably sufficient to assess post-operative recovery. Results were mostly obtained from studies with an oncological primary outcome, with highly-selected patients, and the drop-out rate during follow-up was significant. Questionnaires used were not designed for a diverse population. Qualitative studies would help to detail the expectations and impact of focal therapy on men [41]. More evidence is needed from studies using a range of methods to look at sexual function and recovery more broadly and detail individual expectations as primary endpoints.

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Tables and figures

Figure 1. PRISMA flow diagram

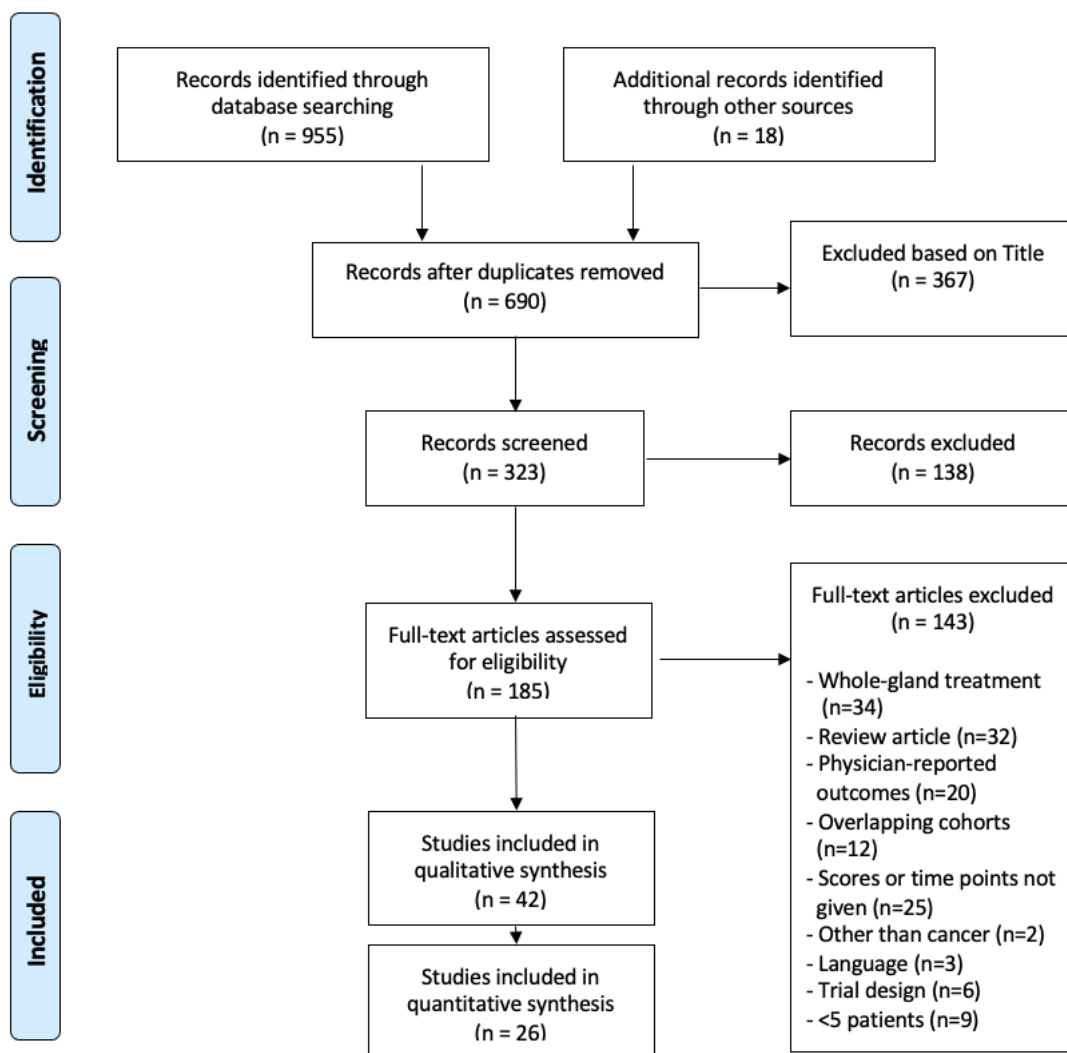


Table 1. Treatment details and outcomes for each study included
 (Design Pro-prospective single-arm study; ProR-prospective registry; Retro-retrospective;
 LDR-low dose rate; VTP-vascular targeted photodynamic therapy; HIFU-high intensity
 focused ultrasound; TULSA-transurethral ultrasound ablation; HDR-high dose rate; PRO-
 patient reported outcome; NR-not reported; IQR-interquartile range; SD-standard deviation;
 N-number; IIEF-international index of erectile function; SHIM-sexual health inventory for
 men; PQLS-prostate quality of life survey; EPIC-expanded prostate cancer index composite;
 EFD-erectile function domain; Funding I-Industry; NI-Non-industry)

Study	Year	Design	Focal energy type	Template (mean/median volume treated - cc/ablation area diameter-mm)	Patients treated/evaluated (sexual outcomes) N	Acceptability (PRD questionnaire s completed at baseline and follow-up) N (time point-months)	Number potent patients (pre-op)	Age median(IQR) mean (SD) [range]	Sexual outcome evaluation tool	Evaluation time points (months)	Results (PRO) median (IQR) mean (SD) [range]	Post-op ED medication N or % (time point)	Incontinence (last follow-up) N (%)	Need for radical treatment N (%)	Follow-up (months)	Funding	
Lindner [17]	2009	Pro	Laser ablation	Focal (2.2cc)	12/12	NR	NR	56.5(51-62)	IIEF-5	0/1/3/6	22/21/20/23	NR	0/12 (0)	2/12 (17)	NR	NI	
Bahn [36]	2012	Retro	Cryotherapy	Hemiblastion	73/69	63/73 (0)	42/63	64 (47-79)	IIEF-5	0/12/24	22 (13-25)/17 (5-24)/19 (5-25)	NR	0/70 (0)	4/70 (5.7)	3.7 (1-8.5)	None	
Oto [15]	2013	Pro	Laser ablation	Focal (NR)	9/9	NR	6/9	61 (52-77)	SHIM	0/12/36	23 (11-24)/24 (19-24)/22 (12-23)	NR	0/9 (0)	NR	NR	NI+	
Barret [34]	2013	ProR	Cryotherapy LDR Brachytherapy VTP HIFU	Hemiblastion	50/50 12/12 23/23 21/21	NR	NR	66.5 (61-73)	IIEF-5	0/12	19 (9-25)/ 14 (8-25) 21 (10-25)/ 14 (8-24) 23 (17-25)/ 13 (7-25) 20 (15-25)/ 14 (8-25)	NR	0/106 (0)	NR	9 (6-15)	None	
Cosset [42]	2013	Pro	LDR Brachytherapy	Focal (14cc)	21/21	NR	NR	62.3 (56-74)	IIEF-5	0/2/6/12	20.1 (5-25)/18.6 (5-25)/19.1 (5-25)/19.8 (5-25)	NR	0/21 (0)	0/21 (0)	NR	NR	
Durand [43]	2014	Pro	Cryotherapy	Hemiblastion	64/48	25/48 (0) 8/48 (6)	37/48	66.6 (50.4-77.1)	IIEF-5	0/3/6	17 (7-21)/12 (5-17)/13 (2-17)	NR	0/48 (0)	3/48 (6.2)	13.2 (7.4-26.5)	NR	
Bargawi [44]	2014	Pro	Cryotherapy	Focal (NR)	62/62	NR	NR	60.5 (6.8)	SHIM	0/3/6/12/24	16.1 (8.6)/12.7 (8.1)/16 (8.1)/17.6 (7.8)/19.1 (5.9)	NR	0/62	2/62 (3.2)	28 (26-31)	I	
Azrouz [18]	2015	Pro	VTP	Hemiblastion (23cc)	117/117	NR	NR	62.2	IIEF-5	0/1/3/6	19.4/12.9/15.3/15.3	NR	NR	NR	NR	I	
Eggerer [45]	2016	Pro	Laser ablation	Focal (1.5mm)	2/227	NR	NR	62	SHIM	0/3/12	21.5 (10.5)/19 (14.5)/19 (14.5)/21 (10.5)	NR	1/27 (3.7)	1/27 (3.7)	NR	NI	
Taneja [11]	2016	Pro	VTP	Hemiblastion	30/28	28/30 (0)	NR	63 (47-74)	IIEF-5	0/1/3/6/12	18 (10-26)/14 (5-22)/15 (7-23)/15 (8-23)/14 (5/23)	NR	2/30 (6.7)	NR	NR	I	
Murray [23]	2016	ProR	Irreversible electroporation	Focal (NR)	25/22	22/25 (0) 16/25 (6) 17/25 (12)	13/22	63 (59-68)	PQLS (IIEF-6)	0/6/12	18.6/16.2/21.1	2/22 (0) 2/22 (12)	2/22 (9)	3/25 (12)	10.9	NI	
Natarajan [46]	2016	Pro	Laser ablation	Focal (3cc)	8/8	NR	NR	63 (60-66)	SHIM	0/6	19.5/20	NR	0/8 (0)	NR	NR	NI+	
Yap [46]	2016	Pro	HIFU	Hemiblastion n=20 Focal (NR) n=98	118/118	118/118 (0) 112/118 (12)	NR	63 (52-70)	IIEF-15 IIEF-15-EFD	0/1/3/6/9/12	58 (32-67)/28 (13-50)/39 (21-58)/47 (26-61)/51 (16-64)/47 (28-62) 23 (11-28)/9 (3-22)/15 (6-26)/19 (8-27)/20 (9-29)/20 (9-28)	12/118 (0) 35/118 (3) 51/118 (6) 44/118 (12)	NR	NR	NR	NR	NI
Tejoo [47]	2016	ProR	HIFU	Hemiblastion	71/67	67/71 (0)	21/67	70.2 (6.8)	IIEF-5	0/3	20 (13-21)/16 (8-30.5)	NR	0/67 (0)	NR	12 (6-50)	None	
Ting [19]	2016	Retro	Irreversible electroporation	Focal (NR)	32/25	18/25 (6)	NR	67 (60-71)	EPIC	0/1.5/3/6	56 (51-75)/37 (29-63)/57 (31-65)/55 (34-69)	NR	0/25 (0)	1/25 (4)	8	NI	
Chin [13]	2016	Pro	Transurethral HIFU (TULSA)	Focal (NR)	30/30	29/30 (12)	21/30	69 (67-71)	IIEF-15-EFD	0/1/3/6/12	13 (6-28)/7 (2-12)/11 (4-18)/11 (4-19)/13 (5-25)	NR	0/30 (0)	2/30 (6.7)	NR	I	

Figure 2. Meta-analysis of the difference in mean IIEF-5 scores between baseline and 3 months

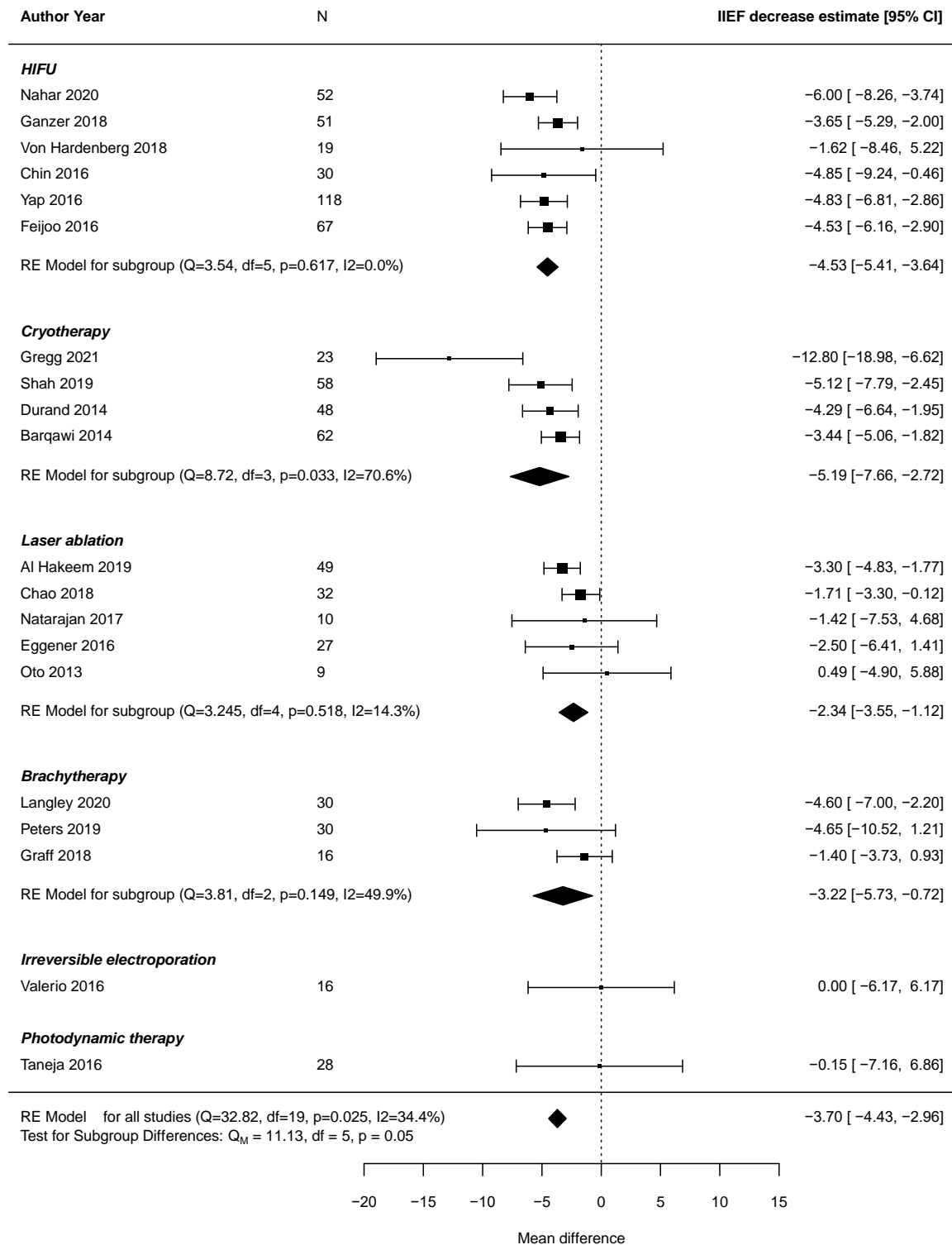


Figure 3. Meta-analysis of the difference in mean IIEF-5 scores between baseline and 6 months

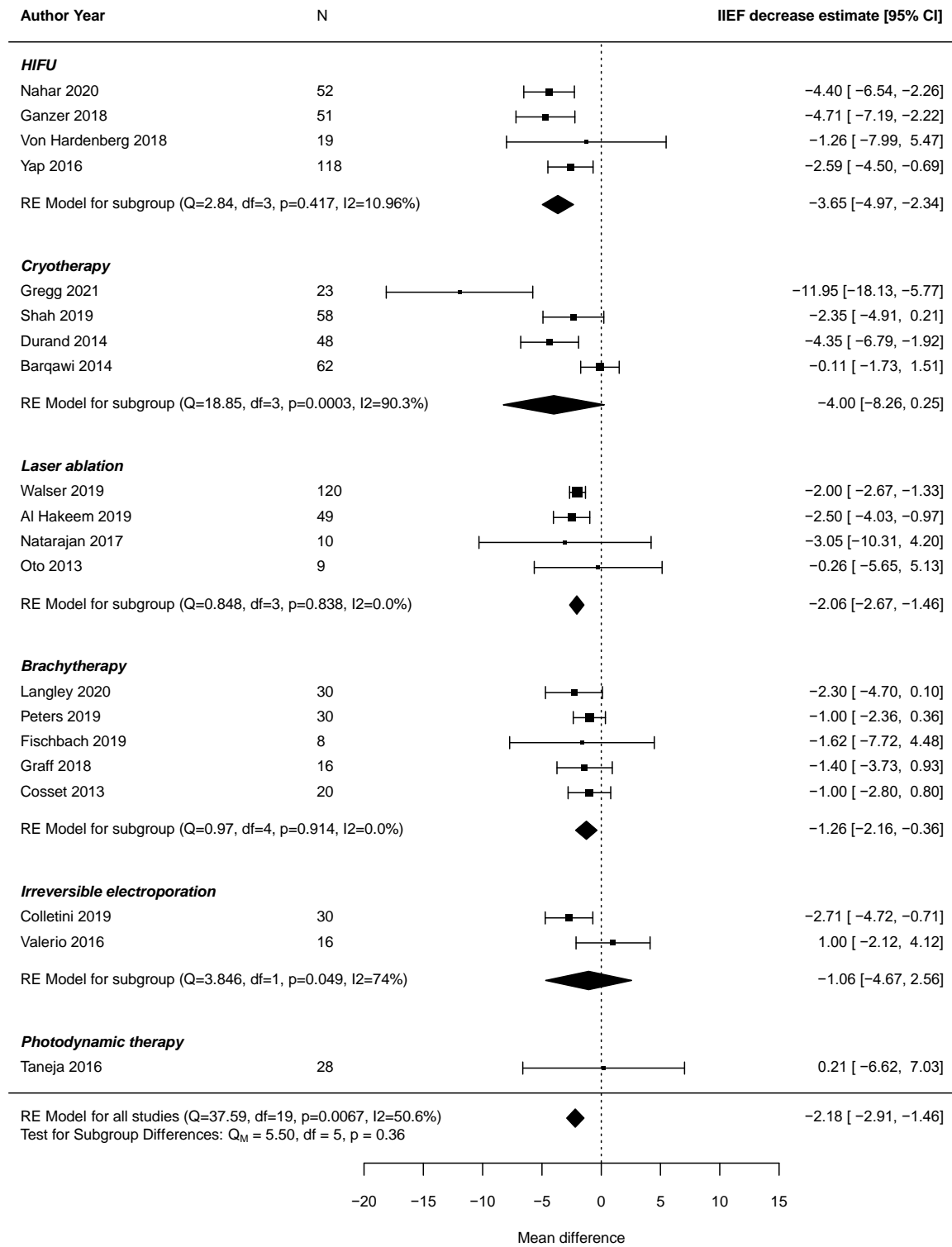


Figure 4. meta-analysis of the difference in mean IIEF-5 scores between baseline and 12 months

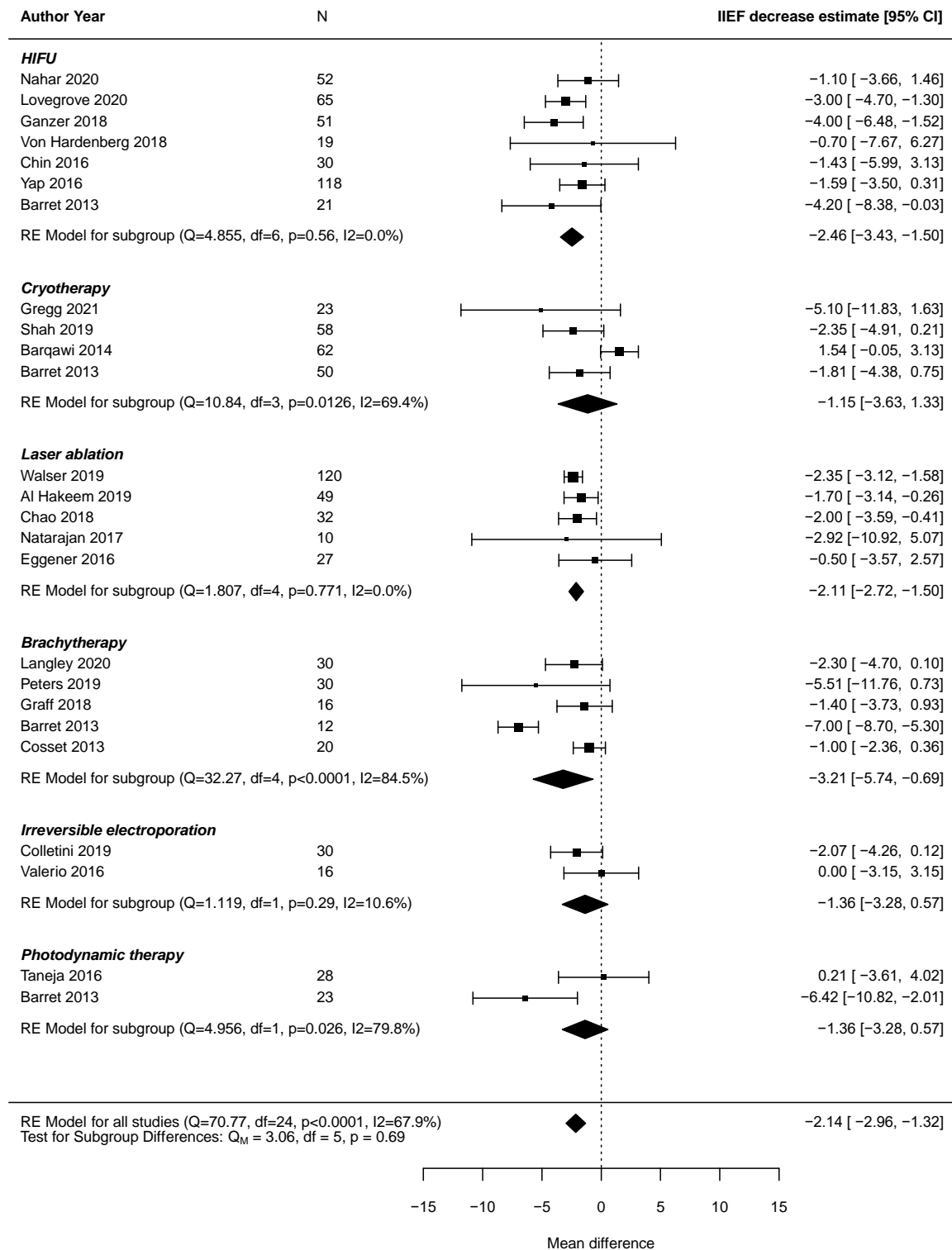
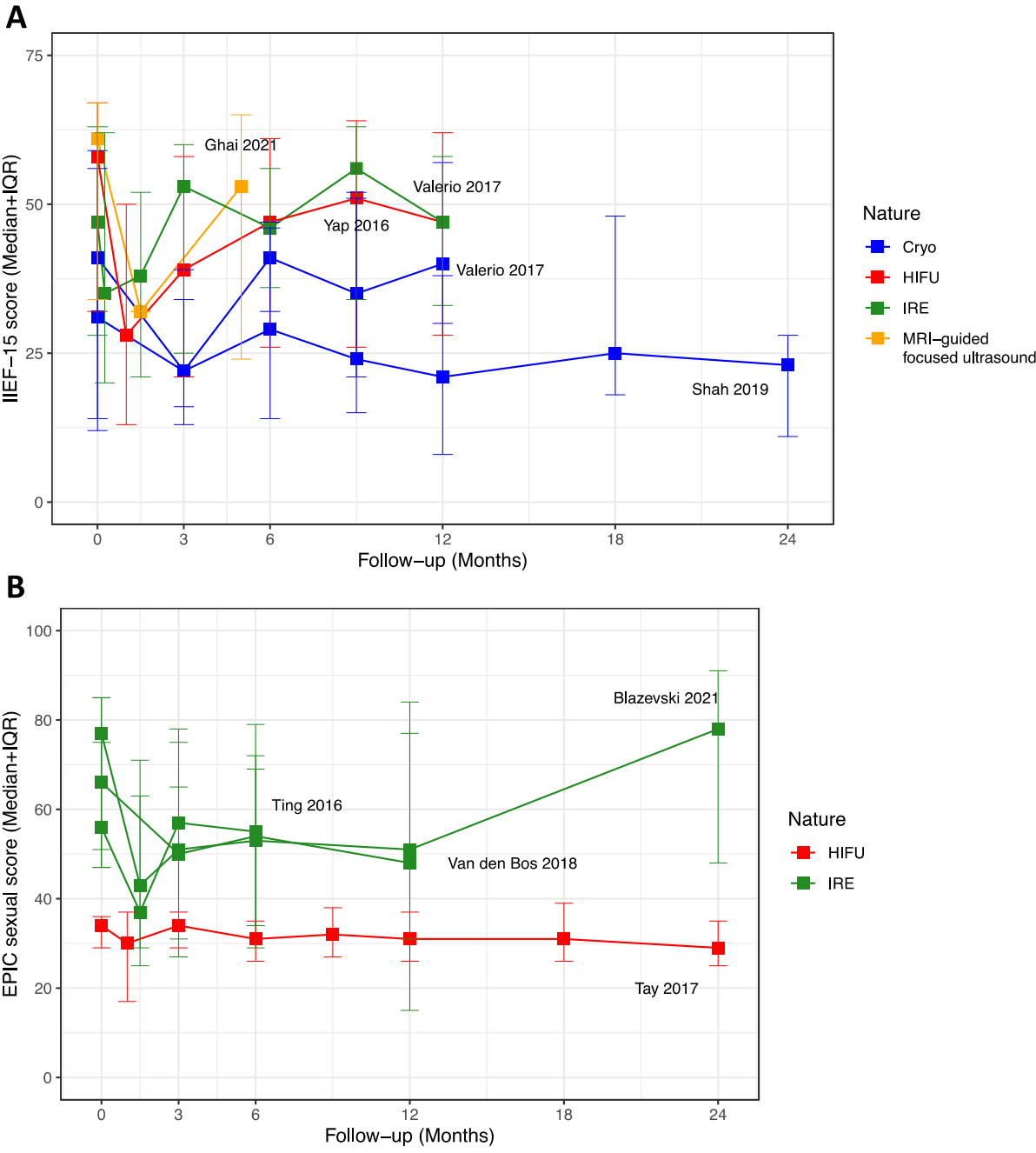


Figure 5. Evolution of mean/median IIEF-15 (A) and EPIC-sexual domain (B) scores



Supplementary material 1. Detailed Boolean search

The definition of the search terms was performed semi-automatically using the 'litsearchr' package in R (version 3.6.1).

A naive search was conducted in Pubmed, Scopus and Web of Science using the terms ((“focal therapy” OR “focal treatment”) AND (“prostate cancer”) AND (“sexual function” OR “erectile function”)).

After removing duplicates by automatically analyzing the titles and abstracts, keywords were extracted and a Boolean search was written. The research formula was modified to exclude salvage treatment.

((“focal therapy” OR “irreversible electroporation” OR “photodynamic therapy” OR “focal ablation” OR “focal treatment” OR “intensity focused ultrasound” OR “laser ablation”) AND (“prostate cancer” OR “prostate” OR “localized pca” OR “significant prostate cancer”) AND (“quality of life” OR “adverse events” OR “erectile dysfunction” OR “erectile function” OR “functional outcome” OR “international index” OR “low morbidity” OR “outcome measurements” OR “sexual function” OR “sexual outcome” OR “IIEF” OR “erection” OR “erectile function” OR “orgasmic function”))

The search was then conducted using the formula defined in Medline, Embase, Scopus and Web of Science, dated 12/11/2019. The Embase search was performed using the “exclude Medline journals” limit. Duplicates were removed automatically using the R 'litsearchr' function, as well as articles without an abstract or a DOI. The search was renewed using the same search terms on 06/03/2020.

((“focal therapy” OR “irreversible electroporation” OR “photodynamic therapy” OR “focal ablation” OR “focal treatment” OR “intensity focused ultrasound” OR “laser ablation”) AND (“prostate cancer” OR “prostate” OR “localized pca” OR “significant prostate cancer”) AND (“quality of life” OR “adverse events” OR “erectile dysfunction” OR “erectile function” OR “functional outcome” OR “international index” OR “low morbidity” OR “outcome measurements” OR “sexual function” OR “sexual outcome” OR “IIEF” OR “erection” OR “erectile function” OR “orgasmic function”)) NOT “salvage”

Supplementary material 2. PICOs

Population

Inclusion: Adult males with localised prostate cancer

Exclusion: Adult males with locally advanced or metastatic prostate cancer, recurrence after primary treatment

Interventions

Interventions: focal therapy

= treatment of a part of the prostate gland preserving prostate tissue

Including: hemi-ablation, zonal ablation, focal ablation

Excluding: whole-gland treatment, salvage treatment

Comparator

No comparator will be studied (irrelevant)

Main outcome

Patient-reported sexual function using questionnaires or qualitative methods

Exclusion: physician-reported sexual function

Additional outcomes

Urinary outcomes (incontinence) and oncological outcome (radical treatment rates)

Supplementary Figure 1. Risk of bias assessment of individual studies

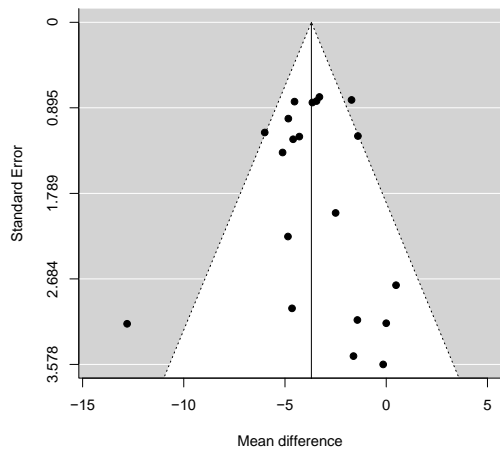
	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17
Lindner 2009	+	+	×	-	-	-	+	+	×	+	+	+	-	×	-	-	-
Bahn 2012	+	×	×	-	-	-	+	+	×	-	+	+	-	+	+	-	+
Oto 2013	+	+	×	-	-	+	+	+	×	+	+	+	+	×	-	+	+
Barret 2013	+	-	×	-	-	+	+	-	×	-	+	+	+	+	-	+	+
Cosset 2013	+	+	-	-	-	+	+	+	×	+	+	+	-	+	-	-	-
Durand 2014	+	+	×	+	-	+	+	+	×	+	+	+	+	×	+	+	-
Barqawi 2014	+	+	×	-	-	+	+	+	×	+	+	+	-	+	-	-	+
Azzouzi 2015	+	+	+	-	-	-	+	+	×	+	+	+	+	×	-	+	-
Eggerer 2016	+	+	×	-	-	+	+	+	×	+	+	+	+	+	×	+	+
Taneja 2016	+	+	+	-	-	+	+	+	×	+	+	+	+	+	-	+	+
Murray 2016	+	-	-	-	-	+	+	+	+	+	+	+	+	+	-	+	+
Natarajan 2016	+	+	×	-	-	+	+	+	×	+	+	+	-	×	-	+	+
Yap 2016	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	-	+
Feijoo 2016	+	-	×	-	+	+	+	+	×	-	+	+	+	×	-	+	+
Ting 2016	+	×	×	+	+	+	+	+	×	+	+	+	+	×	-	+	+
Chin 2016	+	+	+	-	+	+	+	+	×	+	+	+	+	+	+	+	+
Valerio 2016	+	-	×	+	+	-	×	+	×	+	+	+	+	+	+	+	+
Tay 2017	+	+	×	-	-	+	+	+	×	+	+	+	+	+	+	+	-
Srougi 2017	+	×	×	×	-	-	+	+	×	×	+	+	+	+	+	-	×
Natarajan 2017	+	+	×	-	+	-	+	+	×	+	+	+	+	×	-	+	+
Rischmann 2017	+	+	+	-	+	+	+	+	×	+	+	+	+	+	+	+	+
Valerio 2017	+	+	×	-	+	+	+	+	+	+	+	+	+	+	+	+	+
Chao 2018	+	+	×	-	-	-	+	-	×	-	+	+	+	+	+	-	+
Van den Bos 2018	+	×	×	-	-	+	×	+	×	×	+	+	+	-	-	+	+
Graff 2018	+	+	×	-	-	+	+	+	×	+	+	+	+	+	-	+	+
Von Hardenberg 2018	+	+	×	-	+	+	+	+	+	+	+	+	+	+	+	+	+
Ganzer 2018	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+
Werneburg 2018	+	×	×	-	-	-	+	+	+	×	+	+	-	+	-	-	+
Shah 2019	+	-	+	+	-	-	+	-	×	+	+	+	+	+	+	+	+
Colletini 2019	+	+	×	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peters 2019	+	+	×	+	+	-	+	+	×	+	+	+	+	+	+	+	+
Walser 2019	+	+	×	+	-	+	+	+	×	+	+	+	+	+	-	+	+
Fischbach 2019	+	+	×	-	+	+	+	+	×	+	+	+	+	×	-	+	+
Sze 2019	+	×	-	-	-	+	+	+	×	+	+	+	+	+	-	+	+
Al Hakeem 2019	+	+	×	-	-	+	+	+	+	+	+	+	+	+	-	+	-
Lovegrove 2020	+	-	+	-	+	+	×	+	×	+	+	+	-	+	+	-	+
Langley 2020	+	+	×	-	+	+	+	+	×	+	+	+	+	+	-	+	+
Nahar 2020	+	-	×	-	-	+	+	+	×	+	+	+	+	+	-	+	-
Ghai 2021	+	+	×	-	+	+	+	+	+	+	+	+	+	×	-	+	+
Gregg 2021	+	+	×	-	-	+	+	+	×	+	+	+	+	+	-	+	+
Borges 2021	+	×	×	-	+	+	+	+	+	+	+	+	+	+	-	+	-
Blazevski 2021	+	×	×	-	+	+	+	+	×	+	+	+	+	+	-	+	+

D1: Hypothesis/aim/objective of the study clearly stated
D2: Study conducted prospectively
D3: Cases collected in more than one centre
D4: Patients recruited consecutively
D5: Characteristics of the patients included described
D6: Eligibility criteria clearly stated
D7: Patients enter the study at a similar point in the disease
D8: Intervention of interest clearly described
D9: Additional interventions clearly described
D10: Relevant outcome measures established a priori
D11: Relevant outcomes measured using appropriate methods
D12: Relevant outcome measures before and after the intervention
D13: Statistical tests appropriate
D14: Follow-up long enough for important events and outcomes
D15: Losses to follow-up reported
D16: Adverse events reported
D17: Both competing interests and sources of support reported

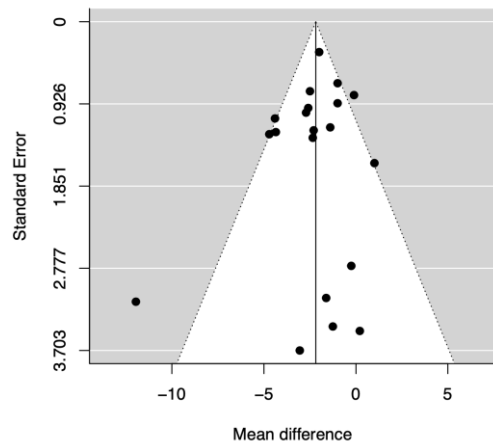
Judgement
× High
- Unclear
+ Low

Supplementary Figure 2. Funnel plots assessing publication bias at (A) 3 months; (B) 6 months; (C) 12 months

(A)



(B)



(C)

