Abstract

Objectives:

To systematically review erectile function (EF) outcomes following primary whole gland (WG) and focal ablative therapies for localized prostate cancer (LPC) to ascertain whether the treatment modality or intended treatment volume affects the time taken to recover baseline EF.

Method and materials:

A systematic review was performed according to the preferred reporting items for systematic review and meta-analysis (PRISMA) statement. Inclusion criteria were men with LPC treated with primary, ablative therapy. Primary outcome was the return to baseline EF measured with objective, validated symptoms scores. Secondary outcome was use of phosphodiesterase inhibitors or erectile aids. Meta-analysis was not performed owing to heterogenous outcome measures.

Results:

Of 222 articles identified in February 2017, 55 studies which reported EF after ablative therapy were identified but only 17 used validated outcome measures and met inclusion criteria. WG cryotherapy was utilized in two studies, WG HIFU in five, focal cryotherapy in two, focal HIFU in three, focal phototherapy or laser therapy in four, vascular targeted photodynamic therapy (VTP) in three and irreversible electroporation in two. WG cryotherapy was associated

with a significant decline in EF at 6 months with minimal improvement at 36 months. Baseline IIEF-15 of patients undergoing focal HIFU fell 30 points at one month but returned to baseline by six months. The remaining focal therapies demonstrated minimal or no effect on EF but the men in these studies had small foci of disease. The review is limited by lack of randomized studies and heterogenous outcome measures.

Conclusions

Most studies assessing the outcomes of focal therapy on sexual function were not of high quality, used heterogenous outcomes and had relatively short follow up, highlighting the need for more robustly designed studies utilizing validated PROMS for comparison. However, FT in general resulted in less impact on EF than WG ablation.

1. Introduction:

Quality of life outcomes including maintaining EF are major factors in the decision to proceed with intervention in men with LPC[1]. Radical prostatectomy (RP), radiotherapy and active monitoring for LPC are associated with equivalent survival at 10 years[2]. Moreover, 17% of men in the ProtecT trial had erections sufficient for intercourse following RP compared with 30% of those on active monitoring[3]. EF was reported with expanded prostate cancer index composite (EPIC) scores unlike in most other LPC radical therapy trials where validated questionnaires have not been used routinely. Ablative therapy (whole gland (WG) or focal) was introduced with the hope of avoiding some of the adverse effects of radical therapy including erectile dysfunction (ED), bladder or bowel dysfunction and urinary incontinence as well as avoiding the psychological burden of active monitoring. Ablative therapies for prostate cancer are now available in many European countries as well as Canada and the USA where HIFU was first approved by the FDA in 2015[4].

Prostate cancer was initially believed to be a multifocal disease[1]. However, histological studies have demonstrated single foci or significant disease in just one half of the prostate[1]. More recently, whole genome sequencing of areas of prostate cancer and normal prostate tissue within single prostate glands have shown common mutations within the cancer and in the normal tissue suggesting there is a ‘field effect’ occurring within the whole gland[5]. It should be clear that a field-effect is not necessarily indicative that new aggressive

tumours will develop in untreated tissue as evidenced by the safe management of patients with active surveillance[2].

Alongside improving imaging and biopsy techniques including MRI fusion, novel understanding of the pathology initiated focal therapy (FT). Ablative energy sources include cryotherapy, HIFU, laser or photodynamic therapy (PT) and Irreversible electroporation (IRE). Cryotherapy was one of the first ablative techniques to be introduced[6]. It induces cell lysis by cooling tissues to –40°C[7]. Autonomic dysfunction occurs if the nearby neurovascular tissues are cooled to 3°C which may be irreversible at -20°C which accounts for the high rates of ED observed after WG cryotherapy. HIFU focuses ultrasound energy leading to tissue ablation via thermal coagulation necrosis and acoustic cavitation[8]. It has the potential of more precise ablation than cryotherapy but many men nevertheless report ED. Photodynamic therapy induces cell death via cytotoxic oxidative stress. IRE uses pulses of direct current to create nanopores within the cell membrane leading to apoptosis[9-11].

There are no published randomized controlled trials (RCT) comparing oncological outcomes of radical therapy and FT for LPC. The PART study is currently in the pilot phase, randomizing men with intermediate risk disease to RP and FT[12]. If ablative therapies are to be offered as viable alternatives to radical treatment and active monitoring, men must be informed of the precise risks of ED in an objective and understandable manner. Currently, ED reporting after FT is not interpretable by patients as many studies within the existing literature either use their own definitions of ED or use no definition at

all[13]. The change in pre-treatment EF, time taken to return to this baseline level and use of any support such as tablets, injections or erectile aids eg Vacuum Erectaid would be meaningful to patients but are not routinely reported.

The effects on EF after ablative therapy have not been systematically reported and compared. This is particularly important for patient counseling as the incidence of decision regret in LPC is related to morbidity, particularly sexual morbidity and decision regret may be reduced by increased information and support prior to the decision[14,15]. This study aims to determine and compare whether the modality and/or intended treatment volume of ablative therapy i.e. focal or WG might affect the severity of ED and return to baseline function.

2. Material and methods:

2.1 Search strategy

A systematic review of the Cochrane library, Scopus and Pubmed was performed from inception to February 2017 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') statement[16]. Search terms included 'erectile dysfunction', 'focal therapy', 'ablation', 'HIFU' and 'cryotherapy'. The full search for PubMed is shown in Appendix A. No time limit for publications was applied. The review was registered with PROSPERO (registration number 42016042070).

2.2 Study eligibility

Study eligibility was defined using the population, intervention, comparator, outcome and study design approach. For inclusion, studies needed to include men with LPC treated with primary ablative therapy either as FT (intervention) or WG therapy (comparator)[17]. Studies needed to report validated EF outcomes such as the EPIC, the UCLA prostate cancer index (UCLAPCI), the prostate cancer quality of life survey, the 15 item international index of erectile function (IIEF-15) or the shortened 5 item international index of erectile function (IIEF-5) also known as the sexual health inventory for men (SHIM) score[18-20].

Included studies needed to contain five or more patients and report EF before ablative therapy with at least six months follow up. Studies reporting scores

as ranges, duplicates, non-English language (if no translation available), reviews, case reports, letters and non-full text articles were excluded. NFW, JN and TY independently reviewed eligibility and assessed bias at study level using Cochrane bias assessment tools. Incongruities were resolved by consensus of all authors.

2.3 Outcome measures

The primary endpoint was the time to return to baseline of a validated EF outcome measure. Secondary endpoint was the use of erectile aids and phospho-diesterase type 5 inhibitors (PDE5-I) following therapy.

3. Results

3.1 Search results

Of 222 studies initially identified on 2 February 2017, 17 studies met the inclusion criteria after removal of duplicates, non-English language, reviews, letters, case reports, non-human studies and non-full text articles (figure 1)[21-35]. Three papers were excluded after full text examination as WG and focal cryotherapy were amalgamated. The included studies with together with bias assessment are shown in table 4.

3.2 Whole gland therapy

WG cryotherapy was used in two of the included studies, the first of which was published in 2006 (figure 2 and table 1)[30,31]. In Liu *et al*'s study, subjects initially had no ED (mean IIEF-5 23.0/25) but reported severe ED six months after therapy and showed no subsequent improvement after 24 months. Malcolm *et al* retrospectively investigated health related quality of life scores using the UCLAPCI in 81 patients treated with WG cryotherapy and compared the outcomes of patients undergoing brachytherapy, open and laparoscopic RP[31]. They excluded patients with sexual function scores less than 30. Their patients showed a similar pattern of decline at six months, which did not improve over the three year study.

WG HIFU was utilized in five studies (figure 3)[22,25,28,30,34]. Liu *et al* found that the baseline IIEF-5 score of their 120 patients fell from 22.1 (no ED) to 8.55/25 (moderate ED) at six months. This rose slightly to 9.36 over 24 months, still corresponsing to moderate ED. Shoji *et al* followed 326 patients who underwent WG HIFU with neuro-vascular bundle (NVB) sparing[34]. Their baseline IIEF-5 was only 6.3 representing severe ED and subjects did not see any positive change in IIEF scores following ablative therapy as would be expected given their very poor baseline function. Li *et al* followed 55 patients in a non-randomized study comparing EF outcomes in WG HIFU and targeted cryotherapy using IIEF-15 EFD[28]. The baseline IIEF-15 EFD for WG HIFU patients was 27.3, which fell to 15.5 at six months but then steadily increased to 22.3 at 24 months, which was not significantly different to baseline. The improvements continued to 36 months (table 2 and figure 3). Patients were

younger (57.5 years) than in the Liu *et al* and Shoji *et al* studies. Patients in the Liu *et al* study also had higher presenting PSA (17.0 vs 7.5). Li *et al* excluded patients over 65 and those with baseline IIEF-15 EFD less than 26 out of 30. The other key difference was that all patients received 50-100mg of Sildenafil three times weekly for the first month and then as needed; they were also encouraged to use a penile vacuum pump after the first month.

In the first published UK series utilizing WG HIFU, Ahmed *et al* reported IIEF-15 scores of 172 men at three monthly intervals up to 12 months[22]. Only 77 and 34 of the 172 men given WG HIFU patients completed IIEF-15 scores at six and 12 months and so it is difficult to interpret the true change from baseline. Chin *et* al reported IIEF-15 EFD as part of a phase one trial into MRI guided trans-urethral ultrasound ablation (MRI-TULSA)[25]. The ablation was described as ‘conservative whole gland’ giving lesions a 3mm margin. Baseline IIEF-15 EFD of 13 fell to seven at one month, and rose to 13 at 12 months, which was not statistically different to baseline.

3.3 Focal therapy

3.3.1 Focal cryotherapy

The search identified two studies utilizing focal cryotherapy[24,28]. Li *et al* 2010 was the earliest FT paper. Mean baseline IIEF-15 EFD of the 47 patients was 27.8. Following focal cryotherapy, IIEF-15 EFD fell to 9.8 at 6 months and steadily rose, such that the difference at 36 months was not statistically significant from baseline (figure 4).

Barret *et al* study reported IIEF-5 scores at baseline and 12 months for 50 patients who underwent focal cryotherapy (hemiablation). Median IIEF-5 at baseline was 19 (IQR 9-25) and 14 (IQR 8-25) at 12 months. They did not report statistical significance. Erectile aid and PDE5-I use were not reported.

3.3.2 Focal HIFU

Focal HIFU was utilized in three studies[21,24,35]. The first to be published was Ahmed et al in 2012, two years after the first focal cryotherapy paper[21].

Yap *et al* amalgamated 118 patients from three prospective, non-randomized, registered trials carried out between 2009 and 2013 (HEMI, FOCAL and LESION-control) including results from the Ahmed *et al* 2012 paper[21,35-37]. Figure 2 shows the total IIEF-15 of the FOCAL (n=42), HEMI (n=20) and LESION-CONTROL (n=56) trials. Baseline age, PSA and Gleason scores were similar. Patients in the FOCAL trial had lesions identified via MRI and template biopsy ablated with 3-5mm margins. The HEMI trial treated the affected lobe with a 5mm section in the contra-lateral lobe. The LESION-CONTROL trial only ablated lesions of 0.5cc and over. The three studies showed a similar pattern of an initial sharp drop at one month. All studies then showed a rise at 3 months and again at six months. When amalgamated, there was no significant difference from baseline and at six, nine and 12 months. There was a similar pattern for the five individual domains of the IIEF (erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction). Patients were not given specific penile rehabilitation but phosphodiesterase-5 inhibitors (PDE-5I) were used by 10% of men at baseline and 37% at 12 months. The IIEF-15 and IIEF-15 EFD scores of men started on PDE-5I improved by 13 and 6 points. No patients required second line PDE-5I or surgical intervention for ED.

3.3.3 Focal photothermal ablation

Focal photothermal or laser ablation was utilized in three phase one and one phase two clinical trials which all used the SHIM (IIEF-5) [26,29,33,38]. Eggener *et al* studied 27 patients who each had one to two lesions ablated using MRI guidance in a phase II trial which was the largest photothermal study identified in the search[26]. The maximum diameter of lesions was 15mm and the estimated volume of each lesion was less than $2cm^3$. Lesions were ablated with 5mm margins except when adjacent to the cavernosal nerves or the urethra. The small (11.6%) fall from baseline of 21.5 points recorded at one and three months was statistically significant from baseline but the difference at 12 months was not. Oto *et al* followed nine men treated with MRI-guided focal laser ablation[38]. Their lesions varied between four and 12 mm. The mean baseline IIEF-5 of 19.0 changed very little over six months though the authors mention that one patient's IIEF-5 fell by 12 points. None of the photothermal ablation papers reported erectile aid and PDE5-I use.

3.3.4 Focal vascular targeted photodynamic therapy (VTP)

The search identified three papers which were phase two clinical trials[23,24,32]. Azzouzi *et al* pooled results of three clinical trials (PCM 201, PCM 202 and PCM 203) including the EF results published by Moore *et al*, also identified in the search[23,32]. The amalgamated 117 patients, which included patients treated with dose escalation, had mean IIEF-15 EFD of 19.4 at baseline. This fell to 12.9 at one month, then rose to 15.1 at three months and 15.3 at six months. The small falls from baseline were not statistically significant.

3.3.5 Focal irreversible electroporation

The search identified two prospective development studies which ablated LPC lesions with IRE [9,11]. The 19 men in Valerio ***et al***'s study only had disease in the anterior prostate gland, which varied in volume between 0.4 and 1.3cm^3. IIEF-15 was reported on a graph in the appendix without numerical values. The Initial IIEF-15 of approximately 47 fell to approximately 35 after one week although the difference does not appear significant. The IIEF-15 then appears to be similar to baseline at three, six, nine and 12 months following treatment. Murray *et al* followed 25 men for over six months and reported the prostate cancer quality of life survey results at baseline (18.6), six months (16.2) and one year (21.1)[9]. It is not stated whether the changes were statistically significant but the changes were clearly very small. PDE5-I were used by two patients at baseline and two at 12 months follow up. The volume and location of the ablated lesions was not reported.

3.4 Comparative studies

Liu *et al*, Li *et al* and Barret *et al* compared different ablative treatments in the same study though none of the studies were randomized[24,28,30].

Liu *et al* prospectively compared WG cryoablation with WG HIFU[30]. The cryotherapy group had larger mean prostate volumes than the HIFU group (36.71ml vs 21.97ml; p=0.00), higher presenting PSA (28.8ng/ml vs 17.0ng/ml; p=0.055) and a higher proportion of over T2b disease (30.7% vs 22.5%; p=0.059). Both groups initially had good EF. There was a significant fall in IIEF-5 score in both groups at 6 months. There was minimal improvement from the initial fall up to 24 months for both modalities (table 1). The fall from baseline was statistically greater for WG cryotherapy than HIFU at all time points.

Li *et al* compared men undergoing WG HIFU and focal cryotherapy: The authors reported penile length, testosterone levels, penile Doppler US peak systolic and end diastolic velocities, resistive index, testosterone levels and IIEF-15 EFD scores at baseline to 36 months (table 2)[28]. The groups were not randomized but appear to have similar median age, presenting PSA, clinical stage and baseline IIEF15 EFD score. IIEF-15 EFD score fell significantly for both modalities from 27.8 and 27.3 out of 30 at baseline for focal cryotherapy and WG HIFU to 9.8 and 15.5 at six months. IIEF-15 EFD for patients who underwent focal cryotherapy remained lower at all time points to 36 months. Scores improved at all time points from six months and there was no statistical difference from baseline at 24 months for WG HIFU and at

36 months for focal cryotherapy. The groups had similar peak systolic velocities (PSV) at baseline, but the WG HIFU patients had better PSV at all other time points. There were no differences in flaccid and erectile penile length or circumference. All patients underwent penile rehabilitation.

Barret *et al* compared focal HIFU, focal cryotherapy, focal VTP and focal brachytherapy: The baseline IIEF–5 score was 19, 23 and 20 for cryotherapy, VTP and HIFU respectively. The IIEF–5 scores fell by 5, 10, and 6 points to 14, 13 and 14 at 12 months. It was not stated whether the differences were statistically significant.

4. Discussion

Deterioration in sexual health after any prostate cancer treatment is challenging to evaluate as it may result from erectile, ejaculatory or orgasmic dysfunction, decreased libido or psychological and relationship changes that occur after therapy. Return to baseline function measured via validated EF outcomes was chosen as an objective outcome that is meaningful to patients and is surprisingly under reported in the literature. Furthermore, it provides a more meaningful index when comparing treatment modalities for LPC.

The search for this systematic review found that non-validated definitions of EF were used in 29 studies. These included 'erections good enough for penetration', 'erections good enough for satisfactory intercourse' and no requirements for PDE-5I. There were 10 papers identified which provided no definition at all. The multiple different methods of reporting ED after ablative therapy meant meta-analysis was not possible. In particular, very few studies report on return to baseline function.

Nevertheless, it appears that focal therapy in general has a less detrimental effect on EF than WG therapies. Focal PT, VTP and IRE appeared to cause very little change from baseline though the men in these studies tended to have low volume lesions. The lack of randomized studies means inter-modality comparison is difficult though from Li *et al'*s and Liu *et al*'s non-randomized comparative studies, it would appear that WG HIFU is associated better EF than both focal and WG cryotherapy[28,30].

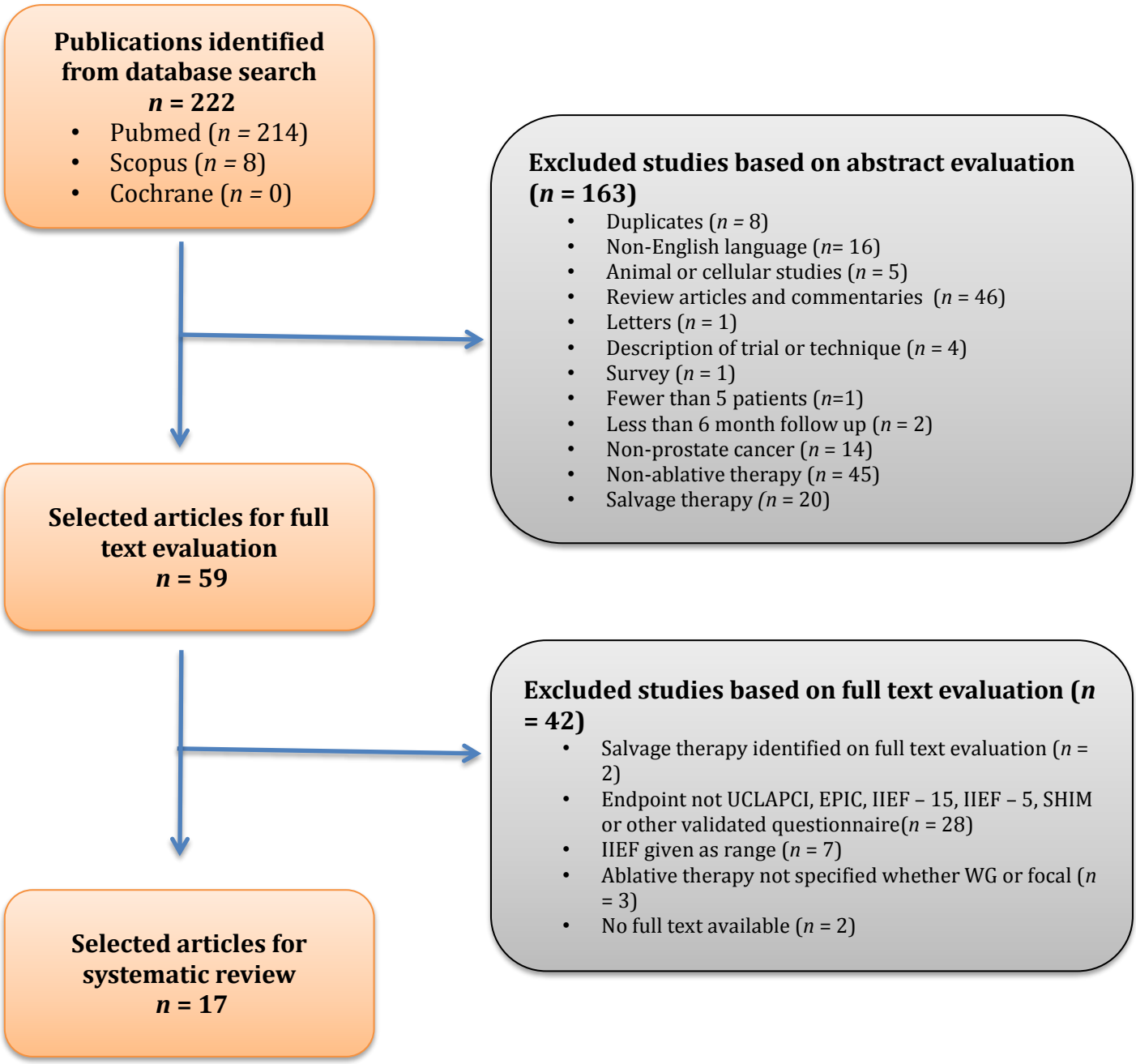
ED after HIFU is likely to result from heat dissemination to the surrounding cavernosal nerves and accessory or aberrant pudendal arteries found in up to 75% of men[28,39]. The cooling effect from cryotherapy extends 5mm from the ice ball and it is recommended to give the cancer focus a 10mm margin[7]. It is therefore more difficult to achieve precise ablation than with HIFU and cryotherapy is hence more likely to cause extensive injury to the NVB[7,30].

Some of the studies incorporated penile rehabilitation, which also makes comparison of results more difficult. Regular use of PDE-5I has been shown to improve PSV and may enhance nerve regeneration after ablation[40]. The role and method of penile rehabilitation after RP remains controversial[41-44]. This study did not identify any randomized studies comparing penile rehabilitation techniques after ablative therapies. The men in Li *et al*'s study all underwent PDE-5I and pump penile rehabilitation after WG HIFU recovered baseline EF by 24 months[28]. The men in Liu *et al*'s study did not receive penile rehabilitation and did not recover their baseline IIEF-5 by 24 months[30]. Despite these findings, there was no robust enough evidence to enable the authors to draw conclusions regarding the effectiveness of penile rehabilitation after ablative therapy and should be the focus of further studies.

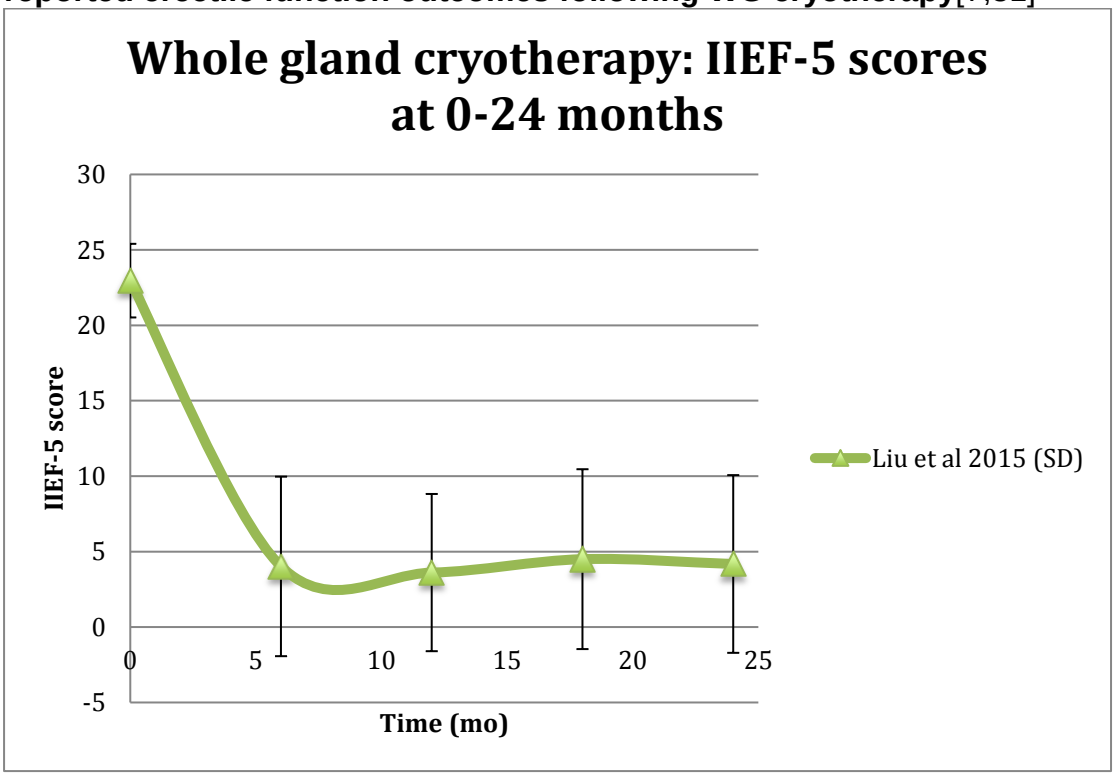
This systematic review is limited by heterogenous definitions of ED and a lack of randomized data. The authors would strongly urge that the design of future trials of ablative therapies utilize objective, validated outcome measures such as the IIEF-5 or EPIC-26 which is within the international consortium for health outcomes measurement dataset at three monthly intervals up to at

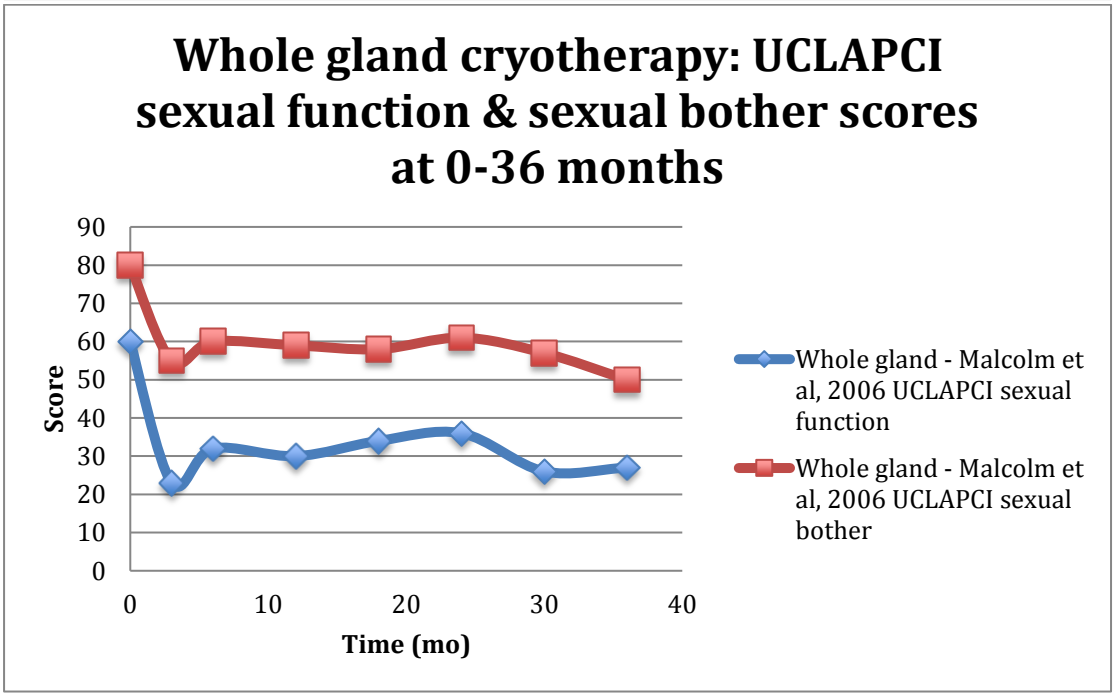
least one year, with return to baseline function as the primary endpoint. This will allow patients to make more informed decisions regarding their preferred treatment of LPC when they weigh up the oncological success and functional outcomes of different treatment modalities.

Legend 1: Figure 1 – Flow diagram of evidence acquisition in a systematic review on erectile dysfunction following whole gland and focal ablative therapies for localized prostate cancer

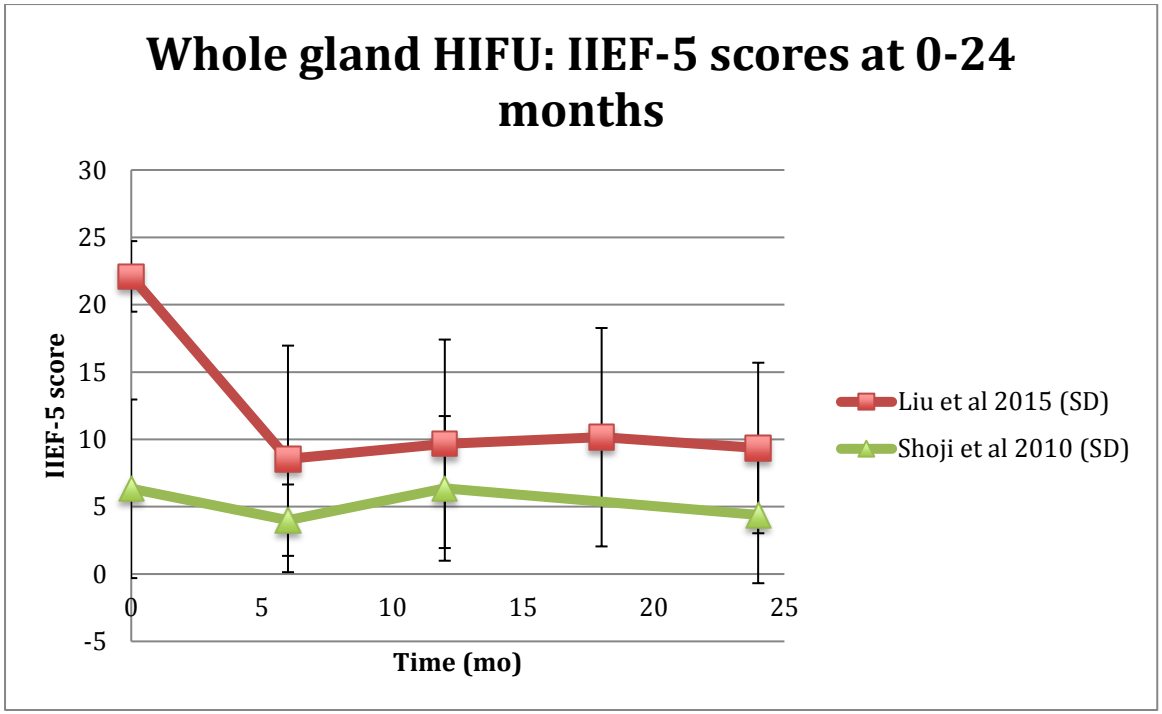


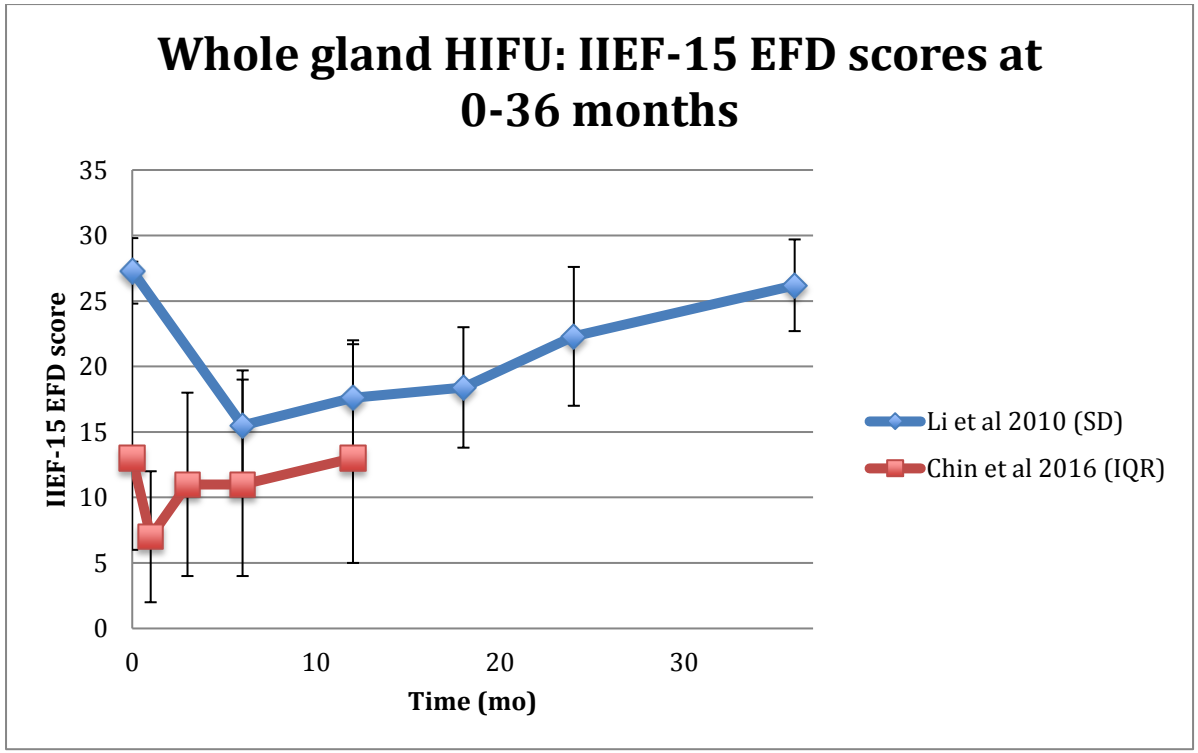
Legend 2: Figure 2 – UCLAPCI sexual function and sexual bother scores, median total IIEF-5 and IIEF-15 EFD scores for studies that reported erectile function outcomes following WG cryotherapy[7,31]

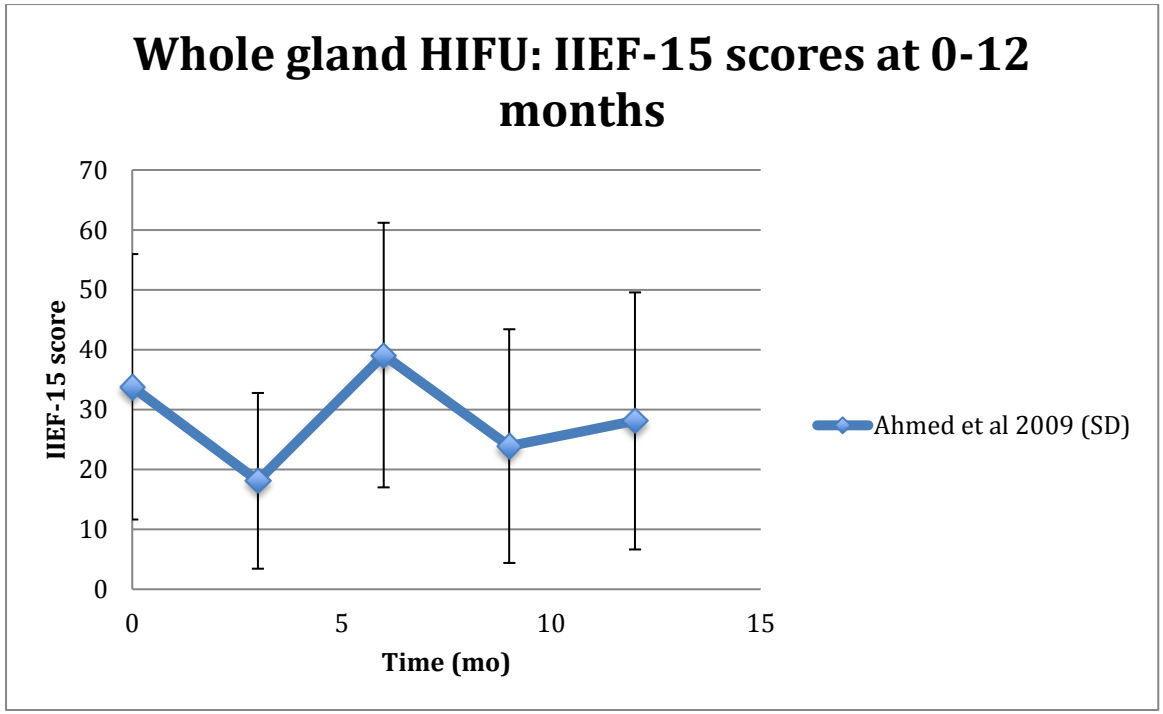




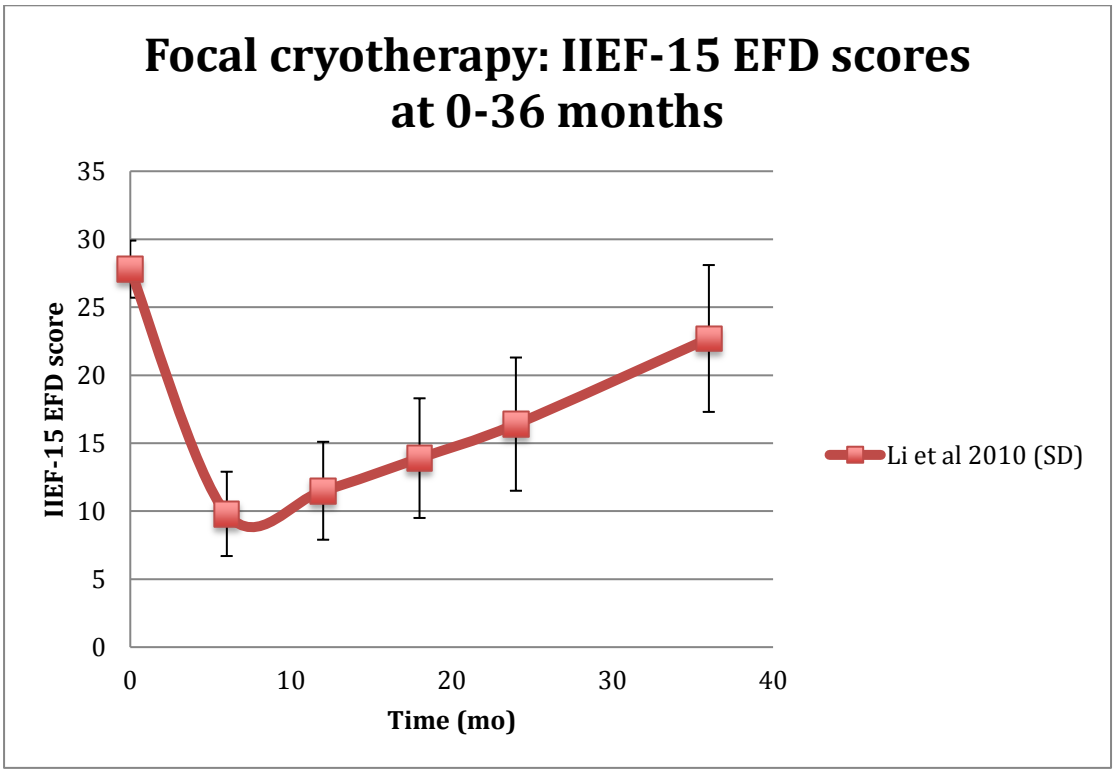
Legend 3: Figure 3 – Median total IIEF-5, IIEF-15 EFD and IIEF-15 scores for studies that reported erectile function outcomes following WG HIFU therapy[7,23,26,29,34]


Whole gland HIFU: IIEF-5 scores at 0-24 months
IIEF-5 score
30
25
20
15
10
5
0
-5
0
5
10
15
20
25
Time (mo)
Liu et al 2015 (SD)
Shoji et al 2010 (SD)

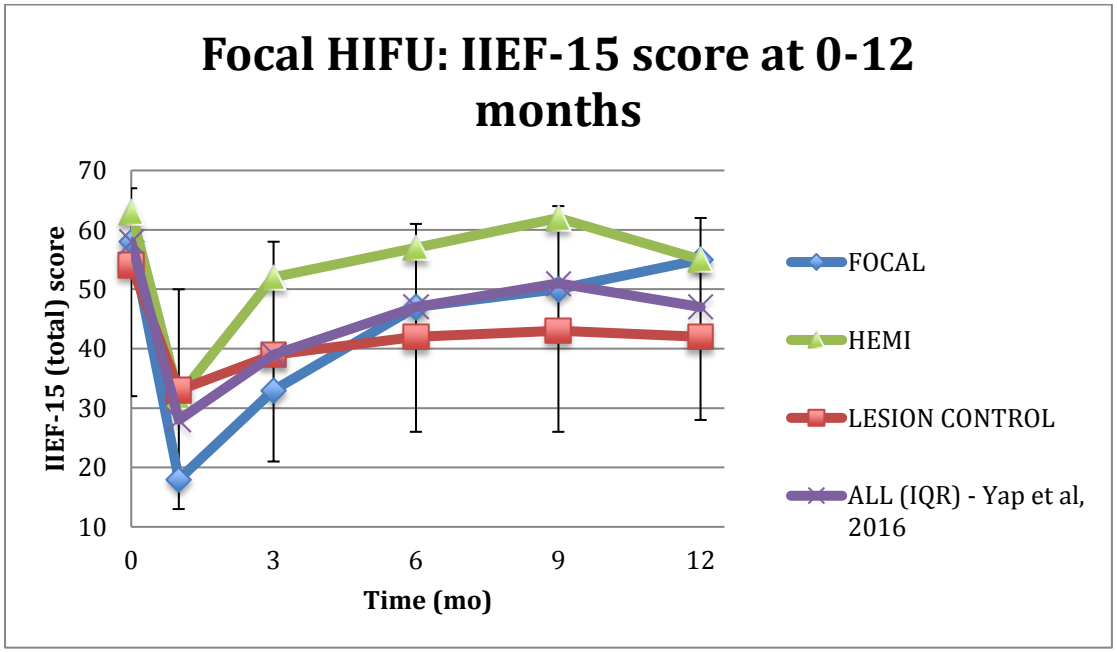

Whole gland HIFU: IIEF-15 EFD scores at 0-36 months
IIEF-15 EFD score
35
30
25
20
15
10
5
0
0
10
20
30
Time (mo)
Li et al 2010 (SD)
Chin et al 2016 (IQR)


Whole gland HIFU: IIEF-15 scores at 0-12 months
IIEF-15 score
70
60
50
40
30
20
10
0
0
5
10
15
Time (mo)
Ahmed et al 2009 (SD)

Legend 4: Figure 4 – IIEF-15 scores for patients undergoing focal cryotherapy[29]



Legend 5: Figure 5 - Median total IIEF-15 scores at baseline to 12 months for studies that reported erectile function outcomes following focal HIFU therapy[35]



Focal HIFU IIEF-15 scores at 0-12 months		**Age**		**Gleason score**									**IIEF-15**
	n	**Median (y)**	**range (y)**	**3+3**	**3+4**	**4+3**	**Time (mo):**	**0**		**1**		**3**	
Trial				**n (%)**	**n (%)**	**n (%)**		**score**	**IQR***	**score**	**IQR***	**score**	**IQR***
FOCAL	42	63	58-66	13 (31)	25 (60)	4 (9)		58	32-67	18	11-47	33	21-55
HEMI	20	60	56-64	6 (30)	12 (60)	2 (10)		63	59-70	32	21-51	52	25-62
LESION CONTROL	56	64	60-68	14 (25)	36 (64)	6 (11)		54	30-65	33	17-53	39	21-56
ALL	118	63	52-70	33 (28)	73 (62)	12 (10)		58	32-67	28	13-50	39	21-58
p (difference from baseline)										0.005		0.009	

*IQR: interquartile range

Legend 6: Table 1 – Liu *et al* IIEF–5 scores at baseline to 24 months[30]

	WG Cryotherapy	**WG HIFU**	**p**
Age [SD] (y)	68.8 [6.5]	68.1 [1.9]	0.33
Prostate volume [SD] (ml)	36.7 [16.9]	22.0 [10.9]	0.000
PSA [SD] (ng/ml)	26.8 [49.3]	17.0 [21.9]	0.055
Gleason score:			0.082
6	41 (36.0%)	36 (30.0%)	
7	38 (33.3%)	57 (47.5%)	
≥8	35 (30.7%)	27 (22.5%)	
T stage:			0.059
<T2b	52 (45.6%)	73 (60.8%)	
T2b	16 (14.0%)	14 (11.7%)	
T2b	46 (40.4%)	33 (27.5%)	
IIEF-5 [SD]			
Baseline	22.96 [2.44]	22.10 [2.62]	0.112
6 months	4.02 [5.95]	8.55 [8.41]	0.017
12 months	3.61 [5.21]	9.67 [7.74]	0.004
18 months	4.50 [5.96]	10.16 [8.11	0.001
24 months	4.18 [5.89]	9.36 [6.33]	0.0028

Legend 7: Table 2– Li *et al* IIEF–15 EFD scores at baseline to 36 months[28]

	Focal Cryotherapy	**WG HIFU**	**p**
Age [SD] (y)	59.2 [4.9]	57.5 [5.7]	0.36
PSA [SD] (ng/ml)	8.2 [3.1]	7.5 [2.4]	0.88
T stage:			0.69
T1c	21 (44.7%)	24 (43.6%)	
T2a	24 (51.0%	26 (47.3%)	
T2b	2 (4.3%)	5 (9.1%	
IIEF-15 EFD [SD]			
Baseline	27.8 [2.1]	27.3 [2.5]	0.735
6 months	9.8 [3.1]	15.5 [4.2]	<0.001
12 months	11.5 [3.6]	17.6 [4.1]	0.021
18 months	13.9 [4.4]	18.4 [4.6]	0.016
24 months	16.4 [4.9]	22.3 [5.3]	0.003
36 months	22.7 [5.4]	26.2 [3.5]	0.042

Legend 8: Table 3 – Time taken for erectile function to return to baseline

Ablative modality	Study	n	Age (y)	Presenting PSA (ng/ml)	Outcome measure	Baseline score	Follow up (mo)	Time points reported (mo)	Time to return to baseline (mo)	Percentage taking PDE-5I
WG therapy:										
WG cryotherapy	Liu *et al*, 2015	114	69.8	26.8	IIEF-5	22.96	24	0, 6, 12, 18 ,24	Significant fall from baseline*****	Not reported
	Malcolm *et al*, 2006	81	71	6.2	UCLAPCI sexual function and bother	60 & 80	36	0, 3, 6, 12, 18, 24, 30, 36	Significant fall from baseline*****	Not reported
WG HIFU	Shoji *et al,* 2010	326	68	12.7	IIEF-5	6.33	24	0, 6, 12, 24	NSC***	Not reported
	Liu *et al,* 2015	120	68.1	17.0	IIEF-5	22.1	24	0, 6, 12, 18 ,24	Significant fall from baseline*****	Not reported
	Ahmed *et al, 2009*	94	64.1	8.3	IIEF-15	33.8	12	0, 1, 3, 6, 9, 12	6****	Not reported
	Li *et al*, 2010	55	57.5	7.5	IIEF-15 EFD	27.3	36	0, 6, 12, 18, 24	24	100%*****
	Chin *et al*, 2016	30	59	5.8	IIEF-15 EFD	13	12	0, 1, 3, 6, 12	3	Not reported
Focal cryotherapy	Barret *et al*, 2013	50	66.5**	6.2	IIEF-5	19	12	0, 12	NSC***	Not reported
	Li *et al*, 2010	47	59.2	8.2	IIEF-15 EFD	27.8	36	0, 6, 12, 18, 24	36	100%*****
Focal therapy:										
Focal HIFU	Yap *et al,* 2015:									
	ALL	118	63	6.8	IIEF-15	58	12	0, 1, 3, 6, 9, 12	6	43%*
	FOCAL	42	60	7.4	IIEF-15	64	12	0, 1, 3, 6, 9, 12		
	HEMI	20	64	6.6	IIEF-15	54	12	0, 1, 3, 6, 9, 12		
	LESION CONTROL	56	63	6.5	IIEF-15	58	12	0, 1, 3, 6, 9, 12		

	Barret *et al,* 2013	21	66.5**	6.0	IIEF-5	20	12	0, 12	NSC***	Not reported
Photothermal	Eggener *et al*, 2016	27	62	4.4	IIEF-5	21.5	12	0, 1, 3, 12	12	Not reported
	Natarajan *et al,* 2015	8	63	10.3	IIEF-5	19.5	6	0, 1, 3, 6	NSC***	Not reported
	Oto *et al*, 2013	9	61	5.5	IIEF-5	19.0	6	0, 1, 3, 6	NSC***	
	Lindner *et al*, 2009	12	56.5	5.7	IIEF-5	22	6	0, 1, 3, 6	NSC***	Not reported
VTP	Azzouzi *et al,* 2015	117	62.2	5.6	IIEF-15 EFD	19.4	6	0, 1, 3, 6	NSC***	Not reported
	Barret *et al*, 2013	23	66.5**	5.7	IIEF-5	23	12	0, 12	NSC***	Not reported
Electroporation	Valerio *et al*, 2017	19	60	7.75	IIEF-15******	47	12	0, 3,6,,9, 12	NSC***	Not reported
	Katie S. Muuray *et al*, 2016	25	63.1	4.3	Prostate quality of life survey	18.6	12	0, 6, 12	Minimal change from baseline	2/25 used PDE5-I at baseline; no de novo use
*	38% of started taking PDE-5I after ablative therapy									
**	This is the median age for all patients, the median ages of the individual groups were not reported									
***	No significant change from baseline score at any time point									
****	A significant number of patients were not followed up from baseline									

***** The EF score did not return to baseline within the follow up period after an initial significant fall

****** All patients were also encouraged to use a vacuum pump

******* Results extrapolated from graph

Legend 9: Table 4 – Papers identified by review with bias assessment

Study	Study type	n (total)	Intervention (n)	End points	Time taken for EF to return to baseline specifically reported	Follow up (months)	Bias assessment
Ahmed et al, 2009[7]	Prospective cohort	24	WG HIFU	IIEF-15	No	12	No control group Low rate of follow up
Ahmed et al, 2012[6]	Prospective development	41	Focal HIFU	IIEF-15	Yes	12	No control group
Azzouzi et al, 2015[8]	Pooled analysis of three prospective cohort studies	114	Focal VTP	IIEF-EF	No (follow up scores less than baseline)	6	None of the studies within the amalgamation had control groups

Barret et al 2013[9]	Prospective cohort	94	Focal cryotherapy (50), focal HIFU (21) & focal VTP (23)	IIEF-5	No	12	Treatment groups not randomised Outcome of interest only reported at baseline and 12 months
Chin et al, 2016[10]	Prospective cohort (phase I trial	30	WG HIFU	IIEF-15 EFD	No	12	No control group
Eggener *et al*, 2016[11]	Phase II trial	27	Focal photothermal	SHIM (IIEF-5)	Yes	12	No control group
Li et al, 2010[13]	Prospective cohort	102	WG HIFU (55) & Focal Cryo (47)	IIEF –EF	No	36	Groups not randomised, all patients encouraged to use a vacuum pump
Lindner et al, 2009[14]	Prospective cohort (phase I trial)	12	Focal photothermal	IIEF -5 (graph only)	No	6	No control group, small study
Liu et al, 2015[15]	Prospective cohort	234	WG HIFU (120) & WG Cryo (114)	IIEF-5	No (follow up scores less than baseline)	24	Treatment groups not randomised and WG cryotherapy group had higher presenting PSA and larger prostate volumes
Malcolm et al, 2010[16]	Prospective cohort	81	WG cryotherapy	UCLAPCI	No (follow up scores less than baseline)	36	No control group

Moore et al 2015[17]	Prospective cohort (phase II trial)	34	Focal VTP	IIEF-5	No (no statistical difference between baseline and any time point in study)	6	No control group
Katie S. Murray et al, 2016[9]	Prospective cohort	24	Nanoknife irreversible electroporation	Prostate quality of life survery	No	12	No control group
Natarajan et al, 2015[18]	Prospective cohort (phase I trial)	8	Focal photothermal	SHIM (IIEF-5)	No (no statistical difference between baseline and any time point in study)	6	Small study, no control group
Oto et al, 2013[38]	Prospective cohort (phase I trial)	9	MRI guided focal laser ablation	SHIM (IIEF-5)	No (no statistical difference between baseline and any time point in study)	6	Small study, no control group
Shoji et al, 2010[19]	Prospective cohort	326	WG HIFU	IIEF-5	No (no statistical difference between baseline and any time point in study)	24	No control group
Valerio et al 2017[11]	Prospective cohort (phase II trial)	19	Nanoknife irreversible electroporation	IIEF-15 (graphony)	No	12	No control group
Yap et al, 2016[20]	Pooled analysis of 3 prospective studies	118	Focal HIFU	IIEF–15 & IIEF – EF	Yes	12	None of the studies within the amalgamation had control groups

Appendix A – Search terms for PubMed

(("focal therapy"[All Fields] OR ("laser therapy"[MeSH Terms] OR ("laser"[All Fields] AND "therapy"[All Fields]) OR "laser therapy"[All Fields] OR ("laser"[All Fields] AND "ablation"[All Fields]) OR "laser ablation"[All Fields]) OR ("high-intensity focused ultrasound ablation"[MeSH Terms] OR ("high-intensity"[All Fields] AND "focused"[All Fields] AND "ultrasound"[All Fields] AND "ablation"[All Fields]) OR "high-intensity focused ultrasound ablation"[All Fields] OR "hifu"[All Fields]) OR ("cryotherapy"[MeSH Terms] OR "cryotherapy"[All Fields]) OR ABLATION[All Fields]) AND ("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR ("prostate"[All Fields] AND "cancer"[All Fields]) OR "prostate cancer"[All Fields]) AND ((("penile erection"[MeSH Terms] OR ("penile"[All Fields] AND "erection"[All Fields]) OR "penile erection"[All Fields] OR "erectile"[All Fields]) AND ("physiology"[Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms] OR "function"[All Fields])) OR ("erectile dysfunction"[MeSH Terms] OR ("erectile"[All Fields] AND "dysfunction"[All Fields]) OR "erectile dysfunction"[All Fields]) OR SEXUAL FUNCTION[All Fields] OR SHIM[All Fields] OR IIEF[All Fields]

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