available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Giorgio Gandaglia, Alberto Briganti, Andrea Salonia and Francesco Montorsi on pp. 852–853 of this issue

The Effects of Focal Therapy for Prostate Cancer on Sexual Function: A Combined Analysis of Three Prospective Trials

Tet Yap [a,], Hashim U. Ahmed [a,b], Richard G. Hindley [c], Stephanie Guillaumier [a,b], Neil McCartan [a,b], Louise Dickinson [a,b], Mark Emberton [a,b], Suks Minhas [a]*

[a] *Department of Urology, University College London NHS Foundation Trust, London, UK;* [b] *Division of Surgery and Interventional Science, University College London, UK;* [c] *Department of Urology, Hampshire Hospitals NHS Foundation Trust, UK*

Article info

Article history:
Accepted October 15, 2015

Associate Editor:
Giacomo Novara

Keywords:
Erectile dysfunction
Prostate cancer
Focal therapy

Abstract

Background: Tissue preservation by means of focal therapy offers some men with clinically significant prostate cancer an alternative to standard care that appears to confer favourable genito-urinary outcomes. The precise estimates of these outcomes have so far been based on small series.
Objective: This analysis pools the sexual domain related patient reported outcomes from three prospective, registered studies that represent a range of inclusion criteria.
Design, setting, and participants: One-hundred and eighteen men with localised prostate cancer (prostate specific antigen $\leq$ 15 ng/ml, Gleason $\leq$ 4 + 3, stage $\leq$ T3aN0M0) treated in a tissue-preserving manner using high intensity focused ultrasound from three registered studies were included. Data on International Index of Erectile Function (IIEF-5) scores and use of phosphodiesterase-5-inhibitors were collected at baseline, and 1 mo, 3 mo, 6 mo, 9 mo, and 12 mo postoperatively. The IIEF-15 total and individual domain scores were used to assess overall sexual function. Urinary function was assessed with the International Prostate Symptom Score (IPSS), IPSS quality-of-life, and UCLA-Expanded Prostate Cancer Index Composite continence questionnaires. General health status was derived by means of the Charlson score. Multiple linear regression was used to assess whether age, grade, stage, qualitative scores (IIEF, IPSS, Expanded Prostate Cancer Index Composite, Charlson), or focal therapy type duration were associated with IIEF-5 and IIEF-15 scores at 12 mo.
Results and limitations: Median age was 63 yr (interquartile range [IQR] 52–70 yr). Median IIEF-erectile score at baseline was 23 (IQR 11–28). This declined significantly to 9 (IQR 3–22, $p < 0.01$) at 1 mo, but improved to 20 (IQR 9–29, $p = 0.30$) at 1 yr posttreatment. Changes in total IIEF and other IIEF domains were only significantly different from preoperative values at 1 mo and 3 mo postoperatively. In the same period, the proportion of men using phosphodiesterase-5-inhibitors was 10% preoperatively, reaching 43% and 42% at 6 mo and 9 months before declining to 37% at 1 yr. The only baseline determinants of postoperative erectile function were total IIEF and IIEF-erectile function scores ($p = 0.002$). The primary limitation of our study is the relatively short follow-up of 1 yr.
Conclusion: Men who received a range of tissue preserving therapies from the three pertinent studies experienced small decreases in total IIEF, erectile, and individual sexual domain scores that are not significantly different to those recorded at baseline. The only determinant of erectile dysfunction after tissue preserving therapy was

* Corresponding author. Department of Urology, University College London NHS Foundation Trust, Blackshaw Road, London SW170QT, UK. Tel. +44 7545130370.
E-mail address: tetyap4@gmail.com (T. Yap).

http://dx.doi.org/10.1016/j.eururo.2015.10.030

preoperative erectile dysfunction status. Tissue preservation confers a high probability of maintaining erectile function that appears independent of all perioperative factors with the exception of baseline status.

Patient summary: In this report, the largest prospectively collected and published set of patients with erectile dysfunction outcomes post–focal therapy for prostate cancer, we have found a return to baseline International Index of Erectile Function–erectile and total International Index of Erectile Function scores by 6 mo post–focal therapy which was maintained at 1 yr, with the majority of patients not on any form of medical treatment for their erectile dysfunction at that point. Focal therapy may represent a suitable alternative for men of any age or comorbidity wishing to maintain erectile function.

1. Introduction

In surgical oncology the standard approach to solid organ tumours is to target the cancerous lesion by means of excision or ablation in conjunction with a tumour free margin. The aim of treatment is to achieve oncological control and at the same time preserve as much function as possible. In most urological oncology this transition from total organ extirpative surgery to organ preserving surgery has occurred (renal cancer, penile cancer) [1]. In prostate cancer, such a transition from an anatomically defined treatment (radical prostatectomy or radical radiotherapy) to one that is contingent on cancer-related attributes (location, burden, multiplicity, and grade) has been proposed [2] as a means to achieve cancer control but at the same time reduce treatment-related toxicity [3].

The likelihood of preserving sexual function is one of the strongest drivers of patient choice in treatment allocation in men with early prostate cancer [2]. This being the case, it is important to have data that are both representative and precise enough to inform men who are considering tissue-preserving therapy as one of their options. However, the data that we currently rely upon are derived from a number of small case series, using a number of energy sources with nonstandardised methods. Moreover, a number of studies have tended to elicit health status using informal methods in a nonindependent manner at a range of time points [4].

In order to correct this, we have pooled functional data from three prospective, registered, ethics committee approved and externally audited studies that were conducted in the UK between 2009 and 2013 (NCT005613314, NCT00988130, NCT00561262). These three studies comprise a broad range of functional status at baseline as eligibility criteria changed over time: firstly, a hemi-ablation trial ('HEMI'); secondly, the focal lesion ablation trial ('FOCAL'); and thirdly, an index lesion ablation trial ('LESION-CONTROL') [5–7]. Moreover, each study tests a different but standardised and quality controlled intervention. For the purposes of this analysis, all the studies had within their protocol a similar detailed and formal assessment of function [5–7]. These together represent the largest prospectively collected data on erectile function outcomes after focal therapy in prostate cancer.

2. Methods

2.1. Study design and patients

Men eligible for this analysis comprised 118 men who were reported in the three trials of focal therapy [5–7]. These trials were conducted in two centres within the UK. Trial characteristics are summarised in Table 1. Eligibility for all three studies was similar from an oncological perspective: men with low, intermediate, and high-risk disease (prostate-specific antigen $\leq$ 15 ng/ml, Gleason $\leq$ 4 + 3, stage $\leq$ T2NoMo), aged 45–80 yr with a life expectancy of 10 yr or more, a prostate volume of $\leq$ 40 ml or maximum anterior-posterior length of $\leq$ 40 mm. Men were carefully characterised using a combination of multiparametric magnetic resonance imaging (mp-MRI) (1.5 T, T2W, diffusion-weighted, dynamic contrast-enhancement) and concordant biopsy (transperineal template-prostate-mapping [TPM] or transrectal biopsies) [8]. Exclusion criteria are detailed in the previous reports [5–7].

The trials were approved by the University College London Hospitals Local Research Ethics Committee A under the auspices of the National Research Ethics Service (UK). The studies were independently audited by hospital research and development officials. Additionally, the protocols for each trial were anonymously peer-reviewed by the National Cancer Research Network (UK) and the Medical Research Council (UK).

2.2. Procedures

Men underwent treatment with a transrectal high intensity focused ultrasound (HIFU) device (Sonablate 500; Sonacare Inc, Indianapolis, IN, USA). This procedure has been previously described in detail [7]. For all three trials, there were three general treatment guidelines. First, a maximum of 60% of the prostate could be ablated. Secondly, the edge of the ablation zone had to be at least 10 mm from a neurovascular bundle (ie, the contralateral bundle, determined on ultrasound). The ablation zone had to be at least 5 mm from both neurovascular bundles if treatment was bilateral. Thirdly, untreated areas could not have any histological evidence of clinically significant prostate cancer (Gleason $\geq$ 3 + 4 and/or cancer core length $\geq$ 4 mm).

The first of the studies to report was the HEMI trial (n = 20). The intervention in this trial was anatomical in that lobe associated with the cancer was treated in its entirely in addition to a 5 mm margin that crossed the midline into the contralateral lobe. In terms of the nature of intervention, the HEMI trial was the most standardised as the same treatment was applied irrespective of the cancer characteristics. The second study to report was the FOCAL trial (n = 42). In this study the intervention was defined by the operator who made rule-based judgments on the treatment plan based on inputs from the mp-MRI (when a lesion was visible) and TPM-biopsies. The areas positive for cancer were treated

Table 1 – Patient characteristics in the three focal therapy trials analysed

Preoperative characteristics	Focal ablation [7]	Hemi-ablation [6]	Lesion control [5]	All groups (p value for difference)*
n	42	20	56	118
Median age/yr (IQR)	63 (58–66)	60 (56–64)	64 (60–68)	63 (52–70) (p = 0.07, Kruskal-Wallis)
Median PSA (ng/ml) (IQR)	7.4 (5.9–9.7)	6.6 (5.5–8.2)	6.5 (4.9–9.7)	6.8 (5.6–9.3) (p = 0.34, Kruskal-Wallis)
Gleason grade (% of group)				
3 + 3	13 (31)	6 (30)	14 (25)	p = 0.98 (Chi-square)
3 + 4	25 (60)	12 (60)	36 (64)	
4 + 3	4 (9)	2 (10)	6 (11)	
Stage (% of group)				
IC	38 (90)	20 (100)	16 (29)	($p < 0.01$, Chi-squared)
IIA	4 (10)	0	9 (16)	
IIB	0	0	18 (32)	
IIC	0	0	13 (23)	
Median total IPSS score (IQR)	7 (4–12)	8 (6–13)	8 (5–9)	8 (5–12) (p = 0.58, Kruskal-Wallis)
Median IPSS Quality of life score (IQR)	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–2) (p = 0.79, Kruskal-Wallis)
Median total EPIC score (IQR)	91 (87–95)	94 (89–96)	90 (87–93)	92 (87–96) (p = 0.86, Kruskal-Wallis)
Median adjusted Charlson score (IQR)	88 (85–93)	NA	87 (84–89)	88 (84–93) (p = 0.12, Kruskal-Wallis)
Median total IIEF score (IQR) (0–75)	58 (32–67)	63 (59–70)	54 (30–65)	58 (32–67)(p = 0.07, Kruskal-Wallis)
Median IIEF-erectile function score (IQR)(0–30)	24 (15–29)	23 (20–25)	22 (10–29)	23 (11–28) (p = 0.39, Kruskal-Wallis)
Median IIEF-orgasmic function score (IQR)(0–10)	10 (8–10)	10 (9–10)	9 (4–10)	10 (6–10)(p = 0.11, Kruskal-Wallis)
Median IIEF-sexual desire score (IQR)(0-10)	7 (5–8)	10 (9–10)	7 (6–8)	10 (0–12) (p = 0.67, Kruskal Wallis)
Median IIEF-intercourse satisfaction score (IQR)(0–15)	9 (0–12)	10 (10–12)	10 (0–11)	10 (0–12)(p = 0.19, Kruskal-Wallis)
Median IIEF-overall satisfaction score (IQR) (0–10)	8 (4–9)	8 (8–9)	8 (4–8)	8 (5–9)(p = 0.07, Kruskal-Wallis)
PDE5-inhibitor use (n [%])	3 (7)	2 (10)	7 (13)	12 (10)(p = 0.68, Kruskal-Wallis)
Median HIFU duration (min) (IQR)	105 (86–122)	115 (105–151)	105 (90–130)	115 (95–140) (p = 0.68, Kruskal-Wallis)

HIFU = high intensity focused ultrasound; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; IQR = interquartile range; NA = not applicable; PDE5 = phosphodiesterase-5; PSA = prostate specific antigen.
* Significance level for difference between groups: $p > 0.05$.

with at least a 3–5 mm margin around the lesion (2–4 HIFU pulses). In areas where a discrepancy between mp-MRI and TPM-biopsies was identified, histopathological findings took precedence. Some cancer lesions were quite close and were therefore included in the same area of treatment. As a result, more than two lesions could be treated as long as there were only two areas of treatment. Designation of individual lesions was usually straightforward but when positive biopsies were close together, lesions were labelled separately if there was at least one intervening normal biopsy. If possible, both neurovascular bundles were preserved. In the LESION-CONTROL trial (n = 56), the treatment covered the area of the gland in which the index lesion or other secondary lesions $\geq$ 0.5 cc were identified with mp-MRI and biopsy.

Assessment of erectile function took place at designated clinic visits that were scheduled at 1 mo, 3 mo, 6 mo, 9 mo, and 12 mo. The International Index of Erectile Function (IIEF-15) total and domain scores on erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction were used to assess overall sexual function. In addition, urinary function was assessed with International Prostate Symptom Score (IPSS), the IPSS quality-of-life questionnaire, and the UCLA-Expanded Prostate Cancer Index Composite (EPIC) continence questionnaire and the Charlson comorbidity score for multivariate analysis [8]. On-demand phosphodiesterase-5 (PDE5) inhibitors were permitted at any time point during follow-up, and patients were counselled on using PDE5 inhibitors for any erectile dysfunction (ED) at each of their visits.

The primary outcome for our pooled posthoc analysis was postoperative erectile function at 12 mo, assessed by means of IIEF questionnaires. Our preplanned analysis related to the identification of any recorded baseline and perioperative factors that predicted the presence or absence of postoperative erectile function.

2.3. *Statistical analysis*

The IIEF questionnaire was tabulated using standard methodology (addition of questionnaire values). Categorical outcomes were reported as point estimates with binomial 95% confidence intervals (CIs) to demonstrate the level of precision. Wilcoxon rank-sum test (two-tailed) was used to assess differences between questionnaire scores measured at baseline and at the 12-mo follow-up visit. Nonparametric tests (Kruskal-Wallis) were used for all analyses comparing the different groups where feasible. Changes over time were reported with box-and-whisker plots. Multiple linear regression was used to assess whether age, Gleason (entered as Gleason 3 + 3, 3 + 4, 4 + 3), stage (IC, IIA, IIB, IIC), Charlson comorbidity score, IIEF, IPSS, and UCLA-EPIC scores, focal therapy type (FOCAL, HEMI, LESION-CONTROL), and therapy duration were associated with IIEF-5 and IIEF-15 scores at 12 mo, adjusting for baseline IIEF. A p-value of 0·05 or less was deemed significant. SPSS (IBM, version 22 13.8.2013) was used.

3. Results

3.1. *Baseline characteristics*

Median age was 63 yr (interquartile range [IQR] 52–70 yr). There were no evidence of any significant differences in any of the baseline characteristics of age, mean prostate specific antigen level, Gleason grade, IPSS, IPSS Quality of life score, EPIC score, adjusted Charlson score, total and component IIEF scores, PDE5i usage, and HIFU duration between the three trial groups. However, patients in the

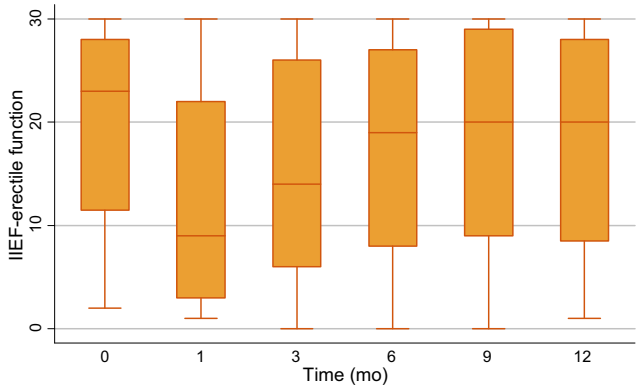

Fig. 1 – Distribution and median International Index of Erectile Function-erectile function from baseline to 12 mo. Median level is represented by the line within the box, margins of the box represent the interquartile range, and the whiskers represent the extremes of distribution. The box plots show a gradual recovery of median International Index of Erectile Function-erectile function to baseline levels at 9 mo and 12 mo posttreatment.
IIEF = International Index of Erectile Function.

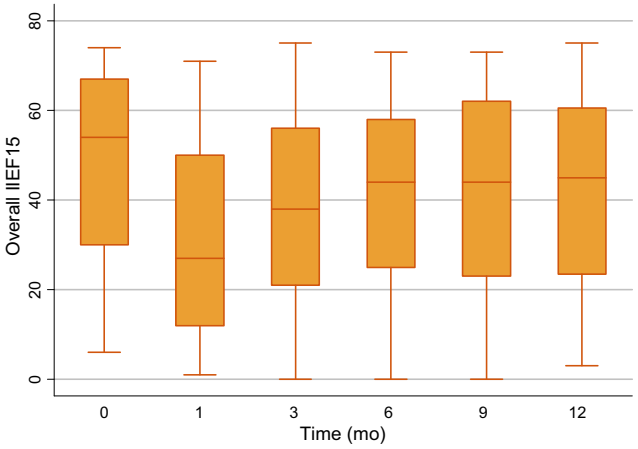

Fig. 2 – Distribution of median International Index of Erectile Function-total from baseline (score = 58) to 12 mo. Median level is represented by the line within the box, margins of the box represent the interquartile range, and the whiskers represent the extremes of distribution. The box plots show a gradual recovery of median International Index of Erectile Function-total to baseline levels at 9 mo and 12 mo posttreatment.
IIEF = International Index of Erectile Function.

LESION-CONTROL trial tended to have higher stage disease with 23% of the cohort having IIC disease compared to none in the other groups (Table 1).

3.2. *Primary outcomes*

Median IIEF-erectile score at baseline was 23 (IQR 11–28). This declined significantly to 9 (IQR 3–22, $p < 0.01$) at 1 mo, but improved to 15 (IQR 6–26, $p = 0.007$) at 3 mo, 19 (IQR 8–27, $p = 0.06$) at 6 mo, 20 (IQR 9–29, $p = 0.59$) at 9 mo, and 20 (IQR 9–28, $p = 0.30$) at 1 yr posttreatment (Fig. 1). Changes in total-IIEF and other IIEF domains were only significantly different from preoperative values at 1 mo and 3 mo postoperatively (Fig. 2). When IIEF-erectile and total scores were compared between the three groups, there was no significant difference at baseline, 1 mo, 3 mo, 6 mo, 9 mo, and 12 mo postfocal therapy (Table 2).

3.3. *Secondary outcomes*

Firstly, the proportion of men using PDE5-inhibitors was 12/118 (10%) preoperatively, 15/118 (13%) at 1 mo, 35/118 (30%) at 3 mo, reaching 51/118 (43%) and 50/118 (42%) at 6 mo and 9 mo before dropping to 44/118 (37%) at 1 yr. PDE5-inhibitor usage was started on patient demand, with sildenafil 100 mg used in the majority (89%). In the same period, the proportion of patients postoperatively on PDE5-inhibitor usage excluding those who were on it preoperatively was 8/106 (8%) at 1 mo, 24/106 (23%) at 3 mo, 40/106 (38%) at 6 mo and 9 mo, dropping to 32/106 (30%) at 12 mo. There was no significant difference in the proportion of patients on PDE5-inhibitors (both total and newly starting) between the three study groups at each time-point (Table 3). No patients sought second-line drug or mechanical therapies for ED.

Table 2 – International Index of Erectile Function (IIEF)-erectile and total IIEF between the three groups at baseline, 1 mo, 3 mo, 6 mo, and 12 mo post–focal therapy, along with IIEF questionnaire completion rates at each time-point

Median value (IQR)	Baseline	1 mo	3 mo	6 mo	9 mo	12 mo
IIEF-erectile (FOCAL)	24 (15–29)	6 (3–20)	12 (7–25)	19 (12–26)	23 (11–29)	21 (11–27)
IIEF-erectile (HEMI)	23 (20–25)	11 (8–22)	22 (7–27)	26 (14–28)	28 (21–29)	25 (14–29)
IIEF-erectile (LESION CONTROL)	22 (10–29)	11 (4–22)	15 (6–26)	16 (5–26)	18 (5–28)	16 (6–27)
IIEF-erectile (IQR) (ALL)	23 (11–28)	9 (3 –22)	15 (6–26)	19 (8–27)	20 (9–29)	20 (9–28)
p value (difference between groups, Kruskal-Wallis)	0.34	0.14	0.61	0.06	0.06	0.10
p value (difference from baseline)	–	0.004*	0.009*	0.06	0.59	0.30
IIEF-total (FOCAL)	58 (32–67)	18 (11–47)	33 (21–55)	47 (27–58)	50 (28–64)	55 (30–63)
IIEF-total (HEMI)	63 (59–70)	32 (21–51)	52 (25–62)	57 (40–64)	62 (49–67)	55 (36–65)
IIEF-total (LESION CONTROL)	54 (30–65)	33 (17–53)	39 (21–56)	42 (24–59)	43 (19–61)	42 (21–59)
IIEF-total (IQR) (ALL)	58 (32–67)	28 (13–50)	39 (21–58)	47 (26–61)	51(26–64)	47 (28–62)
p value (difference between groups, Kruskal-Wallis)	0.26	0.06	0.56	0.85	0.06	0.18
p value (difference from baseline)	–	0.005*	0.009*	0.08	0.57	0.30
IIEF completion rate (all groups)	98%	97%	97%	96%	96%	95%

IIEF = International Index of Erectile Function; IQR = interquartile range.
* Significant difference; significance level: $p > 0.05$.

Table 3 – Phosphodiesterase-5-inhibitor usage between the three groups at baseline, 1 mo, 3 mo, 6 mo, and 12 mo post–focal therapy

	Baseline	1 m	3 mo	6 mo	9 mo	12 mo
N (%) on PDE5-inhibitors (FOCAL)	3 (7)	4 (10)	14 (33)	17 (40)	17 (40)	14 (33)
N (%) on PDE5-inhibitors (HEMI)	2 (10)	5 (25)	7 (35)	9 (45)	7 (35)	7 (35)
N (%) on PDE5-inhibitors (LESION CONTROL)	7 (13)	6 (11)	14 (25)	25 (45)	26 (46)	23 (41)
N (%) on PDE5-inhibitors (ALL)	12 (10)	15 (13)	35 (30)	51 (43)	50 (42)	44 (37)
N (%) on PDE5-inhibitors (NEW)[a]	-	8 (8)	24 (23)	40 (38)	40 (38)	32 (30)
p value (difference between groups, Kruskal-Wallis)[*]	0.68	0.22	0.56	0.93	0.86	0.75

PDE% = phosphodiesterase-5.
[a] Not on PDE5 inhibitors at baseline.
[*] Significance level: $p > 0.05$.

Secondly, in patients started on PDE5-inhibitors postoperatively, there was a significant improvement in IIEF-erectile score of 6 (95% CI 2–10, $p \leq 0.01$) and total-IIEF (13, 95% CI 5–22, $p < 0.01$) compared with those not on PDE5-inhibitors. The change in IIEF-erectile and total-IIEF scores between those who came off PDE5-inhibitors at 12 mo was not significant compared with those that remained on medication (IIEF-erectile difference 1.8, 95% CI 1.5–5.2, $p = 0.27$; total-IIEF difference 1.3, 95% CI 5.5–8.2, $p = 0.69$) and is likely to reflect the recovery of erectile function in patients who stopped PDE5-inhibitors post–focal therapy. Fifty-four percent of men who stopped PDE5-inhibitors by 12 mo reported a return to their baseline IIE-erectile score at 12 mo.

Thirdly, changes in erectile function postoperatively (at 12 mo) were only significantly associated with preoperative total-IIEF and IIEF-erectile function scores ($p = 0.002$), whereas age ($p = 0.62$),focal therapy strategy ($p = 0.21$), and duration ($p = 0.45$), Gleason score ($p = 0.50$), and stage ($p = 0.33$), as well as preoperative Charlson comorbidity scores (with and without adjustment for prostate cancer, $p = 0.65$ and $p = 0.63$), IPSS ($p = 0.87$), IPSS-quality of life ($p = 0.71$), and UCLA-EPIC continence scores ($p = 0.14$) at baseline were not found to be independently associated with total-IIEF and IIEF-erectile scores at 12 mo (multiple linear regression, all $p > 0.05$ as above). For each unit increase of IIEF-erectile function at baseline, the mean increase at 12 mo in total IIEF was 0.60 (95%CI 0.42–0.78, $p < 0.01$) and mean improvement in IIEF-erectile was 0.73 (95% CI 0.43–0.80, $p < 0.01$).

4. Discussion

In summary, our analysis of the pre- and postoperative sexual domains from three prospective, registered studies of tissue preserving therapy has shown that men exposed to a range of interventions experienced a small reduction in mean total-IIEF and IIEF-erectile scores at 6 mo that was not statistically significant. The only determinant of postoperative erectile function status proved to be preoperative erectile function status.

4.1. Clinical implications

Our results compare favourably with studies that used patient reported outcomes following radical whole gland interventions [9–11]. Our results are of considerable utility to men whose choice of treatment is heavily weighted by preservation of sexual function domains. Men with reasonable sexual function at baseline can undergo a broad range of tissue preserving therapy with a high probability of their IIEF score being similar 6-mo postoperatively to that recorded at baseline. In our study, IIEF scores did not vary significantly between those who continued and those who stopped PDE5-inhibitors at 12 mo. Although we cannot be sure, this probably reflects recovery of erectile function, inferred from the rise in IIEF to near baseline levels.

When the current literature for ED in HIFU is reviewed [7,12–32], the range of reported ED ranges from 2% to over 77% in previously potent men. However, almost all of this ED data is from whole-gland ablation. When the focal therapy studies are reviewed only, the rate of ED ranges from 11% to 45% (5,7,15,32; Table 4). The present study of 118 patients undergoing focal therapy represents the largest prospective group with complete and rigorously collected ED information (IIEF data and PDE5-inhibitor usage).

One particular interesting finding was that there was no evidence of significant differences in erectile function outcomes between the three types of focal therapy groups analysed, either when the three groups are compared (Table 2) or when the pairs of groups are compared; although, the possibility is not totally excluded given the variable confidence intervals between groups (Table 5). The similar ED outcomes may be due to patient selection and is of interest as it suggests that tissue preservation by any of the three standardised methods used was associated with a similar likelihood of return to baseline function.

The likelihood of ED in standard therapies such as radical prostatectomy (26–100%), external beam radiotherapy (8–85%), and interstitial radiation (14–61%) have been previously reported and are communicated to patients as part of the consent process [33]. However, consistent patient reported outcome measures data collection has been lacking in previous reported ED outcomes for these modalities, which may explain the large ED outcome differences between randomised controlled trial and cohort studies [34,35].

In contrast to our findings, risk factors that are associated with the occurrence of postradical intervention ED have been described. These include: age, degree of cavernosal nerve-sparing during surgery, cancer stage, and associated comorbidities (eg, Charlson score) [36]. In our study, the ED outcomes post–focal therapy appeared to be independent of

Table 4 – Summary of literature review of erectile dydfunction outcomes in focal high intensity focused ultrasound for localised prostate cancer

Yr	Author	*n*	*n* 1	Type	Mean follow-up (mo)	ED[a] (pre)	ED[a] (post)	PDE5i usage (pre)	PDE5i usage (post)	Median IIEF (pre) (range)	Median IIEF (post) (range)	IIEF difference (*p* value)
2015	Ahmed et al [5]	56	39	F	12	24.1%	33.3%	12.7%	42.6%	NA	NA	NA
2015	Van Velthoven et al [32]	31	22	F	36.3	NA	44.8%	NA	NA	NA	NA	NA
2013	Barret et al [15]	21	21	H	9	NA	NA	NA	NA	20 (15–25)	14 (8–25)	NA
2012	Ahmed et al [7]	41	41	F	1	14.6%	11%	9.0%	45.2%	24	21	0.06

ED = erectile dysfunction; F = focal ablation; H = hemiablation; IIEF = International Index of Erectile Function; *n* = total number of patients; *n* 1 = number of patients with ED outcomes; NA = not available; PDE5i = phosphodiesterase-5 inhibitors; pre = pretreatment; post = posttreatment.
[a] ED defined as inability to penetrate.

Table 5 – Median differences and 95% confidence interval of median differences between two groups

Median difference (IIEF erectile)/ 95% CI (*p* value)*	Baseline	1 m	3 mo	6 mo	9 mo	12 mo
FOCAL vs LESION CONTROL	2 (-1–6), $p = 0.21$	−5 (-6–0), $p = 0.10$	−3 (-5–3), $p = 0.61$	3 (-2–6), $p = 0.41$	2 (-2–6), $p = 0.35$	5 (-1–7), $p = 0.26$
HEMI vs LESION CONTROL	1 (-4–6), $p = 0.76$	0 (-4–6), $p = 0.63$	7 (-3–9), $p = 0.50$	10 (0–12), $p = 0.06$	5 (-1–7), $p = 0.26$	9 (0–10), $p = 0.05$
HEMI vs FOCAL	−1 (-5–30, $p = 0.34$	5 (0–8), $p = 0.09$	10 (-2–11), $p = 0.34$	7 (0–9), $p = 0.06$	10 (1–12), $p = 0.05$	4 (-1–8), $p = 0.22$

CI = confidence interval; IIEF = International Index of Erectile Function.
* Significance level: $p > 0.05$; Mann-Whitney U test.

all these parameters and were only influenced by preoperative ED status. This could have clinical implications in therapy selection for certain groups of patients. The other clinical implication of our finding relates to cost. As a return to baseline was achieved without the need for a formal penile rehabilitation program, it may mean that intensive and costly adjuvant management strategies might be avoided in men undergoing tissue-preserving therapy.

We know very little about the aetiology of ED after focal therapy. What we can say, fairly emphatically, is that in all our cases at least one neuro-vascular bundle was preserved. We can infer little about the bundle on the side of treatment as no test is available that can determine its status. However, we should assume damage to the structures adjacent to the treated lobe. This may result in a combination of vascular (arterio/venogenic) and neural damage. Arteriogenic ED may result from damage to pudendal arteries, which can be aberrant and make up the only arterial supply to the corpora cavernosa. They are present in up to 75% of men, and can occupy a lateral or apical position [37]. Venogenic ED may be secondary to ensuing corporal smooth muscle fibrosis, with increased expression of profibrotic cytokines, such as transforming growth factor beta, which lead to increased collagen smooth muscle ratios [38].

A hypogonadal-state post bilateral cavernous nerve injury has also been demonstrated in a rat model [39]. Following administration of testosterone in hypogonadal rats, some of the pathophysiological changes associated with ED, including collagenisation of penile smooth muscle and endothelial dysfunction, are improved. Cavernous nerve injury via thermal damage may also lead to reduction in nitric oxide synthase-producing nerves [40] as well as corporal smooth muscle atrophy and fibrosis [41]. The delay in return of erectile function post–focal therapy, as with post-radical prostatectomy may reflect a resolving neuropraxia. The result of all of these combined factors may be failure to achieve regular cavernosal cycling and oxygenation between the flaccid and erect states with hypoxic induced structural damage to the cavernosal smooth muscle [42].

Interestingly, after whole gland HIFU, previous authors have reported no reduction in penile length unlike RP, which is thought to involve both cavernous nerve damage and loss of erectile function [43,44]. Although this may be explained by the preservation of erectile function post HIFU, it may also be indicative of an alternative mechanism for ED other than cavernosal fibrosis.

The primary limitation of our study is the relatively short follow-up of 1 yr. Our future work will focus on whether this improvement is further maintained beyond 1 yr, and the proportion still on medical therapy for ED. Our three trials may also have had selection bias in that men with better baseline function compared to the general population may have participated in our trials. Heterogeneity in the treatment administered could potentially also limit the applicability of the current findings. Our most recent multicentre focal-therapy trial (INDEX NCT01194648) will test reproducibility across centres and populations in approximately 350 men. The aim of this study was to specifically report on functional outcomes following focal therapy for prostate cancer and not oncological outcomes. The short to medium cancer control rates have been previously reported by the authors in a prospective cohort of patients [7] and more recently comprehensively analysed in a systematic review and meta-analysis [3].

5. Conclusion

Focal therapy for prostate cancer represents an emerging strategy in targeting and treating malignancy whilst potentially maintaining erectile function and quality of life. In this series, the largest published set of patients with ED outcomes post–focal therapy, we have found a return to baseline IIEF-erectile and total IIEF scores by 6 mo post–focal therapy which was maintained at 1 yr. Also by 1 yr, the majority of treated men were not on any form of medical treatment for their ED. Focal therapy may represent a suitable alternative for men of any age or comorbidity wishing to maintain erectile function.

Author contributions: Tet Yap had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Emberton, Ahmed.
Acquisition of data: Ahmed, Dickinson, Hindley.
Analysis and interpretation of data: Yap, Minhas.
Drafting of the manuscript: Yap, Minhas.
Critical revision of the manuscript for important intellectual content: Yap, Ahmed, Hindley, Guillaumier, McCartan, Dickinson, Emberton, Minhas.
Statistical analysis: Yap, Minhas.
Obtaining funding: Emberton, Ahmed.
Administrative, technical, or material support: Dickinson, McCartan.
Supervision: Emberton.
Other: None.

Financial disclosures: Tet Yap certifies 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: Emberton and Ahmed received funding and/or support from Sonacare Inc, GlaxoSmithKline, Advanced Medical Diagnostics, Sophiris Biocorp, TROD Medical, and Angiodynamics for clinical trials. Emberton is a paid consultant of Steba Biotech. Emberton and Ahmed have received funding from Sonacare Inc. (manufacturers and distributors of the Sonablate 500 high-intensity focused ultrasound device) for conference attendance and lectures at academic meetings. Emberton and Hindley hold shares in Nuada Medical Ltd. and are on the board. All other authors declared no conflicts of interest.

Funding/Support and role of the sponsor: The trials within this report were funded by the UK Medical Research Council, the Pelican Cancer Foundation, Prostate Cancer UK (previously Prostate Action), and St Peters Trust, and sponsored by University College London Hospitals NHS Foundation Trust. We thank the men who agreed to participate in this trial, and Jane Coe and Victor Abu for their invaluable help and support during the duration of the study. Emberton and Ahmed receive funding for other research projects from the Wellcome Trust, National Institute of Health Research-Health Technology Assessment program, National Institute of Health Research-i4i program, the US National Institute of Health—National Cancer Institute, and Prostate Cancer UK. Emberton receives funding in part from the UK National Institute of Health Research University College London Hospitals/University College London Biomedical Research Centre.

References

[1] Ljungberg B, Bensalah K, Bex A, et al. EAU Guidelines on Renal Cell Carcinoma, updated 2015. http://uroweb.org/wp-content/uploads/10-Renal-Cell-Carcinoma_LR.pdf

[2] Ahmed HU, Pendse D, Illing R, et al. Will focal therapy become standard of care for men with localised prostate cancer? Nat Clin Pract Oncol 2007;4:632–42.

[3] Valerio M, Ahmed HU, Emberton M, et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. Eur Urol 2014;66:732–51.

[4] Ahmed HU, Berge V, Bottomley D, et al. Can we deliver randomized trials of focal therapy in prostate cancer? Nat Rev Clin Oncol 2014;11:482–91.

[5] Ahmed HU, Dickinson L, Charman S, et al. Focal ablation targeted to the index lesion in multifocal localised prostate cancer: A prospective development study. Eur Urol 2015;68:927–36.

[6] Ahmed HU, Freeman A, Kirkham A, et al. Focal therapy for localised prostate cancer: a phase I/II trial. J Urol 2011;185:1246–54.

[7] Ahmed HU, Hindley RG, Dickinson L, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol 2012;13:622–32.

[8] Madersbacher S, Marberger M. High-energy shockwaves and extracorporeal HIFU. J Endourol 2003;17:667–72.

[9] Cordeiro ER, Cathelineau X, Thuroff S, et al. HIFU for definitive treatment of prostate cancer. BJU Int 2012;110:1228–42.

[10] McCullough A, Kau E, Kaci L, Lepor H. A 12 month longitudinal study of treatment seeking behavior in 200 men after radical retropubic prostatectomy. J Urol 2000;169:379.

[11] Andrea Salonia, Burnett Arthur L, Markus Graefen, et al. Prevention and management of postprostatectomy sexual dysfunctions part 2: Recovery and preservation of erectile function, sexual desire and orgasmic function. Eur Urol 2012;62:273–86.

[12] Crouzet S, Chapelon JY, Rouvière O, et al. Whole-gland ablation of localised prostate cancer with high-intensity focused ultrasound: oncologic outcomes and morbidity in 1002 patients. Eur Urol 2014;65:907–14.

[13] Berge V, Dickinson L, McCartan N, et al. Morbidity associated with primary high intensity focused ultrasound and redo high intensity focused ultrasound for localised prostate cancer. J Urol 2014;191:1764–9.

[14] Ganzer R, Fritsche HM, Brandtner. A fourteen-year oncological and functional outcomes of high-intensity focused ultrasound in localised prostate cancer. BJU Int 2013;112:322–9.

[15] Barret E, Ahallal Y, Sanchez-Salas R, et al. Morbidity of focal therapy in the treatment of localised prostate cancer. Eur Urol 2013;63:618–22.

[16] Inoue Y, Goto K, Hayashi T, et al. Transrectal high-intensity focused ultrasound for the treatment of localised prostate cancer. Int J Urol 2011;18:358–62.

[17] Elterman DS, Barkin J, Radomski SB, et al. Results of HIFU treatment of prostate cancer: early Canadian experience at a single centre. Can J Urol 2011;18:6037–42.

[18] Shoji S, Nakano M, Nagata Y, et al. Quality of life following HIFU for the treatment of localised prostate cancer: a prospective study. Int J Urol 2010;17:715–9.

[19] Ripert T, Azémar MD, Ménard J, et al. Transrectal HIFU treatment of localised prostate cancer. Prostate Cancer Prostatic Dis 2010;13:132–7.

[20] Ahmed HU, Zacharakis E, Dudderidge T, et al. HIFU in the treatment of primary prostate cancer: the first UK series. Br J Cancer 2009;101:19–26.

[21] Uchida T, Shoji S, Nakano M, et al. Transrectal high-intensity focused ultrasound for the treatment of localised prostate cancer: eight-year experience. Int J Urol 2009;16:881–6.

[22] Blana A, Murat FJ, Walter B, et al. First analysis of the long-term results with transrectal HIFU in patients with localised prostate cancer. Eur Urol 2008;53:1194–203.

[23] Blana A, Rogenhofer S, Ganzer R, et al. Eight years' experience with high-intensity focused ultrasonography for treatment of localised prostate cancer. Urology 2008;72:1329–33.
[24] Sumitomo M, Hayashi M, Watanabe T, et al. Efficacy of short-term androgen deprivation with high-intensity focused ultrasound in the treatment of prostate cancer in Japan. Urology 2008;72:1335–40.
[25] Poissonnier L, Chapelon JY, Rouvière O, et al. Control of prostate cancer by transrectal HIFU in 227 patients. Eur Urol 2007;51:381–7.
[26] Blana A, Rogenhofer S, Ganzer R, et al. Morbidity associated with repeated transrectal high-intensity focused ultrasound treatment of localised prostate cancer. World J Urol 2006;24:585–90.
[27] Colombel M, Poissonnier L, Martin X, et al. Clinical results of the prostate HIFU. Project Eur Urol 2006;5:491–4.
[28] Uchida T, Ohkusa H, Nagata Y, et al. Treatment of localised prostate cancer using high-intensity focused ultrasound. BJU Int 2006;97:56–61.
[29] Uchida T, Ohkusa H, Yamashita H, et al. Five years' experience of transrectal high-intensity focused ultrasound using the Sonablate device in the treatment of localised prostate cancer. Int J Urol 2006;13:228–33.
[30] Gelet A, Chapelon JY, Bouvier R, et al. Transrectal high intensity focused ultrasound for the treatment of localised prostate cancer: factors influencing the outcome. Eur Urol 2001;40:124–9.
[31] Gelet A, Chapelon JY, Bouvier R, et al. T ransrectal high-intensity focused ultrasound: minimally invasive therapy of localised prostate cancer. Endourol 2000;14:519–28.
[32] Van Velthoven R, Aoun F, Limani K, Narahari K, Lemort M, Peltier A. Primary zonal high intensity focused ultrasound for prostate cancer: Results of a prospective phase 2a feasibility study. Prostate Cancer 2014;2014:756189.
[33] Burnett AL, Aus G, Canby-Hagino Ed, et al. Erectile function outcome after clinically localised prostate cancer treatment. J Urol 2007;178:597–601.
[34] Chou R, Dana T, Bougatsos C, et al. Treatments for localised prostate cancer: systematic review to update the 2002 U.S. Preventive Services Task Force Recommendation: Evidence Syntheses no. 91, Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.
[35] Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localised prostate cancer. N Engl J Med 2013;368:436–45.
[36] Kendirci M, Hellstrom WJ. Current concepts in the management of erectile dysfunction in men with prostate cancer. Clin Prostate Cancer 2004;3:87–92.
[37] Walz J, Burnett AL, Costello AJ, et al. A critical analysis of the current knowledge of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. Eur Urol 2010;57:179–92.
[38] Leungwattanakij S, Bivalacqua TJ, Usta MF, et al. Cavernous neurotomy causes hypoxia and fibrosis in rat corpus cavernosum. J Androl 2003;24:239–45.
[39] Vignozzi L, Filippi S, Morelli A, et al. Cavernous neurotomy in the rat is associated with the onset of an overt condition of hypogonadism. J Sex Med 2009;6:1270–83.
[40] Carrier S, Zvara P, Nunes L, et al. Regeneration of nitric oxide synthase-containing nerves after cavernous nerve neurotomy in the rat. J Urol 1995;169:1722–7.
[41] User HM, Hairston JH, Zelner DJ, et al. Penile weight and cell subtype specific changes in a post-radical prostatectomy model of erectile dysfunction. J Urol 2003;169:1175–9.
[42] Mooreland RB. Is there a role of hypoxemia in penile fibrosis: A viewpoint presented to the Society for the Study of Impotence. Int J Impot Res 1998;10:113–20.
[43] Li LY, Lin Z, Yang M, et al. Comparison of penile size and erectile function after HIFU and cryoablation for localised prostate cancer: a prospective pilot study. J Sex Med 2010;7:3135–42.
[44] Frey AU, Sønksen J, Fode M. Neglected side effects after radical prostatectomy: a systematic review. J Sex Med 2014;11:374–85.