

Review

Focal Therapy for Prostate Cancer: The Impact on Sexual Function

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Abstract: Focal therapy (FT) has emerged as a potential treatment for localized prostate cancer (PCa) with encouraging functional outcomes. According to the compelling evidence based on meta-analyses and recent trials, erectile function (EF) is mostly retained at 6 and 12 months after FT when compared to baseline. These findings are consistent across different energy sources reported to date. However, overall, quality of life, including impotence, was not the endpoint for most studies. Additionally, impotency has not been consistently reported in most of the recent literature. Furthermore, confounding factors such as baseline potency and usage of phosphodiesterase 5 inhibitors (PDE5-I) were also frequently undisclosed. Long-term functional outcomes are awaited. To fully comprehend how FT affects EF, more extensive long-term randomized clinical trials using EF as a primary outcome are needed.

Keywords: prostate cancer; focal therapy; erectile function



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1. Introduction

Focal therapy (FT) is a promising treatment option for men with localized prostate cancer. The premise is that cancerous foci are selectively treated while sparing healthy prostate tissue and critical components including the urethral sphincter and neurovascular bundles [1,2]. Thus, sexual and urinary outcomes are preserved while cancer control is achieved.

The goal of this narrative review is to describe the most updated and high evidence level research on erectile function (EF) and FT. Herein, we report the EF of the five most frequently utilized FT energy sources to treat prostate cancer (PCa) between 2015 and 2020 [1,2]

2. Focal Therapy Modalities and the Impact on Sexual Function

2.1. High-Intensity Focused Ultrasound (HIFU)

HIFU is a technique that uses sonic waves generated by a transducer to accurately transfer thermal energy to the target tissue, destroying it by mechanical, thermal, and cavitation effects [3].

In a study, Abreu et al. [4] reported on 47 patients who were retrospectively examined for functional outcomes and underwent HIFU and completed baseline and post-HIFU questionnaires. The median baseline International Index of Erectile Function (IIEF)-5 [5] score was 22 at baseline vs. 21 ($p = 0.99$) post-HIFU (best value within 2 years), demonstrating excellent potency preservation.

A study conducted by Lovegrove et al. [6] analyzed a total of 355 men that underwent focal HIFU procedures and 65 men that underwent a repeat focal HIFU. After a single focal

HIFU treatment, the mean change in IIEF (EF domain) was -0.4 ($p = 0.02$) at 1–2 years, with no subsequent decline. Erectile dysfunction was reported in 9.9% of men at baseline, 20.8% at 1–2 years and 18.3% at 2–3 years (baseline vs. 1–2 years, $p = 0.08$; 1–2 years vs. 2–3 years, $p = 0.7$). After the second focal HIFU treatment, a mean decrease in EF score of -0.2 at 1–2 years ($p = 0.6$) occurred.

2.2. Cryotherapy (CRYO)

CRYO uses alternating cycles of tissue freezing and thawing to permeabilize cellular membranes and cause apoptosis and cell death [3].

Marra G et al. [7] analyzed long-term outcomes in two prospective series of 121 patients undergoing CRYO and 459 patients on active surveillance (AS) for the treatment of low- to intermediate-risk PCa. The median IIEF-5 at baseline and after CRYO were 10 and 14.5 ($p = 0.02$), respectively.

Shah et al. [8] examined 58 men within a prospective registry who received focal CRYO for mostly anterior clinically significant localized PCa. The IIEF (EF domain), recovery was evaluated up to 18 months after CRYO. The likelihood of recovering to baseline function was 85% at 12 months, and 89% at both 18 and 24 months. Only the preoperative IIEF-EF score (hazard ratio 0.96, 95% confidence interval [CI] 0.93–0.999, $p = 0.04$) was an independent predictor of a worse EF outcome. One of the key limitations was that only approximately 50% of the patients answered the questionnaire.

2.3. Vascular Targeted Photodynamic Therapy (VTP)

VTP generates radical oxygen species in the lighted area by using a light-activated intravenous drug that causes vascular necrosis and tumor death [3].

In a study conducted by Lebdaï et al. [9], 82 patients with low-risk PCa who received VTP with padeliporfin were assessed prospectively. The median IIEF-5 was 23 at baseline, 20 at 6 months, and 22 at 12 months. Since the IIEF-5 score at 12 months was comparable to the baseline, the impact on EF 12 months after VTP is minimum.

Azzouzi et al. [10] conducted a phase III randomized controlled trial to compare 206 patients undergoing VTP vs. 207 patients on AS. Although transient worsening in IIEF-15 score was observed in VTP group, the score became similar between the groups after 24 months follow-up. Adverse events were identified and graded with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Grade 1–2 and 3 ejaculation failure were observed 7% and 1% in VTP group, and <1% and 0% in AS group, respectively. Grade 1–2 and 3 erectile dysfunctions occurred 37% and 1% in VTP group, and 10% and 1% in AS group, respectively.

2.4. Irreversible Electroporation (IRE)

IRE causes apoptosis and cell death by creating pores in the cell membrane using electrical pulses between electrodes [3].

Colletini et al. [11] conducted a prospective phase II trial in which 30 patients with localized low-risk PCa were treated with IRE and their oncologic and functional outcomes were examined prospectively. At baseline, 83% of patients were able to obtain an erection sufficient for sexual intercourse, with a slight decline to 79.3% at 12 months ($p > 0.99$). Median IIEF-5 score was 21 at baseline, 19 at 6 months ($p = 0.4$) and 20 at 12 months ($p = 0.07$).

Prospective analyses of functional outcomes following IRE were performed on 60 patients by Scheltema et al. [12]. Erections sufficient for sexual intercourse were retained in 27 men (68%) out of the 40 potent men at baseline.

2.5. Focal Laser Ablation (FLA)

FLA causes coagulative necrosis and cell death by delivering heat by laser fiber probes implanted transperineally or transrectally into the visible prostate tumor [3].

A single-center prospective trial conducted by Walser et al. [13] reported functional outcomes of 120 patients with low- to intermediate-risk PCa treated with FLA. Median

Sexual Health Inventory for Men (SHIM) score was 24 at baseline, 22 at 6 months, and 22 at 12 months. There were no significant changes in SHIM scores at any time point when compared with baseline ($p = 0.51$).

Two non-randomized prospective trials [14,15] evaluated functional outcomes after FLA in 71 patients. In both studies, SHIM scores decreased from baseline throughout the first 3 months and gradually increased throughout subsequent months, returning to similar baseline scores at 12 months.

3. Impact on Sexual Function Regardless of Focal Therapy Energy Sources

We summarized the findings from the most updated and high evidence level studies on EF following FT in Table 1.

As demonstrated by the comprehensive systematic review and meta-analyses conducted by Fiard et al. [16] the most often utilized questionnaire to evaluate EF after FT for PCa (30/42 studies) was IIEF-5 [4], with completion rates at 18–24 months ranging from 24–100%. After the transient decrease in EF at 3 months (IIEF-5 decline estimate -3.70 [95% CI $-4.43, -2.96$]), improvements were seen at 6 months (-2.18 [$-2.91, -1.46$]) and 12 months (-2.14 [$-2.96, -1.32$]) returning to baseline levels. No statistically significant difference was found among the different energy types at 6 and 12 months ($p = 0.36$ and 0.69 , respectively). Studies reporting significant and long-lasting postoperative decline of EF scores were more likely to involve patients with impaired baseline sexual function. Overall, functional outcomes were not the endpoint and were not consistently reported. Therefore, there might be a risk of underestimation of EF after FT. Lack of randomization was a limitation of most trials.

A total of 6 of the 42 trials that were analyzed, reported using phosphodiesterase 5 inhibitors (PDE5-I) before FT, while twelve reported using PDE5-I following FT. At baseline, 7% to 14% of patients were being treated with PDE5-I. In all but one of the trials, the percentage of men on PDE5-I increased following treatment, ranging from 12.5% to 47% of patients. Overall, the results were acquired from prospective studies or clinical trials; however, confounding factors such as baseline potency rate and usage of PDE5-I were frequently not disclosed.

It should be noted that the IIEF-5 was first created and validated in a group of men with erectile dysfunction who had been in a committed relationship with a female partner for at least six months [22], raising concerns about its applicability to sexual minorities, and its measurement properties have recently come under scrutiny [23]. Additionally, it excludes orgasms, ejaculation, and sexual desire, in favor of a singular focus on erectile function. Only five studies in this analysis employed the IIEF-15 questionnaire, which is more comprehensive and takes into consideration most of these areas. The definition of ED was not clear in most studies.

When compared to radical prostatectomy (RP), radiotherapy (RT), and brachytherapy (BT), results from previously mentioned FT studies are encouraging. A prospective, longitudinal, multicenter study [24] analyzed a cohort of 1027 men with clinical stage T1 and T2 prostate cancer who had elected RP, RT, or BT as primary treatment. At two years following radical treatment, 65% of men in the RP group, 63% of men in the external RT group, and 57% of men in the BT group reported experiencing erectile dysfunction.

Table 1. Summary of erectile functional outcomes of FT studies.

First Author, Year	Study Design	Ablation Modality	Number of Patients	Mean IIEF-5 Difference Compared to Baseline			Questionnaire Used	Definition of ED	Erectile Functional Outcome
				3 mo	6 mo	12 mo			
Fiard, 2022 [16]	SR & MA	HIFU	3/6/12 mo 337/240/356	−4.5	−3.7	−2.5			
Abreu, 2020 [4]	Retrospective analysis	HIFU	47	NR	NR	NR	IIEF-5	NR	Median IIEF-5 score was 22 at baseline vs. 21 post-HIFU ($p = 0.99$).
Lovegrove, 2020 [6]	Multicenter prospective registry	HIFU	Primary HIFU 355 Secondary HIFU 65	NR	NR	−3.0	IIEF-5	NR	Q2 from IIEF-5 was evaluated. The score change between baseline vs. 1–2 yr after primary HIFU was −0.4 ($p = 0.02$).
Rischmann, 2017 [17]	Multicenter prospective trial	HIFU	111	NR	NR	−1.2	IIEF-5	NR	A total of 78% of patients returned to good erectile function defined as IIEF-5 ≥ 16 at 12 mo.
Fiard, 2022 [16]	SR & MA	CRYO	3/6/12 mo 191/191/193	−5.2	−4.0	−1.2			
Marra, 2022 [7]	Single-center prospective registry	CRYO	121	NR	NR	NR	IIEF-5	NR	Median IIEF-5 score was 10 at baseline. After FT, IIEF-5 was 14.5 ($p = 0.02$).
Shah, 2021 [8]	Multicenter prospective registry	CRYO	58	NR	NR	NR	IIEF-15	The threshold and inferiority limit for minimally clinically important differences for the IIEF-EF subdomain was set as ≥ 4 .	Median IIEF-15 score was 31 at baseline, 22 at 3 mo, 29 at 6 mo, 21 at 12 mo.
Gregg, 2021 [18]	Single-center prospective trial	CRYO	20	−18.0	−15.0	−6.0	IIEF-5	NR	Median IIEF-5 score decreased from 29 at baseline to 11 at 3 mo, 14 at 6 mo, 23 at 12 mo, 26 at 18 mo, 18 at 24 mo.
Fiard, 2022 [16]	SR & MA	FLA	3/6/12 mo 127/188/238	−2.3	−2.1	−2.1			
Walser, 2019 [13]	Single-center prospective trial	FLA	120	NR	−2.0	−2.4	SHIM	NR	Median SHIM score was 24 at baseline, 22 at 6 mo, and 22 at 12 mo.
Al-Hakeem, 2019 [14]	Single-center prospective trial	FLA	49	−3.3	−2.5	−1.7	SHIM	NR	Median SHIM score was 19.3 at baseline, 16 at 3 mo, 16.8 at 6 mo, and 17.6 at 12 mo.
Chao, 2018 [15]	Single-center prospective trial	FLA	32	−1.7	NR	−2.0	SHIM	NR	Median SHIM score was 22 at baseline, and 20 after 12 mo
Fiard, 2022 [16]	SR & MA	VTP	3/6/12 mo 28/28/51	−0.2	−0.2	−1.4			

Table 1. Cont.

First Author, Year	Study Design	Ablation Modality	Number of Patients	Mean IIEF-5 Difference Compared to Baseline			Questionnaire Used	Definition of ED	Erectile Functional Outcome
				3 mo	6 mo	12 mo			
Lebdai, 2017 [9]	Single-center prospective trial	VTP	82	NR	−3.0	−1.0	IIEF-5	NR	Median IIEF-5 was 23 at baseline, 20 at 6 mo, 22 at 12 mo
Azzouzi, 2017 [10]	Multicenter randomized controlled phase 3 trial	VTP	206	NR	NR	NR	IIEF-15	NR	Transient worsening in IIEF-15 score was observed in VTP group; however, the score became similar between the groups after 24 months follow-up. Grade 1–2 and 3 ejaculation failure were observed 7% and 1% in VTP group, and <1% and 0% in AS group, respectively. Grade 1–2 and 3 erectile dysfunctions occurred 37% and 1% in VTP group, and 10% and 1% in AS group, respectively.
Taneja, 2016 [19]	Multicenter prospective trial	VTP	28	−3.0	−3.0	−4.0	IIEF-5	NR	Patients had a baseline IIEF-5 score of 18, 14 at 1 mo, 15 at 3 mo, 15 at 6 mo, and 14 at 12 mo. EF declined over time from baseline, but not to dysfunctional levels
Azzouzi, 2015 [20]	MA consists of three phase 2 trials	VTP	117	−4.3	−4.1	NR	IIEF-5	NR	IIEF-5 score was 19.4 at baseline, 12.9 at 1 mo, 15.1 at 3 mo, and 15.3 at 6 mo.
Fiard, 2022 [16]	SR & MA	IRE	3/6/12 mo 16/46/46	0.0	−1.1	−1.4			
Collettini, 2019 [11]	Single-center prospective trial	IRE	30	NR	−2.0	−1.0	IIEF-5	NR	Erections sufficient for intercourse baseline vs. 6 mo vs. 12 mo: 83.3% vs. 66.7% and 79.3%. IIEF-5 scores decreased from 21 at baseline to 19 at 6 mo and 20 at 12 mo.
Scheltema, 2018 [12]	Single-center prospective trial	IRE	60	NR	NR	NR	EPIC	NR	At baseline, 40 men had erections sufficient for intercourse, of whom 27 men (68%) maintained their erectile ability to have intercourse during the course of this study.

Table 1. Cont.

First Author, Year	Study Design	Ablation Modality	Number of Patients	Mean IIEF-5 Difference Compared to Baseline			Questionnaire Used	Definition of ED	Erectile Functional Outcome
				3 mo	6 mo	12 mo			
Valerio, 2017 [21]	Single-center prospective trial	IRE	16	NR	NR	NR	IIEF-15	NR	Erections sufficient for intercourse at baseline were 75% vs. 69% at 6 mo. Probability of returning to baseline value at 24 mo was 89%.

CRYO, cryoablation; ED, erectile disfunction; EPIC, Expanded Prostate Cancer Index Composite; FLA, focal laser ablation; FT, focal therapy; HIFU, High-Intensity Focused Ultrasound; IIEF-5; International Index of Erectile Function; IRE, irreversible electroporation; MA, meta-analysis; NR, not reported; RCT, randomized controlled trial; SHIM, Sexual Health Inventory for Men; SR, systematic review; VTP, Vascular-Targeted Photodynamic treatment.

Men undergoing RP miss ejaculation while they still can achieve a “dry orgasm” [25]. Some patients complain that their orgasm is not as strong or pleasurable as it used to be, although this could be a psychological effect rather than a consequence of RP [26]. Additionally, the loss of a visible ejaculation can be significant for some men and their partners. Although ejaculation dysfunction is not commonly reported among FT studies, three prospective studies on focal HIFU disclosed ejaculation-related adverse events [27–29]. Out of the 51 patients reported by Ganzer et al. [27], 1 presented with ejaculation pain, and 1 developed aspermia. Hardenberg et al. [28] reported that 1 out of 24 patients developed anejaculation. Furthermore, in a study by Shoji et al. [29], 70% of patients who had erectile function without using PDE5-I before treatment still maintained ejaculation 12 months after treatment. Noweski et al. [30] reported the results from two clinical phase 2 studies on focal VTP. During a 3.5 yr follow-up of 68 patients, Clavien Dindo grade 1 ejaculation sequelae were reported by 5 patients. Based on these previous studies, ejaculation function may be well preserved by HIFU and VTP in contrast to RP. Further investigations focusing on ejaculation function after FT are warranted.

Furthermore, a study by Kadono et al. [31] evidenced that RP can cause a penile length shortening in the short-term following surgery, with no statistically significant differences at 12 months when compared to baseline. This short-term penile length shortening may also influence a patient’s choice regarding treatment for localized PCa.

4. Conclusions

Overall, focal therapy allowed for sexual function recovery at 1-year after treatment. Prospective randomized controlled trials are needed to better understand the difference between each PCa treatment modality. Prioritizing EF as a primary endpoint would be ideal to see in future studies. FT could be considered a good treatment option for men that desire to maintain sexual function post-treatment.

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