



The use of low-intensity extracorporeal shockwave therapy in management of erectile dysfunction following prostate cancer treatment: a review of the current literature

Ashley N. Matthew¹, Devin E. Rogers¹, Gabrielle Grob¹, Minna Blottner², Sarah Kodama², Sarah C. Krzastek^{1,3}

¹Division of Urology, Virginia Commonwealth University, Richmond, VA, USA; ²School of Medicine, Virginia Commonwealth University School of Medicine, Richmond, VA, USA; ³Division of Urology, Central Virginia VA Health Care System, Richmond, VA, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: SC Krzastek; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sarah C. Krzastek, MD. Division of Urology, Virginia Commonwealth University, 1200 East Broad St., 7th Floor, East Wing, Box 980645, Richmond 23298, VA, USA; Division of Urology, Central Virginia VA Health Care System, Richmond, VA, USA.

Email: Sarah.krzastek@vcuhealth.org.

Background and Objective: Erectile dysfunction (ED) is a prevalent and impactful complication post definitive management of prostate cancer. The mechanism of ED is thought to be secondary to vascular and neural injury as well as corporal smooth muscle damage with resultant fibrosis. The use of penile rehabilitation in ED following treatment for prostate cancer has been studied. Low-intensity extracorporeal shockwave therapy (Li-ESWT) is a novel treatment for ED thought to stimulate neovascularization and nerve regeneration, and as such, has gained interest in treatment of ED related to radical prostatectomy or radiation therapy. Herein, we performed a narrative review on the use of Li-ESWT in management of ED following treatment for prostate cancer.

Methods: A literature review was performed using PubMed and Google Scholar. Studies evaluating Li-ESWT following prostate cancer treatment were included.

Key Content and Findings: We identified three randomized controlled trials and two observational studies that assessed use of Li-ESWT for ED after prostate surgery. Use of Li-ESWT across most studies showed improvements in the International Index of Erectile Function-erectile function (IIEF-EF) domain scores, but this improvement was not statistically significant. Additionally, use of Li-ESWT in an early versus delayed fashion does not appear to affect changes in long-term sexual function scores. No data on use of Li-ESWT after radiotherapy were identified.

Conclusions: There is a paucity of data regarding use of Li-ESWT for penile rehabilitation in treatment of ED post-prostate cancer therapy. Current protocols for Li-ESWT are not standardized and have a limited number of participants with short duration of follow-up. Additional evaluation is needed to determine optimal Li-ESWT protocols. Ideally, studies should have longer follow-up to truly evaluate the clinical significance of Li-ESWT in the treatment of post-prostatectomy ED. Furthermore, the role of Li-ESWT after radiotherapy remains elusive.

Keywords: Extracorporeal shockwave therapy (ESWT); penile rehabilitation; prostatectomy; radiation; erectile dysfunction (ED)

Submitted Nov 30, 2022. Accepted for publication May 09, 2023. Published online May 22, 2023.

doi: 10.21037/tau-22-791

View this article at: <https://dx.doi.org/10.21037/tau-22-791>

Introduction

Erectile dysfunction (ED) affects over 18 million adult males in the USA and has a known negative impact on mental health and quality of life (1-3). The most common type of ED is vasculogenic, which results from abnormalities in the arteries or veins of the penis, causing inadequate blood flow or poor retention of blood in the penis (4). ED may also be psychogenic, relating to heightened anxiety and excess norepinephrine; neurogenic, resulting from a deficit in nerve signaling; or endocrine-related.

There are many steps involved in the initiation and maintenance of an erection resulting in different etiologies of ED when these steps go awry. An erection occurs when nitric oxide (NO) is released from non-adrenergic non-cholinergic (NANC) nerve fibers with sexual stimulation, which activates guanylyl cyclase and increases the concentration of cyclic GMP in the smooth muscle cells of the penis. Parasympathetic cholinergic nerve fibers release acetylcholine which activates adenylyl cyclase and increases the concentration of cyclic AMP. Intracellular calcium then decreases, and the smooth muscle cells of the penis relax, allowing blood to fill the corpus cavernosa. Venous outflow is blocked due to the compression of the subtunical venules which allows the penis to maintain rigidity (4). Any interference in this process can cause ED.

ED is especially prevalent among prostate cancer patients as ED is a common side effect of treatment options including radical prostatectomy (RP) and radiation therapy (RT). A longitudinal study conducted by Alemozaffar *et al.* found that 60% of men who underwent RP and were potent prior to surgery had ED 2 years following surgery (5). Younger age, fewer comorbidities, lower PSA, and better pretreatment sexual health scores were associated with a greater probability of obtaining an erection two years after prostate cancer treatment (5). An additional factor to consider is surgical experience and expertise. It is well known that RP takes significant technical skill as it is a complex surgery. Thus, incidence of ED post-RP varies across studies (6). Similarly, rates of post-RT ED are also highly variable, ranging from 6% to 70% depending on the modality of radiation delivery (7-9).

Following RP, ED often results from damage to the cavernosal nerves or neuropraxia (10). Nerve sparing techniques have been shown to significantly improve erectile function recovery following RP, yet many patients who undergo a bilateral nerve sparing RP still experience ED in the postoperative period (11). This may be due to

mechanical stretching of the nerves, thermal damage from cautery instruments, ischemic injury, or local inflammation caused by surgery (12). Injury to cavernosal nerves in rats has been shown to induce veno-occlusive dysfunction, or venous leak, and contribute to a loss of corporal smooth muscle cells (13). RP is also associated with an increase in fibrosis of the corpus cavernosum and a loss of elasticity of erectile tissue (14).

Interestingly, ED after RT has a similar pathophysiology to RP with resultant neuronal, vascular endothelial and smooth muscle damage (15-17). Radiation causes cellular death by irreversible DNA damage, and indirect DNA damage from hydroxyl free radicals results in “off-target effects” (18). Neuronal injury has been observed in rat models following radiation (15). Both smooth muscle and endothelial vascular damage lead to corporal fibrosis and ultimately veno-occlusive dysfunction (19). However, unlike RP where ED is often seen in the immediate post-operative period, the effects of RT are gradual, with worsening ED reported 1–2 years post radiation (9).

Given the high prevalence of post-prostate cancer therapy ED, significant attention has been paid to the concept of “penile rehabilitation” via various treatment modalities, including phosphodiesterase-5 inhibitors (PDE5i). PDE5i prevent the degradation of cyclic GMP thus increasing its concentration in the smooth muscle cells of the penis which has been shown to preserve smooth muscle content as well as reduce corporal fibrosis in rats following cavernosal nerve injury (20-23). In addition to PDE5i, other standard penile rehabilitation treatments include vacuum erection devices, intraurethral alprostadil suppositories, and intracavernosal injections (24). While penile rehabilitation following radical prostatectomy is widely practiced, controversy remains regarding the effectiveness of various protocols (25,26).

A novel treatment for ED with promising preliminary results is low-intensity extracorporeal shockwave therapy (Li-ESWT). Unlike other current ED treatment options which provide symptomatic relief, Li-ESWT aims to address the underlying pathophysiology of ED. Li-ESWT uses an electrohydraulic or electromagnetic generator to deliver targeted sound waves to multiple sites on the penis, typically the two corpus cavernosa and two crura, with an energy density of 0.09 mJ/mm² (27). Li-ESWT was first trialed for vasculogenic ED in 2010 based on its ability to promote neovascularization in the heart (28). Li-ESWT has also been shown to induce the synthesis of NO in penile tissue and support stem cell proliferation (29,30). Multiple

Table 1 Literature search strategy summary

Items	Specification
Date of search	July 2022 to March 2023
Databases and other sources searched	PubMed, Google Scholar
Search terms used	“Low-intensity extracorporeal shockwave therapy” “penile rehabilitation prostatectomy” and “erectile dysfunction
Timeframe	No limitation on publication year
Inclusion and exclusion criteria	Inclusion criteria: randomized controls trials, retrospective studies
Selection process	Literature search was conducted independently by GG, AM and DR; consensus was obtained by open discussion.

meta-analyses have suggested that Li-ESWT is an effective treatment for ED and is associated with an improvement in International Index of Erectile Function-erectile function (IIEF-EF) domain scores as well as play a role in neurogenesis (31,32).

Given the role of Li-ESWT in neovasculogenesis and neurogenesis, it is believed that this therapy may have benefit in treatment of post-prostate therapy induced ED. Despite the significant burden of ED among the large number of prostate cancer survivors around the world, there are currently only a limited number of Li-ESWT studies that have been done on patients following treatment for prostate cancer. The goal of this manuscript, therefore, is to review the current literature on the effectiveness of Li-ESWT for management of ED in prostate cancer patients following definitive treatment. We present this article in accordance with the Narrative Review reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-791/rc>).

Methods

To perform this narrative review, we conducted a comprehensive literature review using PubMed and Google Scholar. There were no restrictions on publication years. The search keywords included “low-intensity extracorporeal shockwave therapy”, “penile rehabilitation prostatectomy”, “penile rehabilitation radiotherapy” and “erectile dysfunction”. Literature search was conducted independently by GG, AM, DR and SK. Consensus was obtained by open discussion. We reviewed references in the studies to includes studies that would be relevant to this review. We included all randomized control trials that evaluated the impact of Li-ESWT after prostatectomy. We

included full-text English articles in peer-reviewed journals (*Table 1*).

Restoration of erectile function following therapy for prostate cancer

Penile rehabilitation

ED after RP is common immediately following surgery, with variable recovery over time ranging from 54–90% at 12 months and 63–94% at 24 months (33). These wide ranges may be in part due to differing definitions and methods of evaluating the change in erectile function, aging population with longer follow-up, erectile function status prior to treatment, medical comorbidities, and variability in surgeon skill. The pathophysiology of post-RP ED is multifold, including neural injury, vascular injury, and corporal smooth muscle damage (34,35). Similarly, ED following RT is also highly variable, and may be due to delayed-onset neuronal and vascular endothelial damage. Efforts to perform and evaluate the effectiveness of various penile rehabilitation methods following treatment for prostate cancer have been an area of interest for many years.

Penile rehabilitation is defined as the use of any drug, device or other therapy at or after prostate cancer treatment to maximize erectile function recovery (36). Numerous studies have been conducted to evaluate different penile rehabilitation methods specifically following RP, including pelvic floor physical therapy, regular dosing of sildenafil, vardenafil and tadalafil, flexible dosing of sildenafil and vardenafil, on-demand dosing of vardenafil and tadalafil, alprostadil intracavernosal injection (ICI), intraurethral alprostadil therapy, hyperbaric oxygen, penile vibratory stimulation, aerobic training, tacrolimus, vacuum erection/constriction devices, nerve grafting, platelet-rich-plasma,

and stem cell therapy. Some of these methods are in the early stages of development and the effects of most therapies in post-prostatectomy patients are currently being investigated through systematic reviews and meta-analyses (37–39).

Heterogeneity in the literature identified by these systematic reviews and meta-analyses have led to controversy regarding the efficacy and implementation of penile rehabilitation modalities after prostatectomy. The most recent systematic review on this topic concluded that sildenafil 100 mg regular daily dosing is the best penile rehabilitation strategy, with pelvic floor muscle training also showing effectiveness in increasing the erectile function recovery rate, while on-demand dosing of PDE5i appears to be less effective (38). Conversely, a 2018 Cochrane Review reports that schedule PDE5i may have little or no effect on both short-term and long-term erectile function after prostatectomy (37). Another 2017 systematic review by Liu *et al.* also concluded that administration of PDE5is, vacuum erection devices, and intracorporeal injection after RP can increase erectile function during treatments, but current evidence does not support the idea that penile rehabilitation with PDE5is improves recovery of spontaneous erectile function (39).

Despite advances in methods and new research, penile rehabilitation remains a controversial topic in the medical community. The 2018 AUA guideline on ED gave the moderate recommendation that men who desire preservation of erectile function after treatment for prostate cancer by RP or radiotherapy should be informed that early use of PDE5i post-treatment may not improve spontaneous, unassisted erectile function with level C evidence grade (26,40–44). The panel reported that early PDE5i use had not been shown to improve unassisted erectile function, although most studies reported that PDE5i are effective in assisting erections on-demand during the trials. The guideline also discussed the importance of psychological support in penile rehabilitation efforts and emphasized pre-treatment education regarding post-treatment ED (40–44). Despite the promising trajectory of penile rehabilitation research, these statements are in-line with the research performed at the time and reflect the low-level of evidence in support of different penile rehabilitation techniques.

Few studies have been performed to evaluate the role of Li-ESWT in penile rehabilitation (45–47). Li-ESWT has been shown to aid in peripheral nerve regeneration and neovascularization (32,48,49). As the main pathophysiological mechanisms of ED after prostate cancer

therapy are neural injury, vascular injury, and corporal smooth muscle damage, Li-ESWT may show promise in the realm of penile rehabilitation after prostate cancer treatment.

Use of Li-ESWT following radical prostatectomy

Vardi *et al.* were the first to demonstrate a possible role for shockwave therapy in vasculogenic ED (28). In this study, 20 men with vasculogenic ED underwent shockwave therapy twice a week for 3 weeks which resulted in improvement in the International Index of Erectile Function ED (IIEF-ED) domain score, as well as improvement in erection duration, penile rigidity, and penile endothelial function. While this study was small, it was promising, which has given rise to increased research on this application in the treatment of vasculogenic ED (50–54). Subsequently, Yuan and colleagues performed a systematic review of eight randomized controlled trials which compared Li-ESWT or Li-ESWT + PDE5i to sham treatment and demonstrated that the addition of Li-ESWT resulted in improvements in International Index of Erectile Function Score (IIEF) and Erection Hardness Score (EHS). Generally, Li-ESWT was safe and effective (55). In fact, higher mean IIEF and increases in IIEF and EHS scores across treatment groups have been observed in most RCT that compare Li-ESWT to sham treatment (52). These findings in vasculogenic ED, and the early use of PDE5i following prostatectomy being purported to ameliorate the effects of cavernous nerve injury following surgery (56), have unsurprisingly led to the study of the effects of Li-ESWT on post-prostatectomy ED.

The first study published on the use of Li-ESWT for treatment of ED following bilateral nerve sparing RP was performed by Frey *et al.* (57). Eighteen patients (16 included in the analysis) underwent robotic nerve sparing prostatectomy 1 year prior to inclusion in the study. The Storz Duolith T-Top Ultra[®] device was used to administer treatments twice a week for a 6-week period. 3000 shocks were administered at 5 Hz in doses of 1,000 shockwaves with energy density of 20, 15 and 12 mJ/mm². Shocks were directed at the root of penis, penile shaft, and a few millimeters proximal to glands. Baseline IIEF score was 9.5 (range, 5–20). Improvements were reported at 1- and 12-month following Li-ESWT, with increases in IIEF scores of +3.5 points (9.5–14.5; $P=0.004$) and +1 point (9.5–10; $P=0.04$), respectively. However, most men in the study were on erectogenic agents at baseline including

PDE5i or alprostadil intraurethral suppository in addition to receiving Li-ESWT. While this study did show that Li-ESWT may improve erectile function after bilateral nerve sparing prostatectomy, no study participants were able to have unassisted erections sufficient for intercourse.

Similarly, Baccaglini *et al.* conducted a clinical trial to assess the effect of Li-ESWT following RP (45). In this randomized, open label trial with 2 parallel arms, 77 patients were followed after surgical intervention. Both the control (N=41) and intervention groups (N=36) were started on 5 mg of daily tadalafil after removal of the urethral catheter. The experimental group underwent Li-ESWT using the Renova Direx® device starting 6 weeks post-prostatectomy for a total of 8 weeks, receiving 2,400 shocks per session over 4 regions over the penile shaft and crura at a frequency of 5 Hz and energy density of 0.09 mJ/mm². There was a 2-week PDE5i washout period for both arms where tadalafil was stopped to assess the final IIEF-5 score without PDE5i use. At 16 weeks post-op, IIEF-5 scores were improved in the Li-ESWT group but the primary end point of ≥4 points between treatment arms was not reached. In fact, no significant difference was observed between the control and intervention group when assessing for an IIEF-5 score ≥17.

Li-ESWT for penile rehabilitation has also been studied post nerve-sparing cystoprostatectomy. The surgical approach of radical prostatectomy differs from radical cystoprostatectomy as additional nerve damage may result with extensive pelvic dissection in the latter. However, rates of ED after cystoprostatectomy have been reported in 20–80% of men which is similar to rates post-prostatectomy (5,58). Additionally, Walsh and Mostwin showed that in nerve sparing radical prostatectomy and radical cystoprostatectomy, rates of potency at 1 year were similar at 86% and 82%, respectively (59). Given similar rates of ED following both surgical procedures, it is likely a similar pathophysiologic mechanism is involved. As such, Li-ESWT may be effective in treatment of ED following radical cystoprostatectomy. In a randomized control trial by Zewin *et al.*, 128 patients who underwent radical cystoprostatectomy were followed for 36 weeks in 3 arms: treatment with Li-ESWT (N=42), treatment with PDE5i (N=43), and no-treatment control (N=43) (46). Patients in the Li-ESWT arm underwent 12 sessions of 1800 shocks per session over 9 weeks, with a frequency of 2 Hz and energy density of 0.09 mJ/mm². This group used the Omnispec ED 1000® device and delivered shocks to 5 sites including to the distal, mid and proximal shaft, and both sides of the crura. At completion of the study, there were no

differences in the IIEF-EF score across groups. However, 16% more patients in the Li-ESWT arm reported recovery of potency.

The aforementioned studies evaluated the use of Li-ESWT immediately post-surgery. However, Inoue and colleagues assessed the role of early *vs.* delayed intervention of Li-ESWT post-prostatectomy in a monocenter study (47). In the early intervention group (N=5), Li-ESWT was performed three times a week for two weeks during admission and once per week in the outpatient setting for six weeks. In contrast, patients in the delayed intervention group (N=11) were treated twice per week for the first 3 weeks following surgery, followed by a 3-week rest period, then an additional 3 weeks of treatments twice per week, for a total of 12 sessions. Patients treated with early or delayed Li-ESWT were compared to 178 patients in the non-intervention group. Using the Dornier Aries® device, 1,500 shockwaves were administered at 2 Hz and 0.09 mJ/mm² to 5 sites on the penis (distal, mid and proximal shaft, and bilateral crura) with each session. In this study, sexual function (SF) scores were used to assess the effect of Li-ESWT on erectile function. Patients in the early Li-ESWT treatment group reported significantly higher baseline SF scores compared to delayed and non-Li-ESWT groups (P=0.0001). SF scores at 6, 9 and 12 months were significantly higher in both the early and delayed Li-ESWT intervention groups over the non-Li-ESWT groups (P=0.0171, 0.0188 and 0.0051 respectively). Though the number of patients who received treatment was low, ultimately, penile rehabilitation with Li-ESWT prior to catheter removal significantly improved sexual function in this study. However, there was no difference in SF between the early and delayed intervention group at each time point.

Motil *et al.* recently showed some promising data with early Li-ESWT intervention and combination therapy with PDE5i for penile rehabilitation (60). In this randomized, single blinded sham-controlled clinical trial, 32 patients were followed 3 months after nerve sparing RP: 16 in the treatment arm and 16 in the placebo arm (baseline IIEF-5 scores of 5.4±1.2 and 5.9±2.4, respectively). Patient in the intervention arm underwent 4 treatments of Li-ESWT over 4 weeks using a PiezoWave 2 device receiving 4000 shocks to the penile shaft and crura with a primary end point of IIEF-5 scores. In the placebo group, a gel head was used to block shockwaves but both interventions produced similar noises. Thus, blinding the intervention. Interestingly, two months post intervention there was a statistically significant improvement in IIEF-5 scores in the Li-ESWT

Table 2 Summary of studies investigating Li-ESWT following radical prostatectomy

Author	Design	Device	Energy (mJ/mm ²)	Tx protocol	Sessions	ED population	Diagnostic work-up	Number	Outcomes
Frey <i>et al.</i> (57)	Obs	Duolith SD1 T-Top	12/15/20	3 zones ×1,000p (3,000/session); 5 Hz	2x/wk (6 wk)	IIEF-5 >22 or between 5–20 at inclusion	IIEF-5	16	Median IIEF-5 change 6 weeks: +3.5
Inoue <i>et al.</i> (47)	Obs	Omni-spec ED1000	0.09	5 zones ×300p (1,500/session); 2 Hz	E: 3x/wk (2 wk), 1x/wk (6 wk) D: 2x/wk (3 wk), no tx (3 wk), 2x/wk (3 wk)	s/p RALP	QOL survey (SF, SB)	C: 178 E: 5 D: 11	SF, SB change C: –22.3; –19.1 E: –38.5, –30.0 D: –20.5; +12.4
Baccaglini <i>et al.</i> (45)	RCT	Renova Direx	0.09	4 zones ×600p (2,400/session); 5 Hz	1x/wk (8 wk)	IIEF-5 >20, age ≤75; tadalafil	IIEF-5, continence (pad/day)	C: 41 Li-ESWT: 36	Final median IIEF C: 12 Li-ESWT: 10
Zewin <i>et al.</i> (46)	RCT	Dornier Aries	0.09	5 zones ×300p (1,500/session); 2 Hz	2x/wk (3 wk) No tx (3 wk) 2x/wk (3 wk)	Tumor confined to the bladder	IIEF-EF, EHS	C: 43 Li-ESWT: 42 PDE5i: 43	IIEF-15 change 9 mo post-operative C: –11.9 Li-ESWT: –7.8 PDE5i: –7.3
Motil <i>et al.</i> (60)	RCT	Piezo Wave 2	0.16	2 zones ×2,000p (4,000/session); 8 Hz	1x/wk (4 wk)	3 mo post-RP, severe ED, no meds	IIEF-5	Sham: 16 Li-ESWT: 16	Mean IIEF-5, 3 mo Sham: 10.9 Li-ESWT: 15.6

Li-ESWT, low-intensity extracorporeal shockwave therapy; Obs, observational; RCT, randomized controlled trial; IIEF, international index of erectile function; EHS, erectile hardness score; QOL, quality of life; RALP, robotic-assisted laparoscopic prostatectomy; SB, sexual bother SF, sexual function; C, control; E, early; D, delayed; p, pulses; wk, week; mo, month; tx, treatment; PDE5i, phosphodiesterase-5 inhibitors.

intervention group over the sham group (10.1±3.4 and 7.6±1.9, respectively $P=0.005$). Of note, after 2 months authors allowed participants to use oral PDE5i and at 6 months topical as well as intracorporeal injections with prostaglandin E1 for penile rehabilitation. By 6 months, both groups had normalized IIEF-5 scores. Thus, early intervention with Li-ESWT in combination erectogenic agents may have a synergistic benefit for early improvement in erectile function, but the clinical significance of this early improvement remains to be seen as all patients had equivalent improvements in IIEF-5 scores by 6 months.

A summary of treatment protocols and outcomes following Li-ESWT in post-prostatectomy patients is outlined in *Table 2*. Though this current literature review does not represent a systematic review of published studies, one is able to see that there remains a paucity of strong data in this realm of Li-ESWT for management of post-prostatectomy ED. Studies involve a relatively small number of patients, with variable treatment protocols,

with maximum follow up of 12 months. The heterogeneity of treatment devices and protocols for use of Li-ESWT in treatment of vasculogenic ED makes interpretation of data difficult, and that heterogeneity and mixed results make it difficult to make any firm conclusions about the use of Li-ESWT for post-prostatectomy ED as well (61). While positive results have been observed in many of these studies (*Table 2*), the lack of standardization across protocols presents a real challenge for implementing Li-ESWT as optimal device settings and treatment protocol remain to be elucidated. While Li-ESWT may be effective alone or in conjunction with concurrent pharmacological penile rehabilitation, further research needs to be done to assess monotherapy or combination therapy. Additionally, further research is needed to determine the mechanism of action of Li-ESWT in treatment of post-prostatectomy ED, as the anatomic location of shockwave application may not target the deep perineum and bladder neck where the majority of prostatectomy-induced nerve damage may be incurred.

Furthermore, there may be differences in outcomes for different prostate cancer risk groups, which should be evaluated in future studies. Specifically, the use of a therapy that stimulates neovascularization and nerve regeneration following a treatment for malignancy should be further studied in terms of oncological outcomes. Overall, while Li-ESWT remains a promising therapy for mild-moderate vasculogenic ED, the concept of penile rehabilitation remains controversial and the role of Li-ESWT for penile rehabilitation requires further study.

Use of Li-ESWT following radiation

Given that vascular and neural injury are the key insult that cause radiation-induced ED, it is plausible that Li-ESWT may have some benefit in the treatment of ED following RT. To date, there are currently no published RCTs or large studies on the use of Li-ESWT after radiotherapy for treatment of ED (9,62). A case report by Chan and Wong demonstrated improvement in the IIEF-5 score from 10 to 19 after 6 sessions of Li-ESWT over 3 weeks following a protocol similar to Vardi *et al.* (28,63). Interestingly, the patient was able to have a satisfactory erection for intercourse during treatment after a short course of Li-ESWT as most protocols are a minimum of 6 weeks (63).

Though Li-ESWT has not been investigated following RT, other restorative therapies have been evaluated with promising results in rats (64,65). Stem cells (SCs) are naturally occurring cells that have the ability to differentiate into various subtypes (66). Qiu *et al.* showed that intracorporal injection of SCs in rat radiation models showed improved erectile function (9,64). Radiation can cause a delayed onset of ED (9). Interestingly, intracorporal injection of SCs in cavernous nerve injury rat models showed improvement of erectile function in acute and delayed setting with increased intra-cavernous pressure after cavernosal nerve stimulation (65). These promising results in radiation animal models demonstrate possible therapeutic avenues for treatment of radiation induced ED. Other restorative therapies for the treatment of ED including platelet rich plasma and nerve transfer (neurorrhaphy) are currently being studied but their efficacy after radiation have yet to be elucidated (67,68).

Conclusions

ED is highly prevalent and impactful and is a common complication following treatment of prostate cancer with

variable rates and degree of post-therapy recovery. ED post-prostatectomy and radiation is thought to be due to several factors, including neural injury, vascular injury, and corporal smooth muscle damage, with subsequent tissue fibrosis. Various treatment options have been investigated for penile rehabilitation following prostatectomy to promote recovery of erectile function, but the benefits of penile rehabilitation remain unclear. Li-ESWT is a novel treatment for ED thought to stimulate neovascularization and nerve regeneration, and as such, has gained interest in treatment of post-prostatectomy ED as well as radiation. However, few studies have investigated Li-ESWT in this realm. Studies on Li-ESWT for post-prostatectomy ED remain limited and currently no RCTs or large studies have been performed in the post-radiation setting. While some data suggests that Li-ESWT may improve erectile function, the clinical significance and duration of these changes remain to be seen. Additionally, while other restorative therapies have been studied, they remain investigative with more research needed to determine their clinical impact.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://tau.amegroups.com/article/view/10.21037/tau-22-791/rc>

Peer Review File: Available at <https://tau.amegroups.com/article/view/10.21037/tau-22-791/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-791/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. *Am J Med* 2007;120:151-7.
2. Korfage IJ, Pluijm S, Roobol M, et al. Erectile dysfunction and mental health in a general population of older men. *J Sex Med* 2009;6:505-12.
3. Tan HM, Tong SF, Ho CC. Men's health: sexual dysfunction, physical, and psychological health--is there a link? *J Sex Med* 2012;9:663-71.
4. Yafi FA, Jenkins L, Albersen M, et al. Erectile dysfunction. *Nat Rev Dis Primers* 2016;2:16003.
5. Alemozaffar M, Regan MM, Cooperberg MR, et al. Prediction of erectile function following treatment for prostate cancer. *JAMA* 2011;306:1205-14.
6. Bratu O, Oprea I, Marcu D, et al. Erectile dysfunction post-radical prostatectomy - a challenge for both patient and physician. *J Med Life* 2017;10:13-8.
7. Hunt AA, Choudhury KR, Nukala V, et al. Risk of erectile dysfunction after modern radiotherapy for intact prostate cancer. *Prostate Cancer Prostatic Dis* 2021;24:128-34.
8. Crook J, Esche B, Futter N. Effect of pelvic radiotherapy for prostate cancer on bowel, bladder, and sexual function: the patient's perspective. *Urology* 1996;47:387-94.
9. Mahmood J, Shamah AA, Creed TM, et al. Radiation-induced erectile dysfunction: Recent advances and future directions. *Adv Radiat Oncol* 2016;1:161-9.
10. Campbell JD, Burnett AL. Neuroprotective and Nerve Regenerative Approaches for Treatment of Erectile Dysfunction after Cavernous Nerve Injury. *Int J Mol Sci* 2017;18:1794.
11. Tal R, Valenzuela R, Aviv N, et al. Persistent erectile dysfunction following radical prostatectomy: the association between nerve-sparing status and the prevalence and chronology of venous leak. *J Sex Med* 2009;6:2813-9.
12. Burnett AL. Erectile function outcomes in the current era of anatomic nerve-sparing radical prostatectomy. *Rev Urol* 2006;8:47-53.
13. Ferrini MG, Kovanecz I, Sanchez S, et al. Fibrosis and loss of smooth muscle in the corpora cavernosa precede corporal veno-occlusive dysfunction (CVOD) induced by experimental cavernosal nerve damage in the rat. *J Sex Med* 2009;6:415-28.
14. Iacono F, Giannella R, Somma P, et al. Histological alterations in cavernous tissue after radical prostatectomy. *J Urol* 2005;173:1673-6.
15. Ashcraft KA, Hannan JL, Eichenbaum G, et al. Clarifying the Relative Impacts of Vascular and Nerve Injury That Culminate in Erectile Dysfunction in a Pilot Study Using a Rat Model of Prostate Irradiation and a Thrombopoietin Mimetic. *Int J Radiat Oncol Biol Phys* 2019;103:1212-20.
16. Raina R, Agarwal A, Goyal KK, et al. Long-term potency after iodine-125 radiotherapy for prostate cancer and role of sildenafil citrate. *Urology* 2003;62:1103-8.
17. Castle KD, Kirsch DG. Establishing the Impact of Vascular Damage on Tumor Response to High-Dose Radiation Therapy. *Cancer Res* 2019;79:5685-92.
18. Baskar R, Dai J, Wenlong N, et al. Biological response of cancer cells to radiation treatment. *Front Mol Biosci* 2014;1:24.
19. Mulhall J, Ahmed A, Parker M, et al. The hemodynamics of erectile dysfunction following external beam radiation for prostate cancer. *J Sex Med* 2005;2:432-7.
20. Corbin JD. Mechanisms of action of PDE5 inhibition in erectile dysfunction. *Int J Impot Res* 2004;16 Suppl 1:S4-7.
21. Mulhall JP, Müller A, Donohue JF, et al. The functional and structural consequences of cavernous nerve injury are ameliorated by sildenafil citrate. *J Sex Med* 2008;5:1126-36.
22. Kovanecz I, Rambhatla A, Ferrini MG, et al. Chronic daily tadalafil prevents the corporal fibrosis and veno-occlusive dysfunction that occurs after cavernosal nerve resection. *BJU Int* 2008;101:203-10.
23. Sirad F, Hlaing S, Kovanecz I, et al. Sildenafil promotes smooth muscle preservation and ameliorates fibrosis through modulation of extracellular matrix and tissue growth factor gene expression after bilateral cavernosal nerve resection in the rat. *J Sex Med* 2011;8:1048-60.
24. Mobley DF, Khera M, Baum N. Recent advances in the treatment of erectile dysfunction. *Postgrad Med J* 2017;93:679-85.
25. Teloken P, Mesquita G, Montorsi F, et al. Post-radical prostatectomy pharmacological penile rehabilitation: practice patterns among the international society for sexual medicine practitioners. *J Sex Med* 2009;6:2032-8.
26. Burnett AL, Nehra A, Breaux RH, et al. Erectile Dysfunction: AUA Guideline. *J Urol* 2018;200:633-41.
27. Muncey W, Sellke N, Kim T, et al. Alternative Treatment

- for Erectile Dysfunction: a Growing Arsenal in Men's Health. *Curr Urol Rep* 2021;22:11.
28. Vardi Y, Appel B, Jacob G, et al. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. *Eur Urol* 2010;58:243-8.
 29. Gotte G, Amelio E, Russo S, et al. Short-time non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide induced by shock waves treatment. *FEBS Lett* 2002;520:153-5.
 30. Lin G, Reed-Maldonado AB, Wang B, et al. In Situ Activation of Penile Progenitor Cells With Low-Intensity Extracorporeal Shockwave Therapy. *J Sex Med* 2017;14:493-501.
 31. Rizk PJ, Krieger JR, Kohn TP, et al. Low-Intensity Shockwave Therapy for Erectile Dysfunction. *Sex Med Rev* 2018;6:624-30.
 32. Li H, Matheu MP, Sun F, et al. Low-energy Shock Wave Therapy Ameliorates Erectile Dysfunction in a Pelvic Neurovascular Injuries Rat Model. *J Sex Med* 2016;13:22-32.
 33. Ficarra V, Novara G, Ahlering TE, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. *Eur Urol* 2012;62:418-30.
 34. Mazzola C, Mulhall JP. Penile rehabilitation after prostate cancer treatment: outcomes and practical algorithm. *Urol Clin North Am* 2011;38:105-18.
 35. Clavell-Hernández J, Wang R. The controversy surrounding penile rehabilitation after radical prostatectomy. *Transl Androl Urol* 2017;6:2-11.
 36. Mulhall JP. Penile rehabilitation following radical prostatectomy. *Curr Opin Urol* 2008;18:613-20.
 37. Philippou YA, Jung JH, Steggall MJ, et al. Penile rehabilitation for postprostatectomy erectile dysfunction. *Cochrane Database Syst Rev* 2018;10:CD012414.
 38. Sari Motlagh R, Abufaraj M, Yang L, et al. Penile Rehabilitation Strategy after Nerve Sparing Radical Prostatectomy: A Systematic Review and Network Meta-Analysis of Randomized Trials. *J Urol* 2021;205:1018-30.
 39. Liu C, Lopez DS, Chen M, et al. Penile Rehabilitation Therapy Following Radical Prostatectomy: A Meta-Analysis. *J Sex Med* 2017;14:1496-503.
 40. Walz J, Epstein JI, Ganzer R, et al. A Critical Analysis of the Current Knowledge of Surgical Anatomy of the Prostate Related to Optimisation of Cancer Control and Preservation of Continence and Erection in Candidates for Radical Prostatectomy: An Update. *Eur Urol* 2016;70:301-11.
 41. Schover LR, Fouladi RT, Warneke CL, et al. The use of treatments for erectile dysfunction among survivors of prostate carcinoma. *Cancer* 2002;95:2397-407.
 42. al-Abany M, Steineck G, Agren Cronqvist AK, et al. Improving the preservation of erectile function after external beam radiation therapy for prostate cancer. *Radiother Oncol* 2000;57:201-6.
 43. van der Wielen GJ, van Putten WL, Incrocci L. Sexual function after three-dimensional conformal radiotherapy for prostate cancer: results from a dose-escalation trial. *Int J Radiat Oncol Biol Phys* 2007;68:479-84.
 44. Sadovsky R, Basson R, Krychman M, et al. Cancer and sexual problems. *J Sex Med* 2010;7:349-73.
 45. Baccaglini W, Pazeto CL, Corrêa Barros EA, et al. The Role of the Low-Intensity Extracorporeal Shockwave Therapy on Penile Rehabilitation After Radical Prostatectomy: A Randomized Clinical Trial. *J Sex Med* 2020;17:688-94.
 46. Zewin TS, El-Assmy A, Harraz AM, et al. Efficacy and safety of low-intensity shock wave therapy in penile rehabilitation post nerve-sparing radical cystoprostatectomy: a randomized controlled trial. *Int Urol Nephrol* 2018;50:2007-14.
 47. Inoue S, Hayashi T, Teishima J, et al. Effect of penile rehabilitation with low intensity extracorporeal shock wave therapy on erectile function recovery following robot-assisted laparoscopic prostatectomy. *Transl Androl Urol* 2020;9:1559-65.
 48. Peng D, Tan Y, Reed-Maldonado AB, et al. Molecular mechanism of action of low-intensity extracorporeal shockwave therapy for regenerating penile and peripheral nerves. *Turk J Urol* 2020. [Epub ahead of print]. doi: 10.5152/tud.2020.20419.
 49. Lee JH, Kim SG. Effects of extracorporeal shock wave therapy on functional recovery and neurotrophin-3 expression in the spinal cord after crushed sciatic nerve injury in rats. *Ultrasound Med Biol* 2015;41:790-6.
 50. de Oliveira PS, Ziegelmann MJ. Low-intensity shock wave therapy for the treatment of vasculogenic erectile dysfunction: a narrative review of technical considerations and treatment outcomes. *Transl Androl Urol* 2021;10:2617-28.
 51. Chung E, Bailey W, Wang J. A Prospective, Randomized, Double-Blinded, Clinical Trial Using a Second-Generation Duolith SD1 Low-Intensity Shockwave Machine in Males with Vascular Erectile Dysfunction. *World J Mens Health* 2023;41:94-100.

52. Dong L, Chang D, Zhang X, et al. Effect of Low-Intensity Extracorporeal Shock Wave on the Treatment of Erectile Dysfunction: A Systematic Review and Meta-Analysis. *Am J Mens Health* 2019;13:1557988319846749.
53. Yee CH, Chan ES, Hou SS, et al. Extracorporeal shockwave therapy in the treatment of erectile dysfunction: a prospective, randomized, double-blinded, placebo controlled study. *Int J Urol* 2014;21:1041-5.
54. Olsen AB, Persiani M, Boie S, et al. Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study. *Scand J Urol* 2015;49:329-33.
55. Yuan F, Wang Y, Ma Z, et al. Low-intensity extracorporeal shockwave therapy for erectile dysfunction: an overview of systematic reviews. *Transl Androl Urol* 2021;10:3684-96.
56. Täl R, Teloken P, Mulhall JP. Erectile function rehabilitation after radical prostatectomy: practice patterns among AUA members. *J Sex Med* 2011;8:2370-6.
57. Frey A, Sønksen J, Fode M. Low-intensity extracorporeal shockwave therapy in the treatment of postprostatectomy erectile dysfunction: a pilot study. *Scand J Urol* 2016;50:123-7.
58. Chappidi MR, Kates M, Sopko NA, et al. Erectile Dysfunction Treatment Following Radical Cystoprostatectomy: Analysis of a Nationwide Insurance Claims Database. *J Sex Med* 2017;14:810-7.
59. Walsh PC, Mostwin JL. Radical prostatectomy and cystoprostatectomy with preservation of potency. Results using a new nerve-sparing technique. *Br J Urol* 1984;56:694-7.
60. Motil I, Macik D, Sramkova K, et al. Linear Low-Intensity Extracorporeal Shockwave Therapy as a Method for Penile Rehabilitation in Erectile Dysfunction Patients after Radical Prostatectomy: A Randomized, Single-Blinded, Sham-Controlled Clinical Trial. *Urol Int* 2022;106:1050-5.
61. Porst H. Review of the Current Status of Low Intensity Extracorporeal Shockwave Therapy (Li-ESWT) in Erectile Dysfunction (ED), Peyronie's Disease (PD), and Sexual Rehabilitation After Radical Prostatectomy With Special Focus on Technical Aspects of the Different Marketed ESWT Devices Including Personal Experiences in 350 Patients. *Sex Med Rev* 2021;9:93-122.
62. Nguyen DD, Berlin A, Matthew AG, et al. Sexual function and rehabilitation after radiation therapy for prostate cancer: a review. *Int J Impot Res* 2021;33:410-7.
63. Chan CW, Wong CH. Treatment of radiation-induced erectile dysfunction with low-intensity extracorporeal shock wave: A case report. *Australas Med J* 2017;10:901-3.
64. Qiu X, Villalta J, Ferretti L, et al. Effects of intravenous injection of adipose-derived stem cells in a rat model of radiation therapy-induced erectile dysfunction. *J Sex Med* 2012;9:1834-41.
65. Qiu X, Fandel TM, Ferretti L, et al. Both immediate and delayed intracavernous injection of autologous adipose-derived stromal vascular fraction enhances recovery of erectile function in a rat model of cavernous nerve injury. *Eur Urol* 2012;62:720-7.
66. Lin G, Banie L, Ning H, et al. Potential of adipose-derived stem cells for treatment of erectile dysfunction. *J Sex Med* 2009;6 Suppl 3:320-7.
67. Poullos E, Mykoniatis I, Pyrgidis N, et al. Platelet-Rich Plasma (PRP) Improves Erectile Function: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial. *J Sex Med* 2021;18:926-35.
68. Souza Trindade JC, Viterbo F, Petean Trindade A, et al. Long-term follow-up of treatment of erectile dysfunction after radical prostatectomy using nerve grafts and end-to-side somatic-autonomic neurotaphy: a new technique. *BJU Int* 2017;119:948-54.

Cite this article as: Matthew AN, Rogers DE, Grob G, Blottner M, Kodama S, Krzastek SC. The use of low-intensity extracorporeal shockwave therapy in management of erectile dysfunction following prostate cancer treatment: a review of the current literature. *Transl Androl Urol* 2023;12(6):1023-1032. doi: 10.21037/tau-22-791