A systematic review of the role of penile rehabilitation in prostate cancer patients receiving radiotherapy and androgen deprivation therapy

Introduction

Prostate cancer is the second most common cancer in the UK and the most common cancer in men, accounting for approximately 46,700 new cases in 2014 and 13% of all new cancer cases in the UK (1). With greater than 8 in 10 men diagnosed with prostate cancer surviving their disease for ten years or more in England and Wales, the side effects of prostate cancer treatment can have profound effects on patient's quality of life for extended periods of time into survivorship (1).

Treatment induced erectile dysfunction (ED) is an inability to gain and maintain an erection sufficient for sexual activity. It is linked with changes to penile blood flow, androgen deprivation therapy (ADT) mediated loss of libido, nerve damage, psychological changes including depression, anxiety, relationship difficulties, and treatment induced tiredness. Erectile function is a significant marker for quality of life (QoL) (2). With the combined approach of radiotherapy and ADT, the psychological impact of ED can be devastating for patients (3, 4). Erectile function that has been lost cannot easily be regained, highlighting the importance of timely intervention (5).

Penile rehabilitation is defined as "the use of any device, pharmacologic agent, or intervention to promote male erectile function (including girth, length, curvature and quality and longevity of tumescence) as a primer before and after any insult to the penile erectile physiologic axis" (5). The concept of penile rehabilitation came to prominence following the release of sildenafil in 1998 (6). Since then there has been much debate on the potential benefit of penile rehabilitation (5), but little in the way of convincing supporting evidence. Current options for treatment of ED in prostate radiotherapy patients are summarised in Table 1.

No gold standard guidelines exist for the management of ED in patients following radiotherapy and ADT (7-9). Current management for prostate cancer induced ED is consultant dependant and unsupported by high quality data (10-12). NICE guidelines advise that men have early and continuing access to specialist erectile dysfunction services with phosphodiesterase type 5 (PDE5) inhibitors as first-line therapy (13).

Despite these recommendations, penile rehabilitation is not widely discussed by health care professionals. ED is much less likely to be broached with patients than other side effects (14). Reasons for this include inadequate knowledge, a fear of invading patient privacy and embarrassment (14, 15). Thus, men are rarely asked to discuss psychosexual side effects during treatment (16) making it difficult to assess the extent of the problem and address it (17-20).

The significant physical side effects of prostate cancer treatment have a negative impact on psychological wellbeing with psychosexual problems growing in importance over time (16, 21). Prompt identification coupled with advice and treatment can minimise their impact and consequently improve psychological wellbeing and quality of life. This effect continues into survivorship, strengthening the case for tackling the effects of ED in a more methodological and structured way

(21). This systematic review, therefore, aimed to appraise the evidence base for penile rehabilitation management and identify evidence-based recommendations for practice.

Table 1. Erectile dysfunction interventions commonly used by prostate radiotherapy patients

Intervention	Mechanism	Benefits	Barriers to Use
PDE5 Inhibitors	Oral pharmaceutical preventing breakdown of nitric oxide (NO). NO is produced during erection and PDE5 inhibitors prevent NO breakdown leading to an increase in blood flow and penile tumescence and passive occlusion of efferent blood flow leading to erection.	Convenience of use	Require sexual stimulation to function. Reduces spontaneity of sexual activity. Contraindicated with certain common medications including nitrates for angina
Alprostadil IV	Intravenous pharmaceutical that induces penile vascular smooth muscle relaxation, increases blood flow and generates erection without reliance on NO production or an intact nervous pathway.	Faster acting than PDE5 inhibitors	Require manual dexterity to use. Interfere with spontaneity of sexual activity. Injection into penis can be a psychological barrier. Can cause pain, bruising, bleeding, scars, bending of the penis or priapism
Intraurethral alprostadil	Urethral pessary with same mechanism as above.	Faster acting than PDE5 inhibitors	As above. Insertion into penile meatus can be psychological barrier for some patients to use. Can cause local irritation to urethra
Vacuum Erection Devices (VEDs)	Vacuum device placed over penis to cause negative pressure and draw blood into the penis	Can work where pharmacological interventions fail	Require physical dexterity to operate. Interfere with spontaneity of sexual activity. Can be uncomfortable to use. Causes unnatural appearance of erection
Penile prosthesis	Inflatable or rigid implant placed into corpora. Bypasses the physiological requirements for erection	Works if previous interventions failed On-demand erections possible and sufficiently rigid for anal intercourse	Irreversible, invasive and expensive surgical procedure
Psychosexual counselling	Psychological interventions to tackle emotional and psychological barriers to erection	Tackles root psychological causes Realigns current function with desired function.	Patient reluctance to engage with difficult or upsetting topics. Patients can be in denial or believing the problem to be physiological in nature

Method

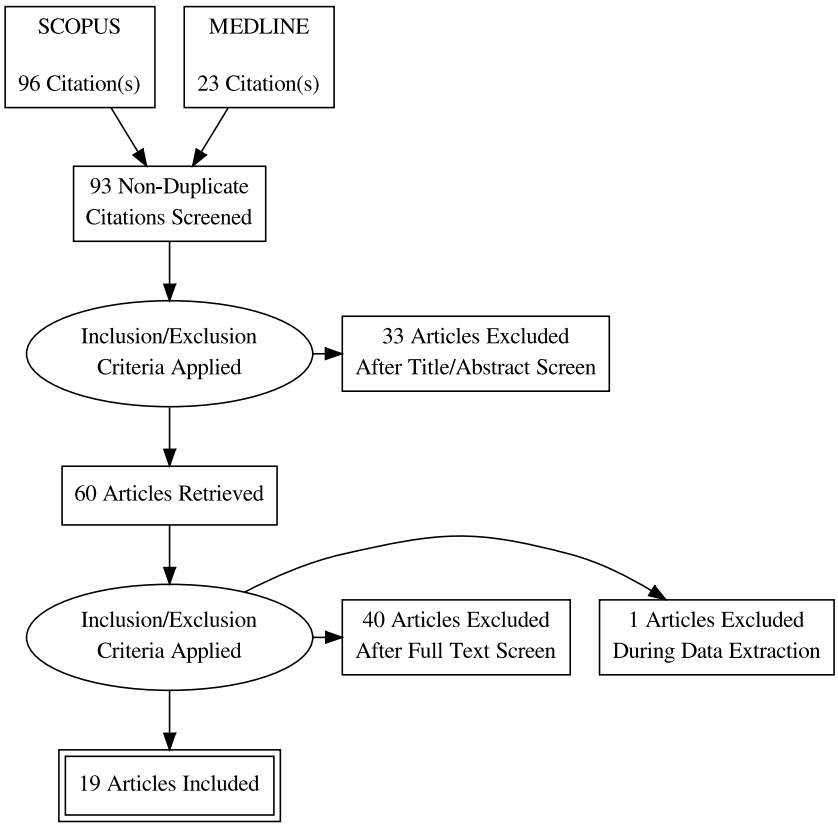
A systematic review of the evidence base was undertaken using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (22). The SCOPUS and Medline (EBSCO) databases were searched using boolean combinations of the key words shown in Table 2.

Additional papers were located from reference lists of returned papers and retrieved . Articles dating from 1998 were included since this corresponds with the advent of sildenafil and the first common usage of the term penile rehabilitation. Articles were included if they related to patients with ED receiving prostate radiotherapy with or without ADT. Articles were excluded if they were not written in English, or if their focus was patients who had undergone prostatectomy or other pelvic surgery likely to cause ED as well as patients with known pre-existing ED. The PRISMA diagram in Figure 1 shows the numbers of papers rejected at each stage of the selection process. For the remaining papers, study quality was graded using Oxford Centre for Evidence-based Medicine – Levels of Evidence and the Scottish Intercollegiate Guidelines Network (23, 24).

Table 2. Search terms

Theme	Keyword
Intervention	Penile rehabilitation; PDE5 inhibitors; Sildenafil; Vardenafil; Tadalafil; Prostaglandin e1; Alprostadil; MUSE; Vacuum erection device; Vacuum constriction device; psych*; counsel*
Erectile dysfunction	Erectile dysfunction; Impoten*; Sexual w/2 dysfunction
ADT	Androgen deprivation therapy; Hormon*; Chemical castration
Radiotherapy	Radiotherap*; Radiation therap*
Prostate cancer	Prostate cancer; Neoplas* w/2 prostate

Figure 1. PRISMA Diagram demonstrating selection of final articles from database searches



Results

This study identified nineteen papers on penile rehabilitation in prostate radiotherapy patients, consisting of eight randomised controlled trials (RCTs), three systematic reviews and eight case studies. Table 3 summarises the key findings from these studies along with appraisal of their methods. Studies in this area are generally deemed of low quality due to use of small recruitment convenience samples that are not sufficiently robust to generate evidence-based findings (25). Four of the eight trials were by the same author (25-28)

Table 3: Summary of Evidence

Study	Design	Participants	Findings	SIGN [24] Rating	Conflicts of Interest
Ohebshalom et al. 2005	Case series	110	More effective in patients post brachytherapy (BT) than external beam radiotherapy. Sildenafil appears to be useful in this group, participants on ADT excluded	Level 4 (HIGH)	None listed

Weber et al. 1999	Case series	100	Sildenafil appears to be useful in this group. Less useful in ADT patients.	Level 4 (HIGH)	None declared
Schover et al. 2002	Case series	1236	Men prefer non-invasive treatments. Benefits of incorporating sexual counselling in to treatment. Sildenafil works to varying degrees from different studies.	Level 4 (HIGH)	None
Teloken et al. 2007	Case series	152	ADT compounded the effects of ED	Level 4 (HIGH)	None
Valicenti et al. 2001	Case series	24	Sildenafil citrate is effective for restoring erectile function and associated satisfaction back to baseline before treatment.	Level 4 (HIGH)	None
Pahlajani et al. 2010	Case series	69	There was a 50% decline in erectile function at 6 and 12 months post BT treatment. Sildenafil did appear useful	Level 4 (HIGH)	None
Schiff et al. 2006	Case series	210	The early use of PDE5 inhibitors after BT is associated with a significant improvement in and maintenance of erectile function compared with late use	Level 4 (HIGH)	None
Teloken et al. 2009	Case series	152	Older age, higher radiation dose, increased time since radiation, and longer time of ADT are independent predictors of decreased sildenafil response after RT for prostate cancer	Level 4 (HIGH)	None
Watkins et al. 2011	RCT	61	Only about one in four patients respond better to sildenafil than to placebo; more study needed.	Level 1 (HIGH)	None
Zelefsky et al. 2014	RCT	279	Patients reported significantly improved erectile function for sildenafil compared to placebo. Radiotherapy induced trauma to the cavernous tissue vascular supply may undergo rehabilitation and repair during sildenafil administration. Sildenafil not as useful in patients on ADT.	Level 1 (HIGH)	Drugs supplied by pharma company
Ilic et al. 2013	RCT	27	There was no evidence that sildenafil provides long-term erectile function for patients	Level 1 (HIGH)	None

			Regular use of sildenafil may improve short-term erectile function		
Ricardi et al. 2010	Randomised, not blinded, no control	52	Both tadalafil formulations generated significantly higher response rates compared with baseline. Once-a-day 5-mg dosing showed higher compliance and marginally better toxicity profile Daily dosing allowed for more spontaneity and less need for planning sexual activity.	Level 1 (HIGH)	None
Incrocci et al. 2001	RCT, double blind, placebo controlled crossover	60	Sildenafil was shown to be effective. Higher dose of 100mg vs 50mg needed post radiotherapy	Level 1 (HIGH)	Supported by pharma company grant
Incrocci et al. 2003	RCT, double blind, placebo controlled crossover	46	Sildenafil was shown to be effective. Higher dose of 100mg vs 50mg needed post radiotherapy	Level 1 (LOW)	Supported by pharma company grant
Incrocci et al. 2006	RCT, double blind, placebo controlled crossover	60	Tadalafil is a good treatment option for patients with ED after radiotherapy. Potential advantage of tadalafil is its efficacy up to 36 h after dosing, allowing patients less need to plan sexual activity in advance.	Level 1 (HIGH)	Drugs and grant support supplied by pharma company
Incrocci et al. 2007	RCT, double blind, placebo controlled crossover	51	Tadalafil is a good treatment option for patients with ED after radiotherapy. Potential advantage of tadalafil is its efficacy up to 36 h after dosing, allowing patients less need to plan sexual activity in advance.	Level 1 (LOW)	Supported by pharma company grant
Yang et al. 2013	Systematic Review		PDE5 inhibitors were safe and efficacious in the treatment of ED after radiotherapy for prostate cancer	Level 2 (HIGH)	None
Candy et al. 2008	Systematic Review		The positive effects on erectile function do not necessarily confer benefits for the patient or their partner.	Level 2 (HIGH)	None
White et al. 2015	Systematic Review		Chosen experts show limited treatment levels for patients.	Level 2 (HIGH)	None listed

Sildenafil was shown to be effective in improving erectile function in three RCTs (25, 26, 29). One study found sildenafil to be effective only in the short term, with little benefit seen at two-year follow-up. Another showed poor outcomes with only one in four patients experiencing a better response to sildenafil than placebo (2, 30). Tadalafil was found to be effective in all three of the RCTs in which it was used (27, 28, 31).

Comparison between studies was performed where uniform scales such as the International Index of Erectile Function (IIEF) (32, 33) were used. For other studies, direct comparison between studies proved difficult, however, as despite the common usage of IIEF, different metrics were reported. No studies were found that assessed the effectiveness of vacuum erection devices (VEDs), intraurethral alprostadil, intercavernosal injection or penile prosthesis for managing erectile dysfunction induced by radiotherapy. No studies were found relating to issues beyond erectile function such as psychosexual counselling, impacts on relationships, QoL or associated patient reported issues including decreased penile length and testicular shrinkage.

Discussion

Despite the range of physical and pharmaceutical interventions, relevant research focussed solely on the use of PDE5 inhibitors (5) and confirmed therapeutic value for sildenafil and tadalafil. Themes from the reviewed papers related to choice of PDE5 inhibitors, timing of intervention and the impact of ADT. The following discussion addresses these themes.

Choice of PDE5 inhibitor

Studies on tadalafil, a more recent PDE5 inhibitor, are reported as showing promise in penile rehabilitation. Tadalafil remains active in the system for 36 hours, allowing for more spontaneous sexual intercourse without the need for on-demand dosing. Pisansky et al. conducted a large RCT using 5mg daily dose tadalafil for men undergoing single modality radiotherapy for prostate cancer (34). This failed to demonstrate improvements in overall erectile function and satisfaction for patients and partners compared to placebo (34).

Incrocci et al. conducted a total of four RCTs into sildenafil and tadalafil between 2001 and 2007 and showed a statistically significant improvement in both studies for around 50% of men receiving the drugs (25, 27). A subsequent open-label extension to both trials, involved 51 participants using sildenafil and 46 progressing on tadalafil (26, 28). Both groups were shown to have a good response in the open label phase, higher than or equal to that in the respective initial phases.

Timing of intervention

Encouraging results (35) indicated that radiotherapy induced trauma to the erectile vascular supply may undergo rehabilitation and repair with early administration of sildenafil. Similar research in patients with erectile dysfunction not associated with prostate cancer treatment supports these findings (36). This provides hope that patients can regain lost function rather than endure palliation of symptoms.

A range of evidence (6, 35, 37, 38) indicates the benefits of early intervention for reducing long-term loss of function. Despite this, sildenafil exhibits a significant drop in efficacy two years post radiotherapy (30, 39), possibly due to delayed side-effects. The early use of PDE5 inhibitors after brachytherapy (BT) is associated with a significant 50% observed decline in erectile function compared with late use (35, 38).

Zelefsky et al. approached penile rehabilitation from an alternate perspective with prophylactic, rather than reactionary, use of sildenafil (29). Sildenafil was commenced three days prior to radiotherapy and continued daily for six months, demonstrating significantly improved erectile function with 78% of patients on sildenafil reporting functional erection versus 48% on placebo (29). While an overall improvement in scores was seen in both arms at 24-month follow-up, the overall benefit in the sildenafil arm over placebo diminished. These results suggest that sildenafil is effective when taken continuously but also that it does not reverse the physiological changes to the erectile mechanism, over a 6-month period. With psychological factors playing a major contributing role to ED it is also possible that there is a considerable placebo effect of taking the drug.

Evidence suggests improved compliance for daily dosing over on-demand when taken alongside other long-term medication as part of an already established routine (41). The sustained blood level of the drug permits spontaneous activity without the need to plan sexual activity in advance (40). Distancing the strict timing schedule of prescribed medication from sexual intercourse can promote the feeling of independent erectile function without the intrusiveness of the intervention drawing focus to the problem (41). Men show a preference for non-invasive treatments, despite invasive treatments being more effective (42). This would appear to be true not only from a physically invasive perspective, but also in an emotionally invasive way as evidenced by improved compliance on daily dose tadalafil versus on-demand (31).

ADT patients

For ADT patients a low or absent libido, coupled with castrate levels of testosterone, will diminish, or completely preclude, sexual activity, rendering the use of on-demand dosing less effective (43). Daily dosing of PDE5 inhibitors can, however, assist with preservation of nocturnal erections which can maintain oxygenation and nutrition of the corpus callosum and protect erectile function during the 6 to 24 month ADT regime (44). With the greatest physiological changes in erectile function occurring within this time frame, it is important that these patients undergo intervention despite the ADT-mediated lack of sexual desire (41). This can prevent ED upon completion of ADT and consequent return of libido. Study outcomes vary considerably amongst patients on ADT, making recommendations for this group problematic. There have been mixed findings of sildenafil usage in this group (45) although a 2013 paper concluded that PDE5 inhibitors were safe and efficacious (46). Low libido and motivation may limit recruitment into these trials compared to post radical prostatectomy studies (47). The studies for this group all conclude that this group experienced a significant deleterious effect on erectile function which highlights the importance of early intervention (40, 48, 49).

Alternative approaches

There is a general theme of ease of use of oral PDE5 inhibitors that make them a convenient choice for patients and practitioners alike (9, 25-28, 31). It is important not to rely solely on PDE5 inhibitors

as men that try a greater number of treatments for ED were more likely to find one that works and more likely to continue using treatments for ED that produced greater improvements in erectile function. While this may seem intuitively logical, it highlights the need to be persistent in the approach to managing erectile dysfunction in this patient group and touches on the need for combining treatment types to achieve maximum results (42). No studies were identified that evaluated alternatives to PDE5 inhibitors such as alprostadil, VEDs, psychosexual counselling or any other intervention for penile rehabilitation.

Psychosexual issues play an important role for these patients (31, 42, 48) and can influence motivation for seeking assistance with erectile function during radiotherapy (4, 50, 51). Early acknowledgement, counselling and management of these side effects can markedly improve patients QoL (13, 38). While numerous studies for these interventions already exist outside of the area of radiotherapy and ADT (52, 53), further study is needed to determine if any of the learning can be transferred to this patient group.

While the evidence has shown that PDE5 inhibitors can address the issue of physical erectile dysfunction, it is clear that they do not address any psychological issues or aid in preservation of penile length and girth. VEDs have been shown to be useful in this respect for patients post radical prostatectomy suggesting a benefit of combining treatment types, however no studies exist for patients treated with radiotherapy and ADT (5). Further research into a multi-modality approach is urgently required.

Limitations of the evidence base

The four Incrocci trials account for half of the eight RCTs available for this patient group (25-28). When taken as four individual studies this can artificially skew findings towards that of one author. Out of eight papers based on case studies returned in this literature search, two are by the same author (40, 49) and appear to involve the same cohort. Using the same convenience sample cohort for two separate studies can disproportionately represent this small group in the published data (54).

Comparison of findings is limited by inconsistencies in the way data was collected between studies with limited use of baseline measures, low sample sizes and an absence of knowledge of existing co-morbidities reducing validity (2, 25-28, 30, 39, 40, 48, 49, 55). Recruitment and compliance issues associated with this group are a further confounding issue with a recent study closing early due to slow recruitment with only 35% of the planned participants (2). In addition to low sample sizes, participation bias must be considered for these studies with increased motivation of participants skewing results in comparison to the general population.

The literature all utilises a quantitative reductionist approach, using the IIEF to categorise the degree of erectile dysfunction at various stages (33). This distils complex issues into a convenient grading which can overly simplify the issues being investigated and not take the wealth of qualitative data that was used to create it into account (56). Consideration of erectile dysfunction in the reviewed evidence failed to include all activities, such as masturbation or oral sex, that do not require the same level of rigidity as penetrative vaginal sex and may constitute acceptable erectile function for some patients. The current evidence base also failed to account for the needs of men who practice anal sex and the requirement for greater penile rigidity to do so. In treating patients, it is more important to assess end

goals and determine satisfaction with sex life on a relative scale than to universally grade erectile function on an absolute scale.

Conclusion

This review has demonstrated that the evidence base relating to penile rehabilitation consists of a number of quantitative studies focussed on PDE5 inhibitors only. The current quantitative approach has so far failed to deliver robust data on the role of penile rehabilitation in this patient group and repeated quantitative RCTs investigating PDE5 inhibitors are unlikely to yield new information. The data has confirmed the effectiveness of PDE5 inhibitors for ED with timing of intervention being of paramount importance for preservation of erectile function. Additional research into the wider range of penile rehabilitation interventions is urgently required to ensure patients have access to those therapies that are most appropriate for them.

The reductionist approach provided by quantitative studies fails to represent the narrative behind the results and the variation in human experience that is so essential for this patient group. Complex, individual, emotional experiences such as those associated with ED are not readily described in numerical terms. Reported outcomes based on subjective, and potentially unknown factors, may account for the significant variations in findings between studies. A paradigm shift towards qualitative research in the field of penile rehabilitation for prostate cancer patients treated with radiotherapy and ADT may be of value in future studies.

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