Development of UK guidance on the management of erectile dysfunction resulting from radical radiotherapy and androgen deprivation therapy for prostate cancer

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SUMMARY

Aim: To develop a management strategy (rehabilitation programme) for erectile dysfunction (ED) after radiotherapy (RT) or androgen deprivation therapy (ADT) for prostate cancer that is suitable for use in a UK NHS healthcare context. **Methods:** PubMed literature searches of ED management in this patient group together with a survey of 28 experts in the management of treatment-induced ED from across the UK were conducted. **Results:** Data from 19 articles and completed questionnaires were collated. The findings discussed in this article confirm that RT/ADT for prostate cancer can significantly impair erectile function. While many men achieve erections through PDE5-I use, others need combined management incorporating exercise and lifestyle modifications, psychosexual counselling and other erectile aids. This article offers a comprehensive treatment algorithm to manage patients with ED associated with RT/ADT. **Conclusion:** Based on published research literature and survey analysis, recommendations are proposed for the standardisation of management strategies employed for ED after RT/ADT. In addition to implementing the algorithm, understanding the rationale for the type and timing of ED management strategies is crucial for clinicians, men and their partners.

Introduction

Prostate cancer is the most common male cancer, accounting for 24% of all new cancer diagnoses (1). Men treated for prostate cancer with radiotherapy (RT), including external beam radiotherapy (EBRT) or brachytherapy (BT), have poignantly described the negative impact of erectile dysfunction (ED) on their sense of masculinity and self-esteem (2).

Androgen deprivation therapy can be used in the neo-adjuvant setting, to reduce prostate gland size, in preparation for radical EBRT or BT and in the adjuvant setting, after radical RT, for up to 3 years in men with high risk disease characteristics at presentation (3). ADT is also used as a primary treatment where cancer has spread beyond the prostate or when disease recurrence/progression has been detected (3). ADT can involve orchidectomy, luteinizing hormone-releasing hormone (LHRH) agonists, gonadotrophin-releasing hormone (GnRH) antagonists and anti-androgens (4). ADT induces a significant reduction in serum testosterone that commonly results in reduced sexual desire and sexual function (5).

Erectile dysfunction in men treated with RT and or ADT is often of multi-factorial aetiology. The precise contribution of physical, psychological and relationship factors arising from the

Review criteria

Research articles (from 2000 to 2014) related to erectile dysfunction (ED) management strategies after radiotherapy (RT), brachytherapy (BT) or androgen deprivation therapy (ADT) for prostate cancer were sought via PubMed and were identified. Search terms used included various combinations of the following terms: penile rehabilitation; erectile dysfunction/erectile function/sexual function + cancer/prostate; sexual dysfunction + cancer/prostate/; erectile dysfunction + radiotherapy/hormonal/androgen; phosphodiesterase type 5 inhibitor + prostate cancer; vacuum erection device + prostate cancer; alprostadil + prostate cancer; intracorporeal/intracavernosal injections + prostate cancer; erectile dysfunction/sexual function + radiotherapy/androgen + psychosexual/psychological/counselling. An overall evaluation of level of evidence was conducted in developing this review, though most of the studies identified were not based on randomised double blind controlled trials. A survey of 28 experts further provided recommendations on treatment-induced ED management strategies in UK clinical practice.

Message for the clinic

Loss of sexual interest and ED are well-known side effects of RT and ADT. ED prevalence after RT is estimated to be 67–85% and may take up to 24 months to develop. Up to ~85% of men receiving ADT develop ED. Currently, there are no UK-wide recommendations for post-RT/hormonal therapy erectile dysfunction (ED) management following treatment for prostate cancer. This paper aimed to review the current state of ED management following RT and/or hormonal therapy for prostate cancer, based on a worldwide literature search, to develop guidelines based on available evidence and current clinical practice. The literature review data are supplemented by recommendations from an expert panel – individuals who have used various strategies in their clinical practice- in order to propose evidence-based recommendations for standardised ED management that can be implemented effectively within a publicly funded UK healthcare system.

diagnosis and treatment of prostate cancer, together with any comorbidities, can be complex to determine but should be taken into account when optimising ED assessment and management.

Radiotherapy and erectile dysfunction

Erectile dysfunction prevalence after RT is estimated to be 67–85% and may take up to 24 months to develop (6–8). RT has an impact on vascular structures leading into and within the penis and radiation damage to these structures mediates the decline observed in erectile function (EF) (9). More specifically, endothelial cell damage and microvessel rupture lead to luminal stenosis and arterial insufficiency over a period of months or years after radiation exposure (10).

In an analysis of 16 men who presented with ED after RT for prostate cancer, the mean interval from treatment to ED presentation was 8 ± 5 months after RT (11). These patients had developed cavernosal artery insufficiency and cavernous venocclusive dysfunction (11). RT-induced corporal tissue fibrosis contributes to the development of venous leak which, by definition, is associated with failure to trap blood in the penis and an inability to maintain erectile rigidity (10).

Erectile dysfunction rates vary from 6% to 51% after BT monotherapy, compared to higher rates of 25–89% in men receiving combined BT/EBRT treatment (10). Research by Merrick et al. demonstrated that radiation doses to the proximal penis were predictive of BT-induced ED (12).

Androgen deprivation therapy and ED

The main goal of ADT is to block the interaction between androgens and the prostate. The most commonly used therapeutic strategy is to decrease testosterone production by means of medical castration (4), in two forms: LHRH analogues (e.g. leuprolide, goserelin, triptorelin or histrelin), and GnRH antagonists (e.g. degarelix) (4). Anti-androgens (bicalutamide) can be used in combination to achieve combined androgen blockade either as first-or second-line therapy or as monotherapy for locally advanced prostate cancer (13).

Loss of sexual interest and ED are well-known side effects of ADT and are usually attributed to the decrease in testosterone levels (14). EF, while not solely dependent on serum testosterone levels, is usually affected in ~85% of men receiving ADT (15). It has been suggested that the testosterone threshold value below which EF is affected is about 10% of the normal range of testosterone and that below this threshold value, EF is affected in a dose-dependent fashion (14).

After prolonged ADT (> 3 months) there is generally a decrease in nocturnal penile tumescence in terms of frequency, degree of rigidity, duration and volume of erection (16). ADT indirectly impacts penile smooth muscle structures through this reduction in penile erections. In the absence of erections cavernosal oxygenation is diminished and smooth muscle cells are then exposed to a prolonged hypoxic environment (14,17).

Delayed orgasm or inability to attain orgasm and reduced orgasmic intensity are also common sexual consequences among patients receiving ADT, with men experiencing both lower penile vibratory thresholds and decreased penile sensitivity (15).

Reduced sexual interest can result in withdrawal of emotional and physical intimacy and may result in significant partner distress (18,19). Indeed, loss of the internal drive to seek sexual stimuli and arousal, changes in orgasm and reduced sexual satisfaction are often described by couples as the most disconcerting sexual side effects of ADT (15).

As well as muting biological libido and sexual motivation (15), ADT can also lead to indirect effects on sexual function and masculinity that include gynaecomastia, weight gain, vasomotor symptoms (hot flushes), fatigue and decrease in testicular and penile size (20,21).

Men undergoing ADT often experience reduced muscle mass and physical activity which can lead to adverse effects such as metabolic syndrome, cardiovascular disease, osteoporosis, depression and anxiety (22–26) and further contribute to a reduced quality of life (QoL) (27,28). Generally, < 20% men undergoing ADT maintain any sexual activity (29).

Combined RT and ADT

Androgen deprivation therapy has been shown to exert a detrimental effect on EF particularly when it is combined with RT (10).

In a study assessing the EF outcomes in 482 men with prostate cancer who were potent before treatment, the 5-year actuarial potency of BT patients was significantly worse when neo-adjuvant ADT had been given (76% vs. 52%). In this study, potency was defined as the ability to achieve an erection sufficient for penetration during intercourse without medications or devices (30). In the Prostate Cancer Outcomes Study of the Surveillance, Epidemiology and End Results programme, it was shown that 69% of the men who were potent before ADT treatment lost their potency after treatment, though there were not any significant differences in rates of ED between the types of ADT therapy (29).

Decreased penile length after RT plus neo-adjuvant or adjuvant ADT has also been observed and

men should be informed before treatment that penile shortening can occur (31).

Men receiving combined RT and ADT who have co-morbid conditions that may impact on their erectile recovery require a holistic approach to the assessment and management of their ED. Pre-existing comorbidities such as diabetes, hypertension or cardiovascular disease; certain prescribed or recreational drugs and psychosocial factors can also affect pretreatment sexual function (32). Indeed, the two most important predictive factors for ED following ADT were age > 70 and the presence of diabetes mellitus (33).

Similar to men undergoing surgery for prostate cancer, baseline EF remains an important predictor of posttreatment EF (34). It is therefore important to manage patient and partner expectations as baseline EF and subsequent recovery rates for EF in this subgroup of men is usually lower than that seen after radical prostatectomy (RP).

These factors must be taken into account in the assessment and management of ED in this group of men. Furthermore, as ADT duration can range from months to years, men and their partners need to understand and recognise the potential effects of treatment on their sexual lives as a lack of preparation for such sexual changes often results in regret, anger or depression (29).

The goal of EF management strategies in men undergoing RT and/or ADT is, therefore, the restoration or maintenance of assisted and non-assisted EF and prevention of both RT and ADT-induced structural changes in the penis.

The benefits of early sexual rehabilitation interventions may not be immediately apparent to men with low sexual interest or delayed development of ED. It is therefore especially important for clinicians to clearly communicate the rationale behind any EF restoration programme (10) and to make men aware that EF will not usually recover spontaneously while ADT is ongoing in the adjuvant setting.

The current options for ED management in the UK include:

- Oral medication [phosphodiesterase type 5 inhibitors (PDE5-Is: sildenafil, tadalafil or vardenafil)]
- Intracorporeal/intracavernosal injections (ICI)
- Intraurethral suppository containing alprostadil
- Vacuum erection device (VED)
- Psychosexual therapy or sexual counselling
- Pelvic floor exercises
- Combinations of the above
- Penile implant: malleable or inflatable as a remaining option

However, most of these treatment options for ED have not been extensively studied in patients under-

going or having undergone RT/ADT and therefore, the recommendations summarised in this article are based, to a greater extent, on clinical practice rather than definitive literature analysis.

Rationale for development of recommendations

With increased detection of cancer, earlier diagnosis and improved treatments the number of people surviving cancer is growing. Consequently there is increased emphasis on QoL, a component of which is sexual function. External beam RT, BT and ADT have an adverse impact on the patient's QoL, especially in men with good pretreatment sexual function. Currently, there is no consensus regarding the diagnosis and management of sexual dysfunction in these patients.

The underlying goal of an EF restoration programme is to replicate the normal physiological conditions of the penis as much as possible using pharmacological manipulation combined with psychosexual therapy to preserve healthy erectile tissue and maximise the potential of mens' future ability to achieve erections without therapy. This article aims to evaluate the EF restoration strategies for ED following radiation/hormonal treatments to propose evidence-based recommendations for standardised ED management that can be implemented effectively throughout the UK.

Stember and Mulhall recently provided recommendations for treating ED after RT/ADT, extrapolating results from post-RP patients and applying similar recommendations to RT/ADT patients (10). In our review, however, we have excluded post-RP literature given that this is the subject of another recent publication (35). In addition, the physiology of ED after RT/ADT is different from that after surgery and management of the condition has to reflect this. Here, we focus on RT/ADT literature as well as utilising clinical experience from a survey of UK clinical oncology, uro-oncology and ED service specialists, including consultants, specialist urology and uro-oncology nurses and psychosexual therapists working in cancer care.

Methods

Literature analysis

A review of published literature was carried out to determine current management options for ED following RT/ADT and establish the evidence grade for each option. The studies identified and used in this literature analysis were graded using the Oxford Centre for Evidence-based Medicine – Levels of Evidence (36).

Search terms used included various combinations of the following terms: penile rehabilitation; erectile

dysfunction/erectile function/sexual function + cancer/prostate; sexual dysfunction + cancer/prostate/; erectile dysfunction + radiotherapy/hormonal/androgen; phosphodiesterase type 5 inhibitor + prostate cancer; vacuum erection device + prostate cancer; alprostadil + prostate cancer; intracorporeal/intracavernosal injections + prostate cancer; erectile dysfunction/sexual function + radiotherapy/androgen + psychosexual/psychological/counselling.

Reviews (except systematic reviews), commentaries and animal studies were excluded. Any studies which did not utilise RT/BT/ADT for the treatment of prostate cancer were excluded. RCTs evaluating the effectiveness of interventions following RP were excluded unless the surgery had occurred at least 5 years before RT or hormone therapy. All studies analysed used at least one intervention for ED management (studies from 2000 to 2014 included; Search carried out January 2014).

Specialists' survey

The recommendations from clinical practice were gained by conducting a survey with 28 experts representing current practice across the UK. The survey investigated current practice in ED assessment and management after RT/hormonal therapy in prostate cancer patients, focusing on questions related to current clinical practice; scope of the problem in the UK and treatment approaches.

Results

Literature search overview

The literature search identified 19 articles after applying the selection criteria. Both randomised and non-randomised studies were included (Table 1). Eleven of the studies selected were not based on randomised double-blind controlled trials.

Studies and patient characteristics from the literature analysis

Of the 4062 patients included in the 19 selected studies (Table 1). Most of the studies were non-randomised uncontrolled studies. Follow-up (F) ranged from 4 weeks up to ≥ 3 years while ED management duration (D) ranged from 6 weeks to 52 weeks (Table 1).

No studies were identified that evaluated the use of VED, intraurethral alprostadil or ICI for men with ED following RT/ADT.

Trial participants were adult males (aged 16 years or over), receiving any RT/hormonal therapy (or who had previously received any) for prostate cancer, and who had experienced any type of ED (however identified) subsequent to their RT/hormonal therapy.

Pretreatment assessment

Partner involvement

Importance of patient and partner involvement in assessing ED prior to treatment has been shown in a previous review of patients after RP (35) and will not be discussed in detail here. Many clinicians are aware that both patient and partner-related factors are important to sexual recovery (54) following treatment for prostate cancer. Men and their partners want to be informed and involved in making decisions with regard to their cancer treatment and management of ED (9,55).

A study of 60 consultations between clinicians, patients and partners showed that sexual functioning was discussed infrequently and, despite the presence of partners in nearly half of consultations, involvement of the partner tended to be minimal (51). Overall, there were limited opportunities in routine follow-up clinics for couples to discuss the specific impact of prostate cancer and its treatments on sexual functioning (51).

A Canadian Working Group that evaluated interventions to limit the physiological and emotional difficulties experienced by men and their partners after ADT recommended providing information about ADT side effects before administration of ADT and, where appropriate, providing referrals for psychosocial support (15). These recommendations included offering psychological interventions for sexual sequelae to men and their partners (15).

In our clinician survey, approximately 89% of the expert respondents agreed that involving partners was beneficial when assessing and managing patients' ED, though they would only involve partners if they attended consultations with patients. However, only 36% of participants routinely involved partners in practice and 11% of respondents either did not feel that involving the partner was important or never had an opportunity to involve partners, suggesting that professional opinion did not always translate into clinical practice. The remaining respondents (53%) did not answer this question in the survey.

Baseline assessment of EF

Approximately 67% of participants reported not having any system/guidance in place for assessment and management of patients with ED prior to RT or ADT. Approximately 50% of the participants would discuss these additional assessments with the patient and ~50% would alter their ED manage-

Table 1 Study and patient characteristics of articles selected for literature review

Study	Level of evidence	No. of patients	Study design	Regimen	Start of treatment (after RT/BT/ADT)	Duration (D) /follow-up (F) (weeks)
Phosphodiesterase type 5 inhibitor (PDE5-Is)						
Zelefsky et al. (37)	1B	279	Randomised study	Daily sildenafil (50 mg) or placebo	3 days pretreatment	D 26 weeks F 104 weeks
Ilic et al. (38)	1B	27	RCT	Daily sildenafil or placebo	4 weeks	D 26 weeks F 104 weeks
Yang et al. (39)	2A	N/A	Systematic review	Efficacy of PDE5-Is (various regimens)	N/A	N/A
Watkins Bruner et al. (40)	1B	115	RCT	On demand sildenafil (50–100 mg) or placebo	26 weeks–5 years	D 25 weeks F 25 weeks
Pahlajani et al. (41)	4	69	Case series	Early (immediately after BT) vs. no treatment with PDE-5-I	Immediately after BT for 52 weeks	D 52 weeks F 52 weeks
Ricardi et al. (42)	1B	86	RCT	On demand 20-mg tadalafil vs. tadalafil 5-mg once-a-day dosing	26 weeks	D 12 weeks F 12 weeks
Teloken et al. (43)	2B	152	Cohort study	None – based on enrolling patients who met certain criteria including sildenafil use	~22 weeks	3.2 years
Candy et al. (6)	2A	959	Systematic review	N/A (included 5 RCTs)	26 weeks–4.5 years	F 6–16 weeks
Incrocci et al. (44)	1B	51	Open-label extension after RCT	Tadalafil 20 mg or placebo and then crossed over, followed by open-label extension phase	52 weeks	D 18 weeks F 18 weeks
Teloken et al. (45)	4	152	Case series	None – based on enrolling patients who met certain criteria including sildenafil use	26 weeks–3 years	3 years
Incrocci et al. (46)	1B	60	Single-centre randomised controlled cross-over trial	Tadalafil 20 mg or placebo on demand then patients crossed over	52 weeks	D 12 weeks F 12 weeks
Schiff et al. (47)	4	210	Case series	PDEIs at < 1 year (early group) or > 1 year after BT (late group)	27 weeks in early and 85 weeks in late group	1.5–3 years
Ohebshalom et al. (48)	4	110	Case series	Sildenafil	35 ± 16 weeks	3 years
Incrocci et al. (49)	1B	60	Open-label phase of 2001 double-blind (DB) study	50 mg of sildenafil, increasing dose to 100 mg	3.3 years	D 18 weeks F 104 weeks
Incrocci et al. (50)	1B	60	Single-centre randomised controlled cross-over trial	On demand sildenafil (50–100 mg) or placebo	3.3 years	D 12 weeks F 12 weeks
Sexual counselling						
Forbat et al. (51)	4	60	Case series	Clinical consultation observation	N/A	N/A
Canada (52)	1B	84	Randomised study	The efficacy, with or without the attendance of a female sexual partner, of sexual counselling	13 weeks–5 years	D 26 weeks F 26 weeks
Lifestyle interventions						
Cormie et al. (53)	1B	57	Randomised controlled trial	Exercise programme vs. usual care	While on ADT	D 12 weeks F 12 weeks

ment plan based on findings from these assessments.

Fifty per cent of survey participants confirmed that they performed a baseline sexual function assessment before radical RT or hormone therapy for prostate cancer. Of the participants who did assess their patients pretreatment, most relied on verbal assessment (Figure 1). The survey further demonstrated that ≥ 90% of ED discussions were generally initiated by the clinician rather than the patient. The majority of participants believed that it should be the urologist or the oncologist who should initiate a discus-
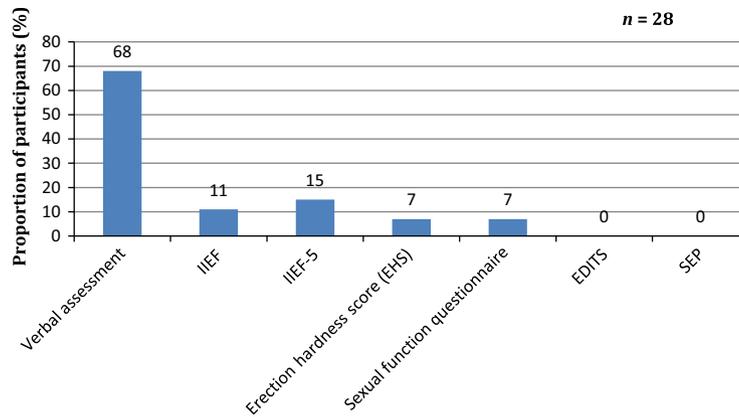
Figure 1 Baseline assessment tools used by survey participants

sion regarding ED with the patient. Other health professionals deemed appropriate to initiate this discussion included specialist nurses, radiographers or the patient's GP (Figure 2).

Most participants agreed that all patient groups should be assessed for ED. However, three participants stated that they would not consider assessing elderly men (though the term 'elderly' was not defined), one participant stated that they would not assess men disinterested in sexual activity and one participant stated that they would not assess men with dementia. Furthermore, 50% of participants agreed that the duration of ADT would not influence their decision to discuss ED with the patient, i.e. whether it was long-term or short-term therapy, they would still consider talking to the patient about it. However, some participants believed that PDE5-Is did not elicit a response after long-term ADT and, with these men, other treatments should be discussed such as VED as well as sexual counselling with the aim to improve sexual desire/interest and provide individual/couple support.

All participants indicated that they would initiate discussions about ED prior to RT or ADT to sufficiently prepare men for ED or loss of sexual desire/interest.

Generally, the following factors (in order of importance as rated by the participants) should be assessed before treatment as these factors are likely to affect EF posttreatment:

- Comorbidities, e.g. cardiovascular disease.
- Current medication e.g. nitrates, antihypertensives, antidepressants.
- General lifestyle factors e.g. smoking, obesity, exercise.
- Metabolic status.

Almost all of the participants stated that there was a checklist in their practice for assessing the factors stated above before initiating treatment.
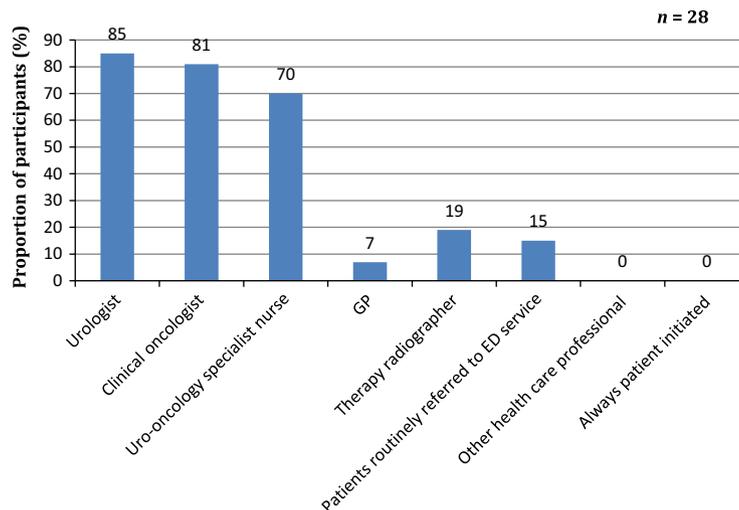
Figure 2 Who initiates ED discussion with patients?

Baseline assessment of testosterone levels

Most participants only occasionally measured testosterone levels before ADT (Figure 3). Testosterone levels were not routinely checked in clinical practice before or after ADT therapy unless there was a clear indication to do this.

Time elapsed from treatment to assessment/ management of ED

According to the literature analysis, the length of time from treatment to initiation of ED management varied from immediately after ADT/RT treatment or during treatment to up to 5 years after treatment. However, improved outcomes were observed with earlier ED management (immediately or within 6 months posttreatment) following BT (41,47). An early vs. late ED management comparison was not found in the literature analysis for ADT.

In the expert panel survey, most participants believed that initiation of ED management was the responsibility of a dedicated ED specialist nurse or urologist, potentially resulting in management delay due to the need for specialist referral and limited access to specialist ED services. It is also noteworthy that most participants would prescribe PDE5-Is if the patient presented with ED, though would consider referral to an ED clinic if the PDE5-Is did not work. Sildenafil was noted as the PDE5-I of choice as it is now available as a more cost-effective generic formulation and its use is no longer under current UK NHS ED drug prescribing restrictions. Most participants also agreed that follow-up and monitoring of response to ED management strategies could be the responsibility of the GP or the ED clinic and that a GP should be involved in all treatment regarding patients' ED. Evaluation of ED treatment efficacy was usually recommended by participants at 3 months after initiation of management and at three monthly intervals thereafter.
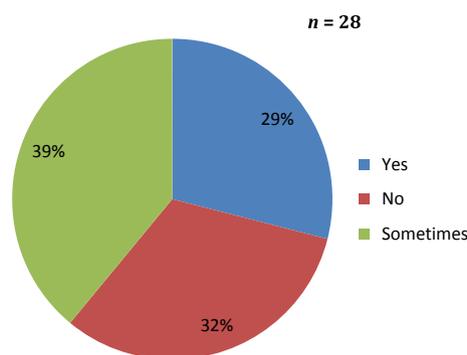
Posttreatment ED management

Current availability of NHS UK management strategies for patients after RT/BT/ADT

Current management strategies and their efficacy/tolerability data from the literature analysis for ED are summarised in Table 2.

Clinical practice: current management strategies for patients after RT/ADT from expert panel survey

- *Immediate referrals:* According to our survey, 21% of participants stated that they would refer patients suffering from ED immediately to a specialist ED clinic without initiating any treatment themselves.
- *Assessment:* A further 29% of participants would assess patients as follows:
  ○ Routine blood tests (fasting blood glucose, free testosterone levels; vascular risk factors, etc.).
  ○ Lifestyle assessment and advice regarding smoking, increased alcohol intake, obesity.
  ○ Assess whether the issue is low sexual interest / desire due to ADT or ED or both.

Appropriate management options would only be considered by these participants after the aforementioned assessments are completed.

- *Patient involvement in treatment decision:* Only two participants stated that they would discuss treatment options with the patient before prescribing.
- *Short vs. long term ADT:* Approximately 61% of the participants stated that they would employ the same treatment for short- and long-term ADT patients. Three participants believed that ED may improve spontaneously after stopping hormones, so there was no need to prescribe any ED treatment. The impact of short vs. long term ADT and role of testosterone are considered further in the discussion section below.
- *ED treatment options:* These were outlined by the participants as per Figure 4A, B.

ED management algorithm

A typical management algorithm employed in clinical practice by the majority of survey participants for ED post-RT/BT/ADT is shown in Figure 5. This algorithm is mainly based on locally agreed practice and not any specific existing national/international guidelines.

Cost-effective ED management strategy in clinical practice

Most participants expressed uncertainty over the most cost-effective strategy for managing ED after RT/BT/ADT. However, PDE5-I use was rated as the most cost-effective strategy (by 20% of the participants) compared with VED or combination strate-

n = 28

Yes 29%
No 32%
Sometimes 39%

Figure 3 Do you measure testosterone levels at baseline and after ADT?

Table 2 Current management strategies for ED after RT/ADT from literature analysis

Strategy	No. of publications	Total no of patients	Results	Adverse events	Summary
Conservative management (exercise programme)	1	57	Significant (p = 0.045) difference in sexual activity following 12-week short-term exercise programme (53) Patients undergoing usual care decreased sexual activity while patients in the exercise programme maintained their level of sexual activity (53) Following the intervention, the exercise group had a significantly higher percentage of participants reporting a major interest in sex (exercise = 17.2% vs. control = 0%; p = 0.024) (53)	N/A	Short/long term exercise programme improves and maintains EF and improved libido
Psychosexual Counselling and Therapy	3	144	Improved outcomes observed with sexual counselling in men and women with/without partners (52) Sexual functioning is discussed infrequently in routine FUP (51) Despite the presence of partners in nearly half of consultations, involvement of the partner tended to be minimal (51)	N/A	Sexual counselling improved ED outcomes for patients and partners Partner involvement in clinical discussions are minimal
Phosphodiesterase type 5 inhibitor (PDE5 I)	15	3532	Efficacious after RT and BT but ADT diminished response to PDE5-I (6,37–39,43–46,49) Better patient satisfaction at 24 months with daily sildenafil (37) Optimal response achieved when PDE5-I initiated 12–24 months after RT (6,41) Significantly better IIEF-5 scores up to 6 months with daily sildenafil after RT, though scores diminished when medications stopped (38)	Mild-to-moderate headaches or facial flushing (37,46,49,50)	PDE5-Is are efficacious after RT/BT but their effect can be diminished after ADT Initiating PDE5-I within 1 year of RT correlates with better outcomes Daily therapy associated with better outcomes in the short and long term and on demand therapy associated with better outcomes in the long term

Table 2 Continued

Strategy	No. of publications	Total no of patients	Results	Adverse events	Summary
			Sexual desire scores remain high up to 24 months after daily sildenafil despite discontinuing treatment (37) Significant increase in mean scores with on demand sildenafil for up to 2 years (43,49) Significantly better IIEF scores with tadalafil after RT over 12 weeks (44,46) Approximately 50% reported successful intercourse with tadalafil (placebo: 9%) (p < 0.0001) over 12 weeks after RT (46,50) The response to PDE5-I treatment is time dependent with a stepwise decrease in all end points examined serially in a 3-year period (43,48) Early use of PDE-5i after BT maintains EF up to 36 months (41,47) No difference between on demand vs. daily use after RT (42) Significantly more functional erections vs. placebo at 24 months despite discontinuing daily sildenafil at 6 months (37) Better compliance observed with once daily dosing (42) Predictors of poor response: older age, longer time after RT, ADT > 4 months duration and RT dose > 85 Gy (43) ADT seems to exert a deleterious effect on PDE5-I response in men undergoing RT (37,47)		Daily dosing associated with better compliance Time-dependent response
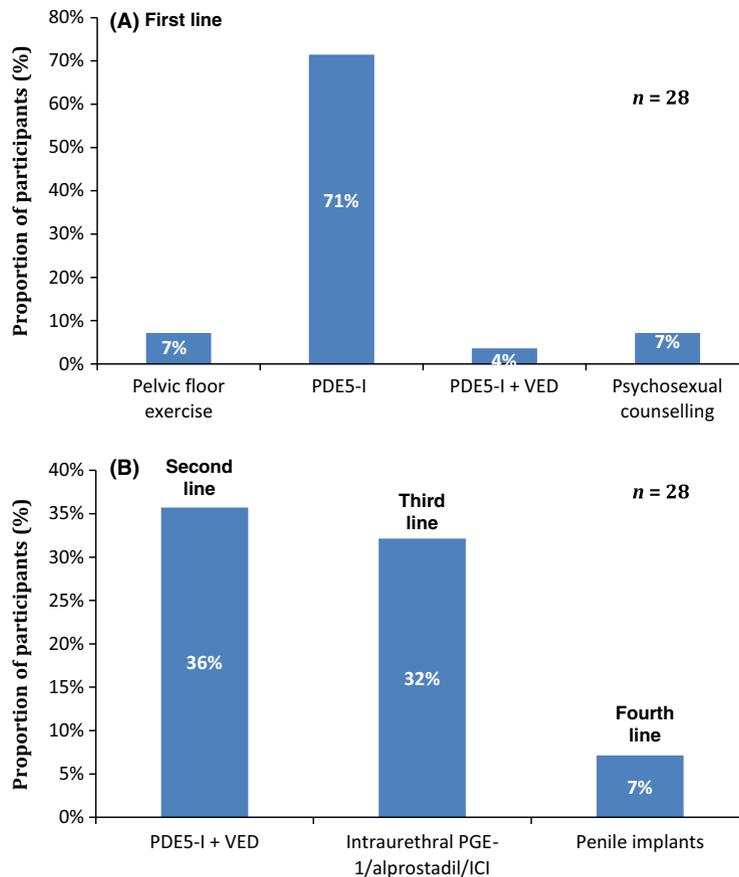
Figure 4 Survey results reflecting current ED management after RT/BT/ADT: (A) First-line management and (B) subsequent management in specialist ED clinic

gies. The participants stated that the reason they thought oral PDE5-Is were the most cost-effective strategy was because they generally worked well for patients and there was no need for onward referral to ED clinics. As sildenafil is now off patent it can be obtained for less than £1/pill.

The most effective strategy depended on patient and partner needs, e.g. low sexual desire may require psychosexual therapy or counselling in addition to PDE5-Is. However, the most commonly favoured combination was VED + PDE5-I (daily or/and on demand). Weekly timetabled sexual activity may also be an option to help couples manage reduced libido.

Follow-up and monitoring
• *Follow-up assessment:* Only 32% of participants stated that they would assess ED at all follow-up appointments, whereas approximately 39% of the participants reported that they would not do so. The remaining participants would only assess ED if directed by the patient.
Follow-up assessments generally comprised informal verbal assessment or formal score-system based assessments if carried out within ED clinics.

• *Monitoring responsibility:* As many as 96% of the participants believed that monitoring and follow-up assessments of ED were the responsibility of uro-oncology or ED specialist nurses.
• *Initial monotherapy strategy success rate:* Initially the majority of patients were treated with PDE5-I monotherapy. The success rate, as reported in our survey, varied from 25% to 95%, with most participants reporting a success rate of ~50%. However, participants felt that the success rate with PDE5-Is was difficult to quantify accurately in clinical practice.

Duration of treatment
In the literature analysis the duration of ED management lasted from 6 weeks up to ≥ 3 years' posttreatment completion.

According to the survey findings, the duration of any treatment ranged from 3 months until the patient no longer needed ED management. The duration of any management strategy probably depends on the underlying cause of ED and hence individualised management in this patient population is very important. Furthermore, the decision to

ED Management Algorithm post RT/ADT
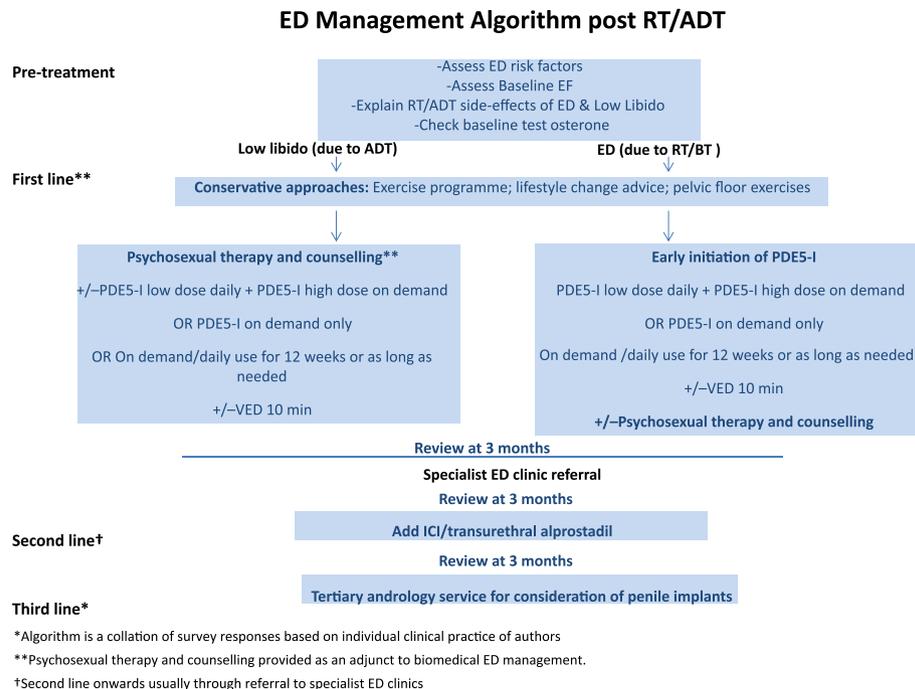
Figure 5 Recommended management algorithm for ED post-RT/BT/ADT. *Algorithm is a collation of survey responses based on individual clinical practice of authors. **Psychosexual therapy and counselling provided as an adjunct to ED treatment. †Pelvic floor exercise advice also provided by physicians

stop ED treatment must be individualised as strict time limits are considered inappropriate.

Discussion

The literature search identified 19 randomised and non-randomised studies. Most studies identified were non-randomised or controlled studies. Findings from both the literature analysis and our clinician survey indicated that resolving ED can improve men's QoL.

Assessment of erectile function

Men and their partners should be counselled prior to commencement of ADT/RT to prepare them for treatment related sexual side effects including ED and loss of sexual interest. Pretreatment EF should be assessed and recorded.

However, involvement of partners at assessment, while recommended in the literature and acknowledged by all clinicians surveyed, depended on patient agreement and presence of partners during clinical consultations.

Predictive factors

The recovery of EF is a multi-factorial process that depends on many variables identified within the literature review and through our clinician survey. These include:

• Patient and partner age
• Pretreatment EF and sexual activity level
• Metabolic status
• Cardiac/cardiovascular function
• Other comorbidities in the patient/partner
• Current medications
• General lifestyle factors, e.g. smoking, obesity, exercise, etc.
• Testosterone levels – normal levels are important for recovery of EF
• The period of time taken for testosterone levels to return to normal after stopping ADT

Management of erectile dysfunction

Goals of ED management/restoration of EF after RT/BT/ADT
All participants in the healthcare professional survey agreed that the goals for managing ED post-RT/BT/ADT should be:
• Achievement/restoration of EF at a level satisfactory to patient/couple or to pretreatment level
• Restoration or maintenance of EF sufficient for successful penetrative intercourse
• Maintain sexual function and penile length

- Improve patient's QoL and sexual self-esteem
- Reduce anxiety levels associated with sexual intimacy

Compared with RP patients, RT patients may be less motivated initially to start or remain compliant with a sexual rehabilitation regimen (10), especially as the addition of ADT will normally reduce sexual interest and drive. In addition, there is a delayed (up to 2 years following end of RT and up to 12–18 months after cessation of ADT) pattern of ED development/ EF recovery. This differs from men after RP who do not have neo-adjuvant ADT. Therefore, it is essential that the rationale for EF restoration is communicated clearly to them. Clinicians should offer men written information about the immediate and longer term impact of RT/ADT on their sexual lives and aim to discuss these anticipated changes with men and their partners. Whenever possible, partners should be included in ED management decisions, as they can be significantly affected by treatment side effects (15,56). The advantages and disadvantages of ED management options should be discussed with the patient and his partner (Table 3) (56). It is particularly important to note that the delayed penile structural changes created by RT necessitate early intervention to try to preserve EF and reduce impact of RT-induced fibrosis. Indeed evidence suggests that PDE5-Is are efficacious if initiated within 1 year of RT and that response to these medications appears to be time dependent (Table 2). In addition, longer term ADT is associated with worse outcomes, so for patients on long term ADT, other factors such as testosterone levels, and exercise programmes should be discussed during initial assessment and patient/couple's expectations are managed.

Oral therapy – PDE5-I
As with patients after RP, the first-line treatment for RT/ADT-induced ED is PDE5-Is, although both clinical opinion and published research indicate that these agents usually have reduced efficacy in men receiving ADT (57).

There is good evidence, from placebo-controlled randomised trials, that PDE5-Is can improve EF in men following RT/BT. Sildenafil (50) and tadalafil (46) have shown effectiveness for the treatment of ED after external beam RT. Incrocci et al. evaluated the effect of 2 weeks on demand sildenafil vs. placebo in 60 men with ED following RT for prostate cancer (50). The starting dose of sildenafil was 50 mg on demand. In most men (90%) this was increased to 100 mg because of an unsatisfactory response at the lower dose. At 6 weeks, participants

crossed over to an alternative treatment for a further 2 weeks.

The tadalafil trial evaluated 60 men with ED after RT who were randomised in a cross-over trial to receive either 20 mg of tadalafil or a placebo daily for 6 weeks (46). The duration of follow-up was 3 months and results showed that tadalafil, given after RT, resulted in successful intercourse, which was reported by almost 50% of the patients (46).

After RT, PDE5-Is assist many men to achieve increased rigidity of erections and thereby contribute to periodic arterial levels of penile oxygenation and facilitate sexual activity. Clinical experience suggests that this approach also helps maintain nocturnal and early morning erections. Hence daily PDE5-I treatment would be a logical approach to adopt, albeit with limited research evidence to support regular preventive use at present (37).

Zelefsky et al. (37) recently reported results from the first prospective, randomised, double-blind, placebo-controlled trial to determine if daily adjuvant use of sildenafil before, during and after radiation therapy preserved EF (37). The trial randomised 279 men with localised prostate cancer treated with RT (± ADT) to daily sildenafil (50 mg) or placebo (2:1 randomisation). The treatment/placebo were initiated 3 days pre-RT treatment and continued daily for 6 months. At 12 months, EF and sexual satisfaction scores were significantly better than placebo. At 24 months, although EF scores were not significantly better than placebo, the overall sexual satisfaction scores remained significantly higher. At 24 months sexual desire scores were significantly higher than placebo despite discontinuing sildenafil 18 months previously. The results of this study support animal data on the potential vascular protective effect of sildenafil, but further research using a longer duration (> 6 months) of PDE5-I therapy following testosterone recovery is warranted to demonstrate fully the clinical benefits for this group of men (37).

In a prospective study, Schiff et al. reviewed patients who underwent BT and subsequently used PDE5-Is on a regular basis (two to four doses per week of 50 or 100 mg sildenafil) (47). Patients were stratified into an early use group (< 1 year post-BT) and a late use group (> 1 year post-BT). At 6-month intervals, 18–36 months after treatment (time points at which all patients had begun PDE5-I use), Sexual Health Inventory scores were significantly better for men in the early intervention group (47). These data suggest that delaying the start of penile rehabilitation after RT/BT is associated with poorer EF outcomes.

Table 3 Advantages and disadvantages for each RT/BT/ADT ED management strategy

Post-RT/BT/ADT ED management strategy	Advantage	Disadvantage
Conservative management (exercise programme)	Short/long term exercise programme improves/maintains EF and improves libido and supports weight management as obesity is an independent risk factor for ED	N/A
Psychosexual Therapy and Counselling	Improves EF outcomes for men and partners Support couples to adopt non-coital alternatives where ED is non-responsive to biomedical management strategies	N/A
Oral medications (PDE-5I)	Easy to take Acceptable to most men and partners Good tolerance generally Does not interfere with foreplay Efficacious after RT/BT Initiating within 1 year of RT correlates with better outcomes	Possible drug interactions and relative contraindications in men with comorbidities/nitrate use Diminished effect after ADT (especially long term ADT) Time-dependent response
Vacuum erection device	Avoids medication – may be more acceptable to some men Non-invasive No systemic effects or medical toxicity Cost-effective Simple to use Improves cavernous oxygenation and helps maintain penile length	Uncomfortable, clumsy, mechanical Erection does not feel/look natural Need for patient/partner commitment to learn Skilled instructor needed Patient and partner acceptance required If used for penetration: can be altered penile sensation
Intraurethral suppository	Relatively easy to learn to use Rapid onset No needles Painless to insert Well-tolerated Local treatment	Can be difficult to insert Urethral 'stinging' May not be effective for all men
Intracavernosal injections	More natural looking erection Quick administration and result Usually effective – direct drug delivery	Possible issue with patient compliance Not acceptable to all men or their partners Good manual dexterity needed Skilled instructor needed Patient (& health professional) fear of priapism Pain and bruising Penile fibrosis at injection site
Combination strategy	May be helpful for those with diminished response to PDE5-Is alone Problems as above with differing combinations therefore additive	Need for more than one intervention Patient commitment Expensive and time consuming Variation in availability across different centres/hospitals in the UK

In a study of patients who underwent either BT or EBRT for localised prostate cancer with or without ADT, men who had the combined treatment had lower mean and EF domain scores on the IIEF questionnaire and worse response to sildenafil at multiple time points during the first 3 years posttreatment (45). The percentage of men responding to sildenafil at 24 months post-RT was 61% for those without ADT and 47% for those with ADT (p = 0.032) (45). In terms of ADT, the efficacy of sildenafil was usually poor, as tissue androgenisation is required for optimal response to PDE5-Is (45). Teloken et al. have shown that the efficacy of sildenafil citrate was significantly decreased in men who underwent ADT along with BT compared with BT alone (45). Worse outcomes for combined therapy patients were seen at all posttreatment follow-up time points, ranging from 6 to 36 months (45).

A placebo-controlled cross-over trial (40) in patients treated with EBRT and neo-adjuvant or concurrent ADT found that the sildenafil effect was significant (p = 0.009) vs. placebo. However, only 21% of patients had a treatment-specific response, improving during sildenafil, but not during the crossed-over placebo phase (40).

Testosterone levels
Evidence supports a role for testosterone in response to endogenous vasodilators with the expression and activity of PDE5-Is shown to be under the control of

androgens (14). A study by Jannini et al., involving 83 men with ED compared to 30 age-matched controls, found reduced total and free testosterone levels in the former group (both p < 0.001), suggesting lower levels of testosterone are associated with the development of ED (58). A significant increase in serum total and free testosterone levels was observed in those men who achieved normal sexual activity 3 months after commencing ED management (p < 0.001), while serum testosterone levels did not change in the men where ED therapy was ineffective (58).

With the advent of PSA testing and newer agents for prostate cancer, men are remaining on ADT for much longer than might have been originally anticipated (59). The impact of ADT on subjective sexual desire is difficult to evaluate and measure. In the Prostate Cancer Outcomes Study, 431 men receiving ADT were examined. Results indicated that 51% of men who were interested in sex before treatment reported 'no interest' after ADT and 73% reported cessation of sexual activity following ADT, irrespective of the type of ADT prescribed (29). In contrast, other studies have found no relationship between testosterone levels and sexual desire (60,61). A study by Martinez-Jabaloyas et al. concluded that androgens are 'necessary but not sufficient' for normal sexual interest and the testosterone threshold value below which desire is affected remains poorly defined (61). Some authors stress that the testosterone threshold value below which sexual behaviour is affected may vary significantly from one individual to another (14). Wu et al. suggested that hypogonadism in men $\geq$ 40 year old can be defined by the presence of at least three sexual symptoms (decreased frequency of morning erection, decreased frequency of sexual thoughts and ED) associated with a total testosterone level of less than 11 nmol/l (3.2 ng/ml) and a free testosterone level of less than 220 pmol/l (64 pg/ml) (62).

A longer duration of ADT results in a decreased likelihood of testosterone level recovery (63–65). Testosterone deficiency is usually a late side effect of radiation therapy (63–65). Most men recover testosterone levels after long term ADT or RT to some extent, depending on their age, but recovery of 'normal' testosterone levels is slow and few recover potency and sexual desire (66).

Androgen deprivation alters the functional responses and structure of erectile tissue and this effect has been shown to be reversed in animals given testosterone (67). Furthermore, PDE5-I activity increased in castrated animals treated with testosterone (67). A recent meta-analysis in men with hypogonadism who did not have prostate cancer stated that total T > 12 nmol/l (> 350 ng/dl) does not require replacement therapy, whereas T < 8 nmol/l does merit treatment (68).

Testosterone replacement for men with persistent low desire, total ED and low T levels following RT/ADT for prostate cancer remains highly controversial, especially in higher risk disease. However, the management of low sexual desire and associated sexual distress in testosterone-suppressed men on ADT may benefit from professional psychosexual or psychological therapy according to our survey analysis.

Nevertheless, PDE5-Is given on demand demonstrate modest efficacy in patients with ADT as per our literature analysis. Other erectile aids that are less well studied in the RT/ADT literature include intracavernosal therapy, vacuum devices and penile implants.

VED/PDE5-I + VED combination
No studies were identified which evaluated the use of VED for men with ED following RT/ADT. However, VED has been shown to significantly improve penile oxygen saturation in patients after prostatectomy and may contribute to the maintenance of both penile structure and length (69).

In the survey analysis, only one participant stated that they would consider VED as a first-line option for ED in combination with PDE5-Is. The majority of survey participants believed that VED could be used as a second line option, added to PDE5-I where there is no response to oral drugs after 3 months. Participants also agreed that VED should be initiated in specialist ED clinics to provide patient education and support compliance with device use.

ICI/Intraurethral alprostadil
No studies assessing the efficacy of ICI/intraurethral alprostadil on sexual dysfunction in men treated with RT/BT/ADT were found. In the survey analysis, most participants stated that they would use ICI/intraurethral alprostadil as third line options after failure of PDE5-I monotherapy and PDE5-I + VED combination therapy.

Exercise programmes
Men who undergo ADT could benefit from exercise by reducing risk factors for metabolic complications, therapy-related comorbidities and physical function decline (24).

In a study by Cormie et al. on men undergoing ADT, significant (p = 0.045) benefits in sexual activity were observed following a 12-week short-term exercise programme (53). Improved levels of sexual interest were also observed following the intervention with significantly more participants in the exercise
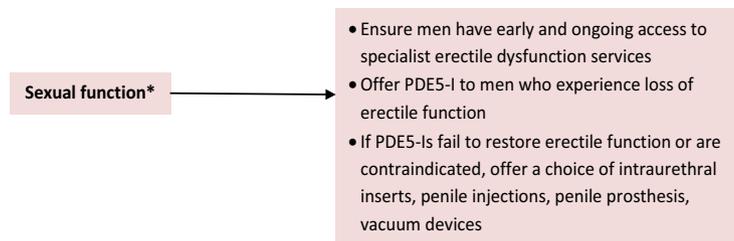
Figure 6 Prostate cancer NICE guidelines (72). *Sexual function term used by NICE though the treatments are solely for erectile dysfunction

group reporting interest in sex (exercise = 17.2% vs. control = 0%; p = 0.024) (53).

Cormie et al.'s (53) findings are supported by results from a combined resistance/aerobic exercise programme that improved management of ADT side effects and significant improvements in sexual function, fatigue and cognitive function (70).

Psychosexual therapy and counselling

Treatment guidelines from the British Society for Sexual Medicine recommend psychosexual counselling and patient education for patients with sexual dysfunction, but men affected by cancer rarely access such services (15,71).

An RCT of group education for men who had RT for prostate cancer (baseline level of sexual function not assessed) found positive sexual outcomes associated with psycho-educational interventions (54).

The efficacy, of a four session sexual counselling intervention (with female sexual partners included/ excluded) was assessed in a pilot RCT in 84 men who had ED as a result of RT or prostatectomy for prostate cancer (52). One group received counselling with their female partners present and the second received counselling without their partner present. The results demonstrated that the presence of a female partner at the counselling sessions did not significantly affect male sexual function and satisfaction (52). However, improved outcomes following sexual counselling for both study groups were observed for male and female participants when compared with baseline.

Hence, referral to appropriate psychological or psychosexual services is important in the management of these men/couples. Sexual counselling, including sufficiently preparing the man and his partner for sexual side effects of their treatment, should ideally be offered before or concurrent with biomedical interventions to be most effective (15).

Surprisingly only 4% of the expert panel surveyed would consider referring this group of men to psychosexual counselling, which may be due to the limited availability of counselling in the NHS. However,

counselling along with ED treatment may be important for men receiving ADT, as shown in our algorithm (see Figure 5).

ED Management algorithm based on literature analysis and clinician survey findings

Stember and Mulhall provided the following recommendation for ED management following RT in a recent review: Patients should initially be prescribed sildenafil to be used at a dose that gives them a penetration hardness erection twice a week. On the remaining five nights, they are advised to use sildenafil 25 mg when going to bed at night (10). The authors further emphasise the importance of communicating the benefit of low-dose PDE5-Is to patients (10).

Intracavernosal injections is the second line therapy recommended by Stember and Mulhall (10). ICI are usually more effective than PDE5-Is in men receiving ADT (10,35). The authors recommend ICI injections up to three times per week, while taking low-dose PDE5-I on the days that the patients do not inject (10). Patients are further instructed to avoid using ICI within 18 h of taking a PDE5-I because the combined effects may increase the likelihood of priapism.

The NICE consultation guidelines on Prostate Cancer recommend offering PDE5-Is to men who experience loss of EF (72). Furthermore, NICE recommend that if PDE5-Is fail to restore EF, or are contraindicated, men should be offered a choice of intraurethral inserts, penile injections, penile prosthesis or vacuum devices (VED). However, NICE do not specify the order of ED management interventions nor do they specify strategies according to specific prostate cancer treatment modality and patient demographics (Figure 6) (72).

Proposed management options to be considered by healthcare professionals are detailed in Table 4. Some recommendations are evidence based, while others are based on consensus opinion generated within the expert panel survey. The recommendations in the algorithm should be considered independently of the patient's relationship status.

Table 4 Summary recommendations for ED rehabilitation programme post-RT/BT/ADT

Summary recommendations for ED rehabilitation programme

Pretreatment recommendations
  Pretreatment discussion with the man and his partner of the impact of RT/BT/ ADT on sexual function, delayed ED development timelines and rationale for ED rehabilitation programme
 Ensure men and couples are sufficiently prepared for disruption to their sexual lives and expectations of EF recovery are realistically managed
  The man and partner's current sexual function should be assessed as part of any ED management programme pre-and posttreatment. Partners may require medical/ psychosexual therapy if they have concurrent sexual difficulties that may jeopardise rehabilitation efforts
  Pretreatment assessment of a couple's readiness to engage in a ED rehabilitation programme is advisable
  Pretreatment assessment of any comorbidities or concurrent medication that would affect sexual function
  Assess patients' contributory lifestyle factors (diet, BMI, alcohol/smoking and physical activity)
  Check baseline testosterone level to exclude an existing testosterone deficiency
Posttreatment recommendations
  Discuss the implementation of an ED rehabilitation programme with men and partners
ED management initiation time
  Consider early initiation of PDE5-I (soon after start of RT/ADT) or within 3–6 months of treatment at least
ED management algorithm
  See Figure 5 for management algorithm recommendations for EF restoration after treatment with RT/ADT
  Determine cause of ED – low sexual desire ± inability to get an erection? Are nocturnal/early morning erections occurring?
  Consider conservative approaches: pelvic floor exercise and lifestyle changes
  Consider first-line treatment with low-dose PDE5-I daily (with higher doses given, on demand × 1 per week minimum if required)
 Combination therapy may be needed for some patients (generally PDE5-I + VED)
 Psychosexual therapy, especially for patients on ADT with persistent low desire + individual/couple distress
  Use the most effective PDE5-I at optimal dose level on at least eight occasions before switching drug/management strategy
 NB. sildenafil is now available in generic form
  Add VED to PDE5-I monotherapy as a second line option
  Add intraurethral alprostadil/ICI followed by implants if initial treatment strategies fail
  Referral to appropriate psychological/psychosexual therapy services
  Counselling to assist couples in adjusting to permanent changes in sexual function
  Timetable sexual intercourse once a week to assist management of low desire
Re-assessment
  Once ED management is initiated, re-assess at regular intervals posttreatment preferably every 3 months
ED management duration
  Recommend trying one strategy on at least eight occasions (or approximately 3 months) before switching to another strategy unless the patient experiences adverse events warranting an early switch
  Individualise duration of management for each man/couple as strict time limits are inappropriate in clinical practice
  Management duration can range from 3 months until the man no longer needs EF support

Summary

Men undergoing RT/ADT for prostate cancer are at increased risk for ED.

In this article, we have proposed a comprehensive ED management algorithm to promote assisted or unassisted EF support for men experiencing ED associated with RT/ADT. Many men achieve assisted erections with PDE5-I use, while others benefit more from a combined ED management approach incorporating biomedical interventions, lifestyle/exercise programmes, psychosexual counselling and other erectile aids.

In addition to implementing this algorithm, understanding the rationale for proactive EF restoration strategies and the management of patient expectations is crucial for clinicians, men and partners in light of the delayed onset pattern of ED following RT/BT and the impact of ADT-induced loss of sexual motivation and desire on their sexual relationship.

Author contributions

Acknowledgements

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