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Review

A systematic review of the effects of hormone therapy on urinary symptoms in men with prostate cancer

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ABSTRACT

Patients with prostate cancer often have lower urinary tract symptoms and are often prescribed hormone therapy. Although it is prescribed with the aim of controlling the cancer, favourable effects on these symptoms have also been reported in many studies. Our aim was to conduct the world's first systematic review of this literature. Articles were included if they quantitatively assessed the effect of hormone therapy on the urinary symptoms of patients with prostate cancer using a standardised scale. Fourteen articles describing 5365 patients were included. The most commonly used test was the International Prostate Symptom Score (IPSS). The median initial IPSS score was 14.3, suggesting moderately severe symptoms. The median improvement in that score was 29%, or approximately 4 points, indicating a clinically significant improvement. For those patients with a higher initial IPSS score, greater improvements were seen. Improvements in other tests, including the urological quality of life score, urodynamics, post-voiding residual volumes and reductions in prostate gland volume, were often also reported. We offer a panel of suggestions for future research.

KEYWORDS: neoadjuvant therapy, prostate, prostatic neoplasms, androgen receptor antagonists, lower urinary tract symptoms.

INTRODUCTION

At the time of receiving a diagnosis of locally advanced or metastatic prostate cancer, patients will often have lower urinary tract symptoms (LUTS) and may be advised to receive hormone therapy (HT). Patients with locally advanced disease may undergo HT in the form of neoadjuvant androgen deprivation therapy (NADT) prior to definitive local treatment. Those with metastatic disease may undergo HT as the sole treatment, or in combination with chemotherapy and palliative measures, such as analgesia for bone pain.

For those with locally advanced disease, the definitive treatment options include radical prostatectomy or external beam radiotherapy (EBRT). Patients undergoing EBRT can obtain better long-term control of the cancer by preceding the EBRT with 3 to 6 months of NADT [1]. NADT is primarily intended to improve the long-term control of the cancer, rather than to provide symptomatic benefits; however, the improvements in LUTS are an important additional benefit. The improvement in LUTS while on NADT is often accompanied by significant reduction in prostate gland volume (PGV). The combined effect of these changes enables patients to better tolerate the effects of radiotherapy on the urinary system [2].

For those with metastatic disease, there may be a range of symptoms from metastases outside the prostate, but local symptoms are often also significant. The important role of HT in keeping these local symptoms at a manageable level is highlighted by the need for other local therapies to be added when the disease becomes hormone-resistant [3]. The effects of HT on LUTS have been reported in many heterogeneous studies

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addressing these two scenarios but have never been systematically reviewed.

In addition, very few reports have investigated the association between improvements in LUTS provided by HT and reductions in PGV. To investigate this, both the LUTS and the PGV would need to be measured accurately. The most commonly used instrument to record urinary symptoms is the International Prostate Symptom Score (IPSS). Although the lack of validation among urological scales in general has been noted [4], the IPSS has been shown to correlate well with other measures of urinary function and has been adopted by the World Health Organisation [5]. Regarding the measurement of PGV, several recent reviews have addressed the accuracy of the available methods [6, 7]. These include Digital Rectal Examination (DRE), Ultrasound (US), Computed Tomography and Magnetic Resonance Imaging (MRI). Of these, the DRE is the cheapest, most frequently used and most readily performed, but it is also the least accurate. Imaging methods are more reliable and, in general, the MRI scan is slightly more accurate than US. Correlations between reductions in LUTS and the PGV have never been reviewed. Our aim was to perform the first ever systematic review of the literature addressing the improvement in LUTS in prostate cancer patients treated with HT, including the association of that with reductions in PGV.

MATERIALS AND METHODS

For this review, the PRISMA, AMSTAR and QUADAS-2 methods were adopted to ensure thoroughness, but not all of the criteria for these were applicable [8-10]. Of these the most applicable is the QUADAS-2 tool which requires consideration of 4 domains including patient selection, the index test, the reference standard and flow/timing. The participants in the studies to be reviewed were men with locally advanced or metastatic prostate cancer and the intervention was any type of HT used to treat it. No comparison between treatments was planned. At the time of submission of the report, no other planned review protocol or similar report was either registered or published. Ethics committee approval was not considered necessary and no funding was sought.

Multiple medical literature databases were accessed in January 2021, including CINAHL Plus, Embase, Medline, Pubmed and ScienceDirect and were searched for abstracts containing the terms “hormone therapy” and “lower urinary tract symptoms” in their title or abstract. The search was repeated with specific drug names including degarelix, triptorelin, leuprorelin and goserelin substituted for the term “hormone therapy”. Titles and abstracts were independently reviewed by the authors and relevant full text articles obtained for further review. Articles were included if they contained original data derived from a quantitative assessment of the effect of HT on LUTS suffered by prostate cancer patients, using a standardised scale and with measurements both before and after a specified period of HT. The most suitable reference standard for measurement of LUTS was considered to be the IPSS, but articles describing other comparable scales were also accepted.

Although there were relevant articles published over a period of more than 60 years, a time limit of 21 years (since the year 2000) was arbitrarily imposed to represent the most recent data and thereby have implications for current treatment regimens. Studies identified by the search terms that were published before that were usually focussed on the use of HT for patients in urinary retention and reported outcomes using rates of catheter removal and other measures of urinary symptoms rather than the IPSS. Studies that were published in a non-English language, involved animal studies or were only published in abstract form were also excluded. Studies that included other major treatments that were likely to impact LUTS scores within the assessment period, particularly brachytherapy, were excluded. Studies in which a minority of patients used other measures to control LUTS, for example tamsulosin, were included.

The articles were then tabulated by author, date and country [11-24]. The type of HT and any significant eligibility criteria were included. The results for the initial IPSS (or equivalent) scores and the change in that score over the longest time period given were rounded up to one decimal place and tabulated (Table 1) so that the range of results could be reviewed across studies. The changes in score were also expressed as a percentage of the initial score, which was then rounded to a whole

Table 1. List of studies reporting the effect of HT on LUTS scores, in chronological order.

Reference name, year, country	Number of patients and eligibility criteria	Hormone treatment	Symptoms assessment interval	Initial mean LUTS score (IPSS unless otherwise stated)	Absolute improvement in mean symptom score at longest interval tested	Scores for quality (Q0-Q3) and freedom from potential bias (FB0-FB3)
Klarskov [11] 2011 Denmark	77	Various forms of ADT	3 monthly to 24 months	14 – used a Danish variant of the IPSS scoring system	10 (71%) (not comparable to studies using IPSS)	Q2 FB2
Axcrona [12] 2012 Multiple European countries	175 PGV> 30mL	RCT: Degarelix vs Gos/Bical Randomised 1:1	12 wks	Degarelix 14.3 Gos/Bical 13.4	4.4 (31%) and 2.7 (20%) resp (NSD between drugs)	Q3 FB0
Anderson [13] 2013 Multiple countries	40 IPSS >12. PGV> 30mL	RCT: Degarelix vs Gos/Bical Randomised 3:1	4,8,12 wks	Degarelix 20.1 Gos/Bical 21.2	11.7 (58%) and 6.0 (28%) resp (NSD between drugs, but stopped early due to poor accrual)	Q2 FB0
Mason [14] 2013 Multiple countries	244 PGV> 30mL	RCT: Degarelix vs Gos/Bical Randomised 3:1	12 wks	Degarelix 9.5 Gos/Bical 8.5	1.7 (18%) and 0.1 (1%) resp (Diff between drugs p=0.044, although more patients had a high initial IPSS in the degarelix group)	Q3 FB0
Lebret [15] 2014 France	1276 Age >75 Yrs	Any GnRH	Between 3 and 6 months	21.1 using QLQ-PR25	4.3 (20%) (P<0.001, but not comparable to IPSS)	Q1 FB1
Choi [16] 2016 Korea	110	Leuprolide/Bical	NS	17.5	5.3 (30%) (greater with HT >1yr)	Q2 FB2
Gil 2017 [17] Multiple countries	2701	Triptorelin	24,48 wks	16.4 (18.4 in the subgroup of 83% with initial IPSS >7)	NS (7.4 (40%) in subgroup, p<0.001)	Q2 FB0
Sood [18] 2017 India	101 Retention >200ml or an IDC	Any ADT (42) or Orch (59)	Monthly to 3 months	NS but 56% were in acute retention	NS (IPSS was 5.9 ADT and 6.8 Orch at 3 months)	Q1 FB2
Zhang [19] 2017 China	45 IPSS >8	Goserelin/Flutamide	8,16,24 wks	21.2	9.4 (44%, p<0.001) (A further 45 pts that also received tamsulosin (RCT) had similar results)	Q2 FB2

Table 1 continued..

He [20] 2018 China	398	Triptorelin plus various antiandrogens	24,48 wks	NS (21.2 in subgroup of 255 pts with IPSS >7)	NS (9.0 (42%) in subgroup)	Q3 FB0
Washino [21] 2018 Japan	32	Gos/Bical	12,24 wks	11.7	2.4 (21%) (Nocturia increased)	Q2 FB2
Yikilmaz [22] 2019 Turkey	51	Goserelin or Leuprorelin (not RCT, 24 and 27 pts resp)	6 months	Goserelin 13.5 Leuprorelin 12.4	4.7 (35%) and 2.5 (20%) resp (diff between drugs p=0.001)	Q2 FB2
Christie [23] 2020 Australia	50	Triptoreline	6,12,18,24 wks	11.8 (20.0 in subgroup with IPSS >11.8 and 14.9 in subgroup with initial PGV>39cc)	1.7 (14%) (5.3 (26%) in subgroup with initial IPSS > 11.8 and 3.5 (24%) in subgroup with initial PGV >39cc)	Q2 FB1
Akpayak [24] 2020 Nigeria	65	Various including orchiectomy	12 months	23	8 (35%, p< 0.0001),	Q1 B2
14 studies 2011-2020 4 in multiple countries	32-2701 pts Total 5365	LHRH agonists most common	4 wks – 24 months	13 articles used IPSS system, range of initial scores 8.5-23	Improvement detected in every series. For those using IPSS, median improvement was	Q1 – 3 Q2 – 7 Q3 – 3 FB0 – 4 FB1 – 2 FB2 – 7

Abbreviations: RCT, Randomised controlled trial; Gos/Bical, Goserelin/Bicalutamide; IPSS, International prostate symptom score; LUTS, Lower urinary tract symptoms; resp, respectively; Diff, difference; NSD, no significant difference; NS, not stated; ADT, Androgen deprivation therapy; GnRH, Gonadotrophin Releasing hormone; Orch, Orchidectomy; yrs, years; wks, weeks.

number. Where data relating to significant subgroups were reported these were also included in the table.

No meta-analysis or quantitative synthesis of the data was attempted. No assessment for the presence of publication bias was considered necessary. However, the QUADAS-2 tool proposes that review-specific signalling questions are developed to assess the quality and the potential risk of bias for each study. The quality of each study was also assessed by considering whether it used a prospective design (including a predetermined sample size and assessment intervals), if the number of patients was high (more than 50 patients) and whether a specific product was tested (total score 0 to 3, a higher score indicating higher quality). We considered the possibility that bias could be present in that the authors of each of the studies might report a stronger effect on urinary symptoms if the study was funded by the company that manufactures the specific product undergoing testing. Thus, a score describing freedom from potential bias was derived in which two points were allocated if there were no manufacturers of any HT product involved in the study. That score was reduced to only one point if a manufacturer had provided funding but were not involved in the analysis and/or writing of the article. An additional point was added if the 'methods' section stated that there was blinding of the researchers to the scores given by their patients (total possible score 0-3, a higher score indicating greater freedom from potential bias).

RESULTS

The initial search strategy yielded 129 titles and searching through their references and citations yielded a further nine that were relevant. When the abstracts were reviewed by the authors independently, only 29 of these were considered further. When complete text versions of those articles were obtained, only 14 had usable data. The process of identification of the relevant articles and studies is described in Figure 1.

The articles reported a wide variety of sample sizes (32 to 2701 patients) but represented a combined total of 5365 patients from countries all over the world and spread across the range of dates, suggesting that the topic has wide and current interest. Two reports described results in individual countries that were each collectively included in a larger international study and, as the results were not substantially different, only the larger international study was listed [25, 26].

All of the articles included patients who had castrate-sensitive prostate cancer and included patients with either locally advanced disease and/or metastatic disease. All described patients who were starting treatment with some form of HT, most commonly androgen deprivation therapy. All of the articles described the use of the IPSS test, except that one used a local Danish variation [11] and one French study used a standardised genitourinary quality of life scoring system [15]. Most reported mean values for total IPSS at the outset and after a specific time interval/s.

Improvements in LUTS were seen in all studies. However, defining the magnitude of the improvement was complicated because some significant differences in eligibility emerged, with some articles including all patients, regardless of initial IPSS or PGV, while others applied eligibility criteria, thus limiting their analyses to those patients with a higher initial IPSS or enlarged PGV. Some included all patients regardless of their IPSS or PGV but then undertook subgroup analyses of patients with higher levels of these items as they were considered more likely to benefit from the treatment.

Twelve of the fourteen studies reported results for the IPSS score, but one of these did not report an initial IPSS score [18]. Of the remaining 11 studies, four (including three randomised trials) reported results for patients receiving specific drugs separately, yielding a total of 15 groups. Of these, the median initial IPSS was 14.3 (range 8.5-23.0) and the median improvement in IPSS was 29% (range 1-58%) [12-14, 22].

There were five studies that reported results for patients with an initial mean IPSS score above a specified threshold value. These included two that specified an IPSS score for entry into the study [13, 19], one of these with separate group reports for different study drugs [13], and three studies that reported significant subgroups with IPSS scores above a threshold value [17, 20, 23]. Thus, there were six groups or subgroups reported from five studies with an initial IPSS threshold. For these 6 groups, the median initial IPSS score was 20.7 and the median percentage improvement was 41%.

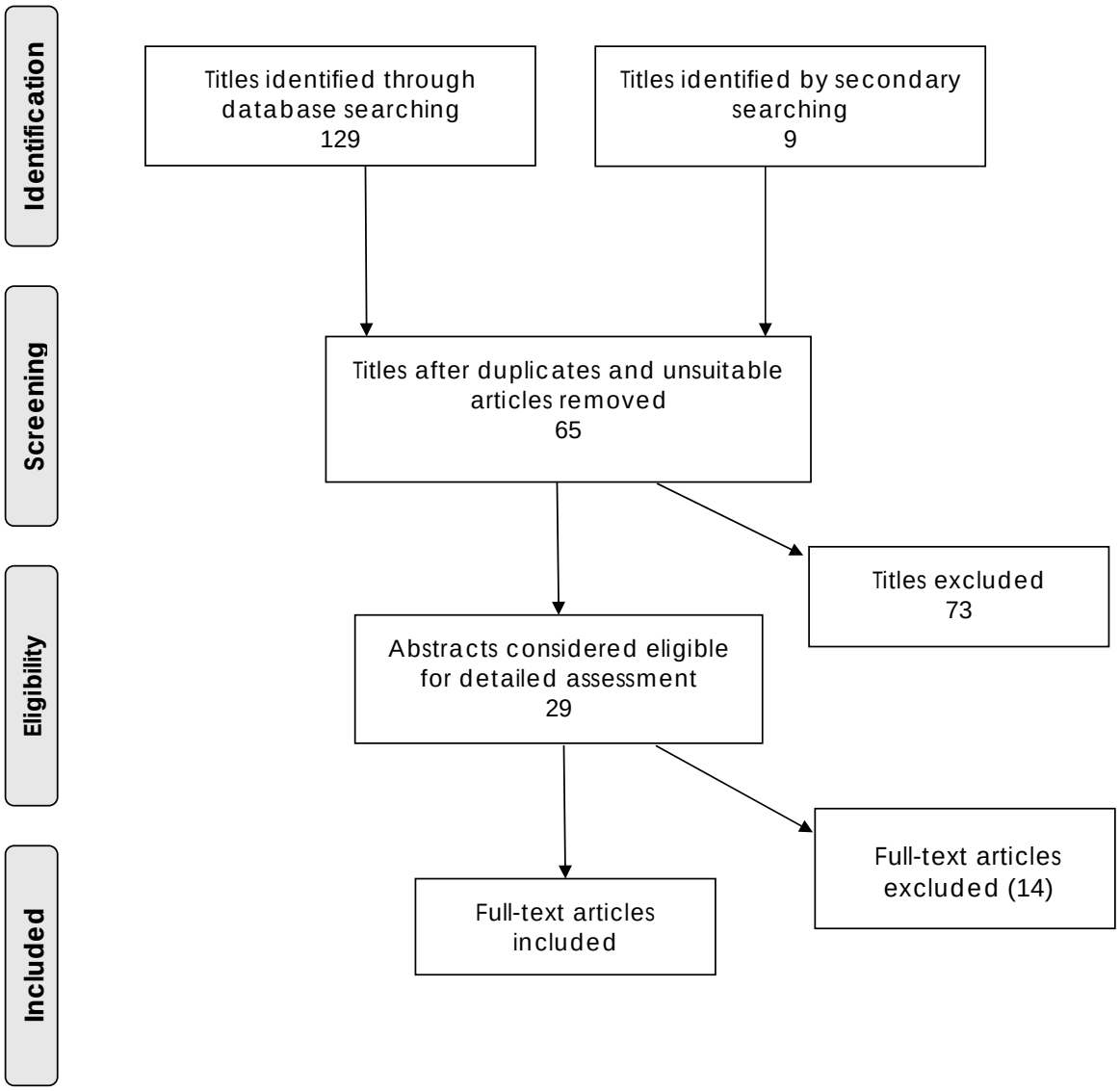

Figure 1. Results of the search strategy.

There were four studies that reported results for patients with an initial mean PGV above a specified threshold value. These included three trials with an eligibility criterion (mean PGV great than 30 mL) and reporting separate results for different study drugs [12-14], and one study which specified results for those with greater than average mean PGV of 39cc [23]. Thus, there were 7 groups or subgroups from four reports that described results for patients with an initial mean PGV threshold. For these 7 groups the median initial IPSS score was 14.3 and the percentage improvement was 24%.

Other eligibility criteria that were applied included patient factors (one study included only patients older than 75 years [15]) and one only included patients that were in urinary retention or required an IDC [18]. Understandably, the latter could not provide initial IPSS scores. However, in the study of older patients, acknowledging that a scale other than the IPSS was used, the mean percentage improvement was lower (20%) than the overall results for all studies. A similar effect for age was noted in a logistic regression analysis of one of the other studies [12].

There were seven studies that used the IPSS score and applied no other eligibility criteria beyond the broad criteria specified in the inclusion criteria of this review, although only six of these reported a score for improvement of their whole group [16, 17, 20-24]. Results for these and regarding groups or subgroups with specific eligibility criteria are summarised in Table 2.

Other measures of urinary function were often included, such as the Qmax urodynamics measurement [13, 18, 19, 22], the post-voiding residual volume [18, 19, 22], the Benign Prostate Hyperplasia Index [12], and most studies included the urological quality of life score that is appended to the IPSS but does not contribute to the total IPSS score. These other tests usually showed close agreement with the IPSS but statistical correlations between those and the changes in the overall IPSS were not reported. Three studies reported separate analyses of the mean voiding and storage subscores [11, 16, 23, 25] and the effect of HT was generally more pronounced on the mean voiding subscore.

Many of these studies also reported significant reductions in the mean PGV [11-14, 16, 18, 21-23]. All used ultrasound to measure the PGV except one that used MRI [23]. Several studies limited recruitment to patients who had an initial PGV greater than a specific threshold [12-14]. However, most made no comment on the association between IPSS and PGV. One study categorised each patient according to their initial PGV and noted greater improvement in IPSS in higher PGV categories [16]. Only one study calculated a correlation between them [23]. In that study, it was noted that although the correlation was not significant, when patients with larger than average initial PGV were considered, a strong association was seen.

Regarding the potential for bias, many of the articles described studies that were funded by pharmaceutical companies and many included employees among the co-authors, suggesting a potential for bias. These studies tended to have a lower freedom-from-potential-bias (FB) score. None of the articles indicated that blinding had been part of the study design, so there were no studies that achieved the maximum possible score for freedom from bias. Regarding the quality scores, those articles describing studies that had the lowest level of freedom-from-potential-bias (FB0), tended to have the highest quality scores (Q3), suggesting that studies with pharmaceutical funding can achieve high quality but with greater potential for bias.

DISCUSSION

This review indicates that most reports describing the effect of HT for prostate cancer on LUTS have used the IPSS system, and all studies have shown at least some symptomatic improvement. Across all groups, the median initial score was 14.3, indicating moderately severe symptoms and that

Table 2. Summary of studies using the IPSS.

Type of study group	Number of study groups	Initial IPSS score (Median and range)	Percentage change over longest time period (Median and range)	Reference numbers
All study groups with IPSS scores	15	14.3 (8.5-23.0)	29 (1-58)	12-14,16-24
Groups or subgroups with an IPSS criterion	6	20.7 (18.4-21.2)	41 (28-58)	13,17,19,20,23
Groups with a PGV criterion	7	14.3 (8.5-21.2)	24 (1-58)	12-14,23
Groups or subgroups with no eligibility criterion	7	13.5 (11.7-23.0)	26 (14-35)	16,16,20-24

score improved by a median of 29%, or approximately four points, indicating significant symptomatic benefit. However, this review has some significant limitations.

First, the studies reviewed were highly variable in design and quality, ranging from small retrospective single institution studies to large prospective international trials. Not unexpectedly, there were no studies with control groups. In many studies the drugs used for HT were not specific and the patients were able to take other medications that could potentially affect their LUTS, such as alpha-blockers. The IPSS was the most commonly used instrument but not all of the studies used it and their results could not be compared with those from other studies. The assessment interval varied widely, but 12 and 24 weeks were most commonly used.

Second, the studies had variable eligibility criteria. Patients with no significant LUTS were often included, even though these patients are unlikely to experience a detectable change in their IPSS scores. When the review was confined to those reports describing groups or subgroups with a specific initial IPSS threshold, greater percentage changes in the scores were seen.

Third, a range of analyses of IPSS results were seen. These included absolute and percentage changes over time in the mean scores, but some studies additionally or alternatively reported changes in the percentage of patients in specific categories such as the proportion of those with moderate or severe symptoms (indicated by a score greater than 13). Others reported the number of patients with an improvement in their score by more than three points, sometimes considered the minimum for clinical significance [27]. Although the best type of analysis is unknown, basic mean and range values for IPSS scores of all of the patients entered into the study should always be reported.

Fourth, some of the studies were sponsored by companies that would have a commercial interest in the outcome. This was reflected in the scores given for freedom-from-potential-bias. However, these studies also tended to have higher scores for quality and incorporated eligibility criteria. Three of the studies involved randomised comparisons of degarelix and goserelin/bicalutamide [12-14]. These studies have been subjected to limited systematic review and pooled analysis with a combined total of 463 patients [28-30]. Each of these reviews concluded a stronger effect on IPSS for the product manufactured by the sponsor.

However, none of these limitations are likely to affect the main conclusions that have been drawn here. The fact that some of the studies were large and were recently published indicates that the level of interest in this topic remains high and we were surprised that no previous systematic review had ever been reported. Further research seems likely to be undertaken and this review could provide some assistance in the design of it. Our advice for future researchers would be to limit eligibility to those with significant initial symptoms. Studies should be limited to test the effectiveness of specific types of HT with other medications added only as part of a predetermined schedule. Symptoms should be measured using the IPSS at intervals that include 12 and 24 weeks and improvements reported using mean and median values (as these can differ). Precautions should be taken to avoid bias. For example, pharmaceutical industry input could be limited to the provision of funding, medication and other forms of support, but with limitations on the roles in management of the data and authorship in order to maintain credibility.

The role of other, more objective, measures and their correlation with the IPSS could be further investigated. The measurement of PGV seems unlikely to play a major role in the investigation of LUTS in this setting as the only study to investigate the correlation between them did not reveal a strong association [23] and repeated imaging is logistically demanding. In this review, reported data from groups and subgroups of patients with an elevated PGV as an eligibility criterion were not noticeably different to data from other patients in terms of their initial mean IPSS scores or their mean IPSS responses to HT. However, tests such as urodynamic studies and personal diaries of urinary volumes and frequency may prove to be more practical ways of confirming and elucidating the subjective impression conveyed by the patient in the IPSS score.

CONCLUSION

In conclusion, we report the first systematic review of the effect of HT on LUTS in prostate cancer

patients. It shows that most patients described in these studies have significant LUTS and that improvement in these occurs when treated by HT. There is significant potential for further research, and we have offered suggestions to help guide that.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest and no financial support to declare.

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