UNIVERSITY^{OF} BIRMINGHAM University of Birmingham Research at Birmingham

Switching cancers

Kourbanhoussen, Kassim; McMartin, Catherine; Lodde, Michele; Zlotta, Alexandre; Bryan, Rik; Toren, Paul

DOI: 10.1016/j.euf.2020.10.002

License: Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version Peer reviewed version

Citation for published version (Harvard):

Kourbanhoussen, K, McMartin, C, Lodde, M, Zlotta, A, Bryan, R & Toren, P 2021, 'Switching cancers: a systematic review assessing the role for androgen suppressive therapy in bladder cancer', *European Urology Focus*, vol. 7, no. 5, pp. 1044-1051. https://doi.org/10.1016/j.euf.2020.10.002

Link to publication on Research at Birmingham portal

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.

Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)

•Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Title: Switching cancers: a systematic review assessing the role for androgen suppressive therapy in bladder cancer

Kassim Kourbanhoussen¹ MD, Catherine McMartin¹ MD, Michele Lodde^{1,2} MD, Alexandre Zlotta³ MD, PhD, Richard T Bryan⁴ MD, PhD, Paul Toren^{1,2} MD, PhD

Author Affiliations

¹Department of Surgery, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada ²Centre de Recherche du CHU de Québec - Université Laval, Oncology Division, Quebec City, QC, Canada.

³Department of Surgery, Faculty of Medicine, Université Laval, Quebec City, Quebec, Canada ⁴Institute of Cancer & Genomic Sciences, University of Birmingham, Birmingham, B15 2TT, United Kingdom.

Corresponding Author:

Paul Toren, MD, PhD, FRCSC Assistant Professor, Université Laval Research Scientist, Centre de Recherche du CHU de Québec- Université Laval and Centre de Recherche sur le Cancer, Université Laval Uro-Oncologist, CHU de Québec-Université Laval 10 McMahon, rm 0877 Québec, QC, Canada, G1R 3S1 paul.toren@crchudequebec.ulaval.ca Tel: 418-525-4444 ext. 17064 Fax: 418-691-5562

Key words: androgen suppression therapy; androgens, bladder cancer, recurrence, incidence, systematic review

Abstract word count: 234 words Patient summary: 46 words Article word count: 2501 words

Funding: PT was supported by a clinician-scientist award from Fonds de Recherche du Québec – Santé (#32774).

Abstract

Context: Bladder cancer demonstrates striking gender-based differences in incidence, with a role for androgens possibly implicated in the development and progression of the disease. Emerging pre-clinical and clinical evidence suggest there may be a role for anti-androgen therapy for bladder cancer.

Objective: This systematic review assessed the current clinical evidence evaluating androgen suppressive therapy (AST) for the treatment or prevention of bladder cancer.

Evidence Acquisition: Following Prisma guidelines, MEDLINE was searched for full-text articles detailing clinical outcomes or incidence of bladder cancer among patients who received AST, defined as gonadotropin-releasing hormone agonists or equivalent, androgen receptor antagonists or 5-alpha reductase inhibitors.

Evidence Synthesis: A total of twelve studies were included. Five studies focused on prostate cancer patients, with one study in men with lower urinary tract symptoms. In these studies, a lower incidence of bladder cancer was observed in 5 studies, with adjusted risk reduction estimates ranging from 7-47%. Six studies evaluating 11,820 bladder cancer patients investigated clinical outcomes among men who received a form of AST. Three out of four studies evaluating recurrence-free survival found a benefit for AST, with adjusted hazard ratios for recurrence of non-muscle invasive cancer ranging from 0.29-0.53. Limitations included a large variability in data sources and methodologies, as well as no data on tolerability.

Conclusions: Current evidence indicates that anti-androgen therapies exert a favorable influence on bladder tumors. Further prospective studies are needed to assess their therapeutic potential.

Patient Summary: Androgen suppressive therapy is commonly prescribed for treatment of prostate-related problems. Prior research indicates there may be a role for these treatments in patients with bladder cancer. In this review, we evaluate the current evidence which strongly suggests these agents may be effective against bladder cancer.

Introduction

The incidence of bladder cancer is 3-4 times higher in men, yet women tend to present with more aggressive tumors which have poorer outcomes¹⁻⁴. Moreover, women have a higher risk of recurrence, while incidence rates appear to be rising more rapidly in men than in women^{5,6}. Recent research and reviews question the etiology of these differences^{1,6-8}, with the role of sex steroids such as androgens re-emerging as an area of interest.

Sex steroids appear to be a major contributor to explain observed epidemiological sex differences in bladder cancer^{1,3,7,9}. The globally increased mortality to incidence ratio for women strongly suggests that biological factors might be one the largest contributing factors to sex differences in incidence and progression rates^{3,7,10}. Sex steroids are known to alter the function of various immune cells^{9,11} and immunological differences between sexes are well established, altering susceptibility to infections, autoimmune disease, response to vaccines and malignancy rates^{9,12,13}. It thus remains an intriguing question whether the biological differences which contribute to a gender-associated dichotomy in bladder cancer incidence and outcomes may be harnessed therapeutically.

Gender differences are pertinent to the topic of androgen suppressive therapy (AST) in bladder cancer, given the respective differences in circulating androgens. Several recent reviews have more extensively addressed the topic of gender differences in bladder cancer^{1,6,8}. Prior research on MIBC molecular subtypes demonstrates higher incidence of basal/squamous tumors in women and higher incidence of luminal unstable tumors in men¹⁴. Interestingly, a pan-cancer TCGA analysis identified relatively few genes with significant expression differences between the genders in bladder cancers when compared to other cancers¹⁵; however, in terms of epigenetic methylation, there was a relatively large number of genes with gender differences compared to other cancers¹⁵. Recent transcriptomic studies in MIBC suggest that higher AR signaling occurs in luminal bladder tumors, as well as higher androgen signaling in luminal papillary tumors in males compared to females¹⁶. In terms of tumoral AR protein expression, a meta-analysis found no gender-based differences¹⁷. This concurs with recently published results in a large series (Figure 1A)¹⁸. Further, our recent analysis of AR expression in patient tumors and the relationship with long-term clinical outcomes did not suggest an interaction between gender and AR expression on clinical outcomes¹⁸ Together, these gender differences in bladder tumor biology support the potential for differences in sex steroid levels to alter bladder tumor

biology, though it remains challenging to dissect their influence on tumor carcinogenesis versus recurrence or progression of known disease.

Numerous preclinical studies have evaluated the role of the AR and androgens in bladder carcinogenesis. Older studies of chemically-induced bladder cancer in rats demonstrated higher bladder cancer incidence rates in ovariectomized female rats given testosterone, and estrogens decreased the incidence in male rats¹⁹. Using AR knockout mice (ARKO), Miyamoto *et al.* demonstrated the importance of the AR in bladder carcinogenesis, with mice lacking AR having lower incidence of carcinogen-N-butyl-N-(4- hydroxybutyl) nitrosamine (BBN)-induced bladder cancer²⁰. Similar studies have demonstrated that castration also reduces bladder cancer incidence in mice²¹. This has been confirmed with urothelial-specific AR depletion studies, which suggest AR signalling may contribute to DNA damage via the p53 pathway²². More recently, single-cell sequencing studies using the MB49 bladder cancer murine model suggest that a testosterone mediated exhaustion of T-cells in the bladder tumor microenvironment via a non-AR dependant mechanism may help explain the higher male incidence of bladder cancer²³.

Pre-clinical evaluation of the role of androgens and AST on bladder cancer recurrence rates is more challenging given the limited models of NMIBC biology. Cell line studies suggest that AR antagonists (such as bicalutamide and enzalutamide) may directly inhibit the growth of bladder cancer cells in vitro^{20,24}. Similarly, murine bladder cancer models suggest that castration or anti-androgens can slow tumor growth^{10,20}. AR expression appears to be increased in chemotherapy-resistant bladder cancer cells lines^{25,26}, with combination anti-androgens and chemotherapy approaches for MIBC suggested by these in vitro studies^{26,27}.

Correlative studies in patients suggest that the AR pathway is related to the progression and recurrence risk of bladder tumors. In the meta-analysis of AR immunohistochemistry in bladder tumors¹⁷, a lack of AR expression was associated with a higher recurrence rate¹⁷. Further, no association was found with AR expression and tumor grade or stage. However, further studies are required given the variability of these latter findings of AR expression and tumor grade and stage, with discordant results even reported from the same laboratory^{18,28,29}. A comparison of the two studies which utilized pathologic tissue sections in both NMIBC and muscle-invasive bladder cancer (MIBC) specimens suggests that AR expression is more common in lower stage tumors at lower risk of progression (Figure 1B)^{18,30}. A smaller study evaluating AR mRNA expression in NMIBC found similar results³¹. Taken together, these studies suggest that AR

expression in bladder tumors may be expressed at a higher frequency in lower stage tumors at lower risk of recurrence or progression.

Therefore, these correlative and pre-clinical studies establish a role for androgens and AR signaling in bladder cancer biology. However, the relative importance of direct effects on bladder tumors vs indirect effects on the immune microenvironment remains incompletely understood and crucially important given the enlarging role of immunotherapy for bladder cancer patients. In this systematic review, we assess the available evidence as to how androgens may be targeted to improve bladder cancer outcomes. Our primary objective is to assess androgen suppressive therapy (AST) as a treatment for bladder cancer patients. We define AST as androgen receptor antagonists or medications which decrease androgen levels, such as 5-alpha reductase inhibitors (5-ARIs), gonadotropin-releasing hormone (GnRH) agonists or antagonists. Specifically, we aim to evaluate the clinical evidence for AST on the incidence of bladder cancer and the clinical outcomes of patients with bladder cancer.

Evidence Acquisition

A search of MEDLINE via PubMed from inception until June 30, 2020 for English or Frenchlanguage studies was performed using the terms "bladder cancer", "urinary bladder neoplasms", or "urothelial carcinoma" (MeSH Term) and one of: "androgen" or "ADT" or "androgen receptor antagonist" or "5α-reductase" or "5ARI" or "anti-androgen" or "bicalutamide" or "enzalutamide" or "abiraterone" or "finasteride" or "dutasteride" or "GnRH agonist" or "GnRH antagonist" or "castration" or "nilutamide" or "flutamide" or "apalutamide" or "darolutamide"; and "humans"(MeSH Term). References from pertinent articles were also reviewed and similar searches performed on Google Scholar.

For inclusion, articles needed to have a full-text article available. Articles were excluded where there was no AST reported in bladder cancer patients. Review of titles, abstracts and, where necessary, full text determined if each study met inclusion and exclusion criteria. Selection of articles was performed independently by two authors (KK, CM), with final selection of studies confirmed by consensus of 3 authors (KK, CM, PT). Figure 2 describes a summary of the search strategy results.

To assess for publication bias, we planned to use funnel plots for outcomes with 10 or more included studies. Risk of bias was assessed using the Risk Of Bias In Non-randomized Studies - of Interventions(ROBINS-I) tool³², summarized in Supplemental Table 1.

Evidence Synthesis

Patient populations

Six studies evaluated the use of AST in bladder cancer patients $(n=11,820)^{33-38}$, while 5 studies evaluated patients with or at risk for prostate cancer³⁸⁻⁴², with one study consisting of patients with both prostate cancer and bladder cancer³⁸. One study re-evaluated data from a clinical trial of finasteride for lower urinary tract symptoms⁴³. Among bladder cancer patients included, 1461(12.4%) received 5-ARIs and 42 (0.4%) received androgen deprivation therapy (ADT). No studies reported use of androgen suppression therapy (AST) in women with bladder cancer. Table 1 summaries the study designs and populations of selected studies. The risk of bias evaluation with ROBINS-I indicates moderate bias present for all but one study, as summarized in Supplementary Table 1.

Effect of AST on bladder cancer incidence

Six studies assessed whether AST decreased the incidence of bladder cancer diagnosis; these are summarized in Table 2. While a statistically lower incidence was only reported in 2 studies (representing 17,815 out of 20,479 cases)^{41,44}, three other studies reported similar non-significant reductions in incidence^{39,40,42}; only the study with the lowest number of incident bladder cancers had odds ratios not in favor of AST use⁴³. Notably, in the study by Morales et al., the decrease in hazard was only in well- and moderately-differentiated tumors, with no decrease in the diagnoses of poorly-differentiated or undifferentiated tumors⁴¹. Differences in bladder grade or stage are not reported in the other studies.

Effect of AST on bladder cancer recurrence and progression

Six retrospective studies reported the effect of AST on patients diagnosed with bladder cancer: four evaluated patients with NMIBC^{33,34,36,38}, one focused on MIBC patients³⁵, and one included all patients with bladder cancer³⁷. The latter Finnish population-based analysis compared outcomes of bladder cancer patients receiving 5ARIs compared to non-users as well as men

receiving alpha-blockers. Despite no differences in Charlson co-morbidity between groups, overall and bladder cancer specific survival was higher among 5ARIs users compared to non-users, with no difference identified for alpha-blocker users vs non-users. This was the only study assessing the effect of dose, with pre-diagnostic benefits significant only after 3 years of use, and post-diagnostic 5ARI use showing dose-dependent effects on bladder-cancer survival. However, a lag time analysis suggested the benefit of 5ARIs did not accumulate with years of 5ARI use. The risk of multiple transurethral resections was significantly lower among alpha-blocker users, with similar non-significant hazard ratios among 5ARI users.

In NMIBC, similar studies from Japan and Florida suggest a decreased recurrence rate among patients on AST, but this was not found in our recent study^{33,34,36}. Our very high (92%) proportion of high-risk patients may explain the differences, with all patients in the Florida study who progressed on AST having high-risk disease. The Florida study also may have incurred bias favoring AST by excluding patients starting ARIs after recurrence or progression. In the Japanese study, there were more patients in the AST group who had a history of recurrent bladder cancer (10(31%) vs 29(15%)), but a non-significant lower rate of high grade bladder cancer in the AST group (15(47%)) vs control group(112(57%)). Taken together, these three series suggest the benefit for AST may be greater in patients with low-risk NMIBC or that the benefit is not observable when concurrent BCG is given. In the largest series of NMIBC patients receiving androgen deprivation therapy for prostate cancer, concurrent immunohistochemistry studies indicated that AR-expressing but not ER-expressing tumors had fewer recurrences, suggesting an AR-mediated mechanism³⁸.

Conclusions

Our systematic review identified 12 studies which evaluated different forms of AST on clinical outcomes in patients. These suggest that use of AST may potentially decrease the incidence of bladder cancer, though the results are inconsistent. However, all but one study to date indicates AST has a favorable effect on the recurrence rates of bladder cancer. This benefit appears most robust in low-grade, low risk NMIBC, where immunohistochemistry studies support a plausible mechanism of action through the AR which is more frequently expressed in these tumors. However, the two studies in MIBC also suggested an overall survival benefit.

The evidence reviewed here is entirely retrospective and derived from cohorts of various sizes

and diverse study populations. The adjustment covariates included in the analyses accordingly varied significantly throughout the studies; no study tested for interactions (e.g. with smoking history and AST). The number of studies included was too low to adequately assess for publication bias of the effects of AST on either incidence or recurrence rates. Evaluating four relevant abstracts excluded from our review due to the lack of a full text , we did not observe a bias with two reporting positive results favoring AST and two reporting negative results. Data on adverse effects of AST were generally not included, although one study reporting a lack benefit of AST for decreasing NMIBC recurrence did, however, observe that patients receiving 5-ARI were more likely to complete the prescribed intravesical BCG therapy³⁴. Of note, the quantity of evidence increased significantly in more recent years, with 10/12 studies published in the last 5 years and half in the last 2 years. Overall, the risk of bias in the studies was moderate, with frequent moderate bias due to confounding (as expected in non-randomized studies). Serious concern about bias was raised in one study which had very low numbers of incident bladder cancer⁴². Evaluating the effect of AST on bladder cancer incidence was also limited by low numbers in two other studies^{39,43}.

The populations studied in our review highlight many caveats to interpreting these results. This includes the potential for selection or health-user biases, though the population-based results by Makëla et al argue against both³⁷. Eight of the studies derive from populations with universal health care access, with two of the remaining four studies evaluating patients in a clinical trial. This also suggests access to care is unlikely to influence the results. Unsurprisingly given the ubiquity of urinary symptoms in elderly men, the vast majority of the studies studied the role of 5ARIs, with 97% of patients receiving 5ARIs and only 3% receiving more potent androgen suppression with medical castration or AR antagonists. Thus, it remains unclear if more potent suppression of the AR axis will have greater benefit, with individual studies possessing insufficient numbers for comparisons³⁶. No studies included women, where AST is infrequently prescribed for endocrine disorders. Further, no studies reported on AST and upper tract urothelial carcinoma. Only one study investigated concomitant biomarkers of response to patients receiving anti-androgens, suggesting a better response among patients with bladder tumors expressing AR³⁸, though the sample size was small.

The effects of AST are not limited to the androgen axis. Inhibition of the AR axis in patients results in perturbation of other sex steroids, including estrogens, which may in turn directly or indirectly influence bladder tumor recurrence or progression. Clinically, 5ARIs increase serum

estrogen levels in women (~30%) and men (~10%)^{45,46}. An even higher reflex increase in estrogens is noted with more potent anti-androgens⁴⁷. It remains possible that these changes in tissue estrogens and the generally recognized effects of estrogen as an immune activator may contribute to the benefit observed with anti-androgens. Notably, expression of ER α or ER β in bladder tumors does not associate with response to androgen suppression in men³⁸, while they are related to prognosis^{29,48}. Thus, it remains possible that independent estrogen signalling pathways in bladder tumors or immune-mediated effects of increased circulating estrogens following AST may partly explain the observed benefits.

Given the concomitant potential bladder outflow benefits and a very favorable safety profile validated in two large prostate cancer chemoprevention trials^{49,50}, there is a compelling case for the prospective evaluation of 5-ARIs as secondary prevention of NMIBC recurrence in men. While it is biologically plausible that the more potent effects of AR antagonists may impart a larger impact, clinical data for use of such therapy is weaker, as is evidence for the use of 5ARIs or other anti-androgens in MIBC. To date, there exists one registered trial evaluating enzalutamide in NMIBC(NCT02605863), although the trial was stopped due to poor accrual at the single institution involved.

In summary, the emerging evidence indicates that androgen suppressive therapies may exert a favorable influence on bladder tumors. Further prospective studies are needed to assess their therapeutic potential.

References

- Uhlig, A. *et al.* Gender Specific Differences in Disease-Free, Cancer Specific and Overall Survival after Radical Cystectomy for Bladder Cancer: A Systematic Review and Meta-Analysis. *J. Urol.* 200, 48–60 (2018).
- 2. Wang, S.-C. *et al.* The gender difference and mortality-to-incidence ratio relate to health care disparities in bladder cancer: National estimates from 33 countries. *Sci Rep* **7**, 4360 (2017).

- Cumberbatch, M. G. K. *et al.* Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018. *European Urology* 74, 784–795 (2018).
- Kluth, L. A. *et al.* Gender-specific differences in clinicopathologic outcomes following radical cystectomy: an international multi-institutional study of more than 8000 patients. *Eur. Urol.* 66, 913–919 (2014).
- Donsky, H., Coyle, S., Scosyrev, E. & Messing, E. M. Sex differences in incidence and mortality of bladder and kidney cancers: national estimates from 49 countries. *Urol. Oncol.* 32, 40.e23–31 (2014).
- Uhlig, A. *et al.* Gender-specific Differences in Recurrence of Non-muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis. *Eur Urol Focus* 4, 924–936 (2018).
- Sadighian, M. & Porten, S. Gender differences in oncologic and functional outcomes in patients with bladder cancer undergoing radical cystectomy with urinary diversion. *Curr Opin Urol* 29, 542–547 (2019).
- Bilski, K., Zapała, Ł., Skrzypczyk, M. A., Oszczudłowski, M. & Dobruch, J. Review on gender differences in non-muscle invasive bladder cancer. *Transl Androl Urol* 8, 12–20 (2019).
- Klein, S. L. & Flanagan, K. L. Sex differences in immune responses. *Nat. Rev. Immunol.* 16, 626–638 (2016).
- Li, P., Chen, J. & Miyamoto, H. Androgen Receptor Signaling in Bladder Cancer. *Cancers* (*Basel*) 9, (2017).
- Boibessot, C. & Toren, P. Sex steroids in the tumor microenvironment and prostate cancer progression. *Endocr. Relat. Cancer* 25, R179–R196 (2018).

- Gubbels Bupp, M. R., Potluri, T., Fink, A. L. & Klein, S. L. The Confluence of Sex Hormones and Aging on Immunity. *Front Immunol* 9, 1269 (2018).
- Mirandola, L. *et al.* Sex-driven differences in immunological responses: challenges and opportunities for the immunotherapies of the third millennium. *Int. Rev. Immunol.* 34, 134–142 (2015).
- Kamoun, A. *et al.* A Consensus Molecular Classification of Muscle-invasive Bladder Cancer. *Eur Urol* 77, 420–433 (2020).
- Yuan, Y. *et al.* Comprehensive Characterization of Molecular Differences in Cancer between Male and Female Patients. *Cancer Cell* 29, 711–722 (2016).
- de Jong, J. J. *et al.* Distribution of Molecular Subtypes in Muscle-invasive Bladder Cancer Is Driven by Sex-specific Differences. *Eur Urol Oncol* 3, 420-423. (2020).
- Sanguedolce, F. *et al.* Role of androgen receptor expression in non-muscle-invasive bladder cancer: a systematic review and meta-analysis. *Histol Histopathol* 18189 (2019) doi:10.14670/HH-18-189.
- Toren, P. *et al.* Androgen receptor and immune cell PD-L1 expression in bladder tumors predicts disease recurrence and survival. *World Journal of Urology* (2020) doi:10.1007/s00345-020-03358-x.
- 19. Okajima, E. *et al.* Effect of sex hormones on development of urinary bladder tumours in rats induced by N-butyl-N-(4-hydroxybutyl) nitrosamine. *Urological Research* **3**, 73–79 (1975).
- Miyamoto, H. *et al.* Promotion of bladder cancer development and progression by androgen receptor signals. *J. Natl. Cancer Inst.* 99, 558–568 (2007).
- Imada, S. *et al.* Promoting effects and mechanisms of action of androgen in bladder carcinogenesis in male rats. *Eur. Urol.* **31**, 360–364 (1997).

- Hsu, J.-W. *et al.* Decreased Tumorigenesis and Mortality from Bladder Cancer in Mice Lacking Urothelial Androgen Receptor. *The American Journal of Pathology* 182, 1811–1820 (2013).
- Kwon, H. *et al.* Distinct CD8⁺ T Cell Programming in the Tumor Microenvironment Contributes to Sex Bias in Bladder Cancer Outcome. *bioRxiv* 2020.04.13.039735 (2020) doi:10.1101/2020.04.13.039735.
- Kawahara, T. *et al.* Enzalutamide inhibits androgen receptor-positive bladder cancer cell growth. *Urol. Oncol.* 34, 432.e15–23 (2016).
- 25. Kameyama, K. *et al.* Enzalutamide inhibits proliferation of gemcitabine-resistant bladder cancer cells with increased androgen receptor expression. *Int J Oncol* **50**, 75–84 (2017).
- 26. Kashiwagi, E. *et al.* Androgen receptor activity modulates responses to cisplatin treatment in bladder cancer. *Oncotarget* **7**, 49169–49179 (2016).
- Tyagi, A. *et al.* Combination of androgen receptor inhibitor and cisplatin, an effective treatment strategy for urothelial carcinoma of the bladder. *Urol. Oncol.* 37, 492–502 (2019).
- 28. Mir, C. *et al.* Loss of androgen receptor expression is not associated with pathological stage, grade, gender or outcome in bladder cancer: a large multi-institutional study. *BJU Int.* 108, 24–30 (2011).
- 29. Miyamoto, H. *et al.* Expression of androgen and oestrogen receptors and its prognostic significance in urothelial neoplasm of the urinary bladder. *BJU Int.* **109**, 1716–1726 (2012).
- Boorjian, S. *et al.* Androgen receptor expression is inversely correlated with pathologic tumor stage in bladder cancer. *Urology* 64, 383–388 (2004).
- 31. Yasui, M. *et al.* Androgen receptor mRNA expression is a predictor for recurrence-free survival in non-muscle invasive bladder cancer. *BMC Cancer* **19**, 331 (2019).

- Sterne, J. A. *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 355, i4919 (2016).
- 33. Wu, S.-C. *et al.* Androgen Suppression Therapy Is Associated with Lower Recurrence of Non–muscle-invasive Bladder Cancer. *European Urology Focus* S2405-4569(19)30141–5 doi:10.1016/j.euf.2019.04.021.
- 34. Al-Hogbani, M., Gilbert, S., Lodde, M., Fradet, Y. & Toren, P. Does 5-alpha Reductase Inhibitor Use Improve The Efficacy of Intravesical Bacille Calmette-Guérin (BCG) for Nonmuscle Invasive Bladder Cancer? *Bladder Cancer* Preprint, 1–7 (2020).
- 35. McMartin, C. *et al.* The use of 5-alpha reductase inhibitors prior to radical cystectomy do they render high-grade bladder tumors less aggressive? *Clin Genitourin Cancer* (2019).
- 36. Shiota, M. *et al.* Suppressed Recurrent Bladder Cancer after Androgen Suppression with Androgen Deprivation Therapy or 5α-Reductase Inhibitor. *J. Urol.* **197**, 308–313 (2017).
- Mäkelä, V. J., Kotsar, A., Tammela, T. L. J. & Murtola, T. J. Bladder Cancer Survival of Men Receiving 5α-Reductase Inhibitors. *J. Urol.* 200, 743-748. (2018).
- Izumi, K. *et al.* Androgen deprivation therapy prevents bladder cancer recurrence. Oncotarget 5, 12665–12674 (2014).
- Wallner, L. P., Wang, R., Jacobsen, S. J. & Haque, R. Androgen deprivation therapy for treatment of localized prostate cancer and risk of second primary malignancies. *Cancer Epidemiol Biomarkers Prev* 22, 313–316 (2013).
- Moschini, M. *et al.* The effect of androgen deprivation treatment on subsequent risk of bladder cancer diagnosis in male patients treated for prostate cancer. *World J Urol* 37, 1127– 1135 (2019).

- Morales, E. E. *et al.* Finasteride Reduces Risk of Bladder Cancer in a Large Prospective Screening Study. *Eur. Urol.* 69, 407–410 (2016).
- 42. Shiota, M. *et al.* Secondary bladder cancer after anticancer therapy for prostate cancer: reduced comorbidity after androgen-deprivation therapy. *Oncotarget* 6, 14710–14719 (2015).
- 43. Sathianathen, N. J., Fan, Y., Jarosek, S. L., Lawrentschuk, N. L. & Konety, B. R. Finasteride does not prevent bladder cancer: A secondary analysis of the Medical Therapy for Prostatic Symptoms Study. *Urol Oncol* 36, 338.e13-338.e17 (2018).
- 44. Chen, C.-C., Huang, C.-P., Tsai, Y.-T., Hseih, T.-F. & Shyr, C.-R. The Genomic Alterations of 5α-Reductases and Their Inhibitor Finasteride's Effect in Bladder Cancer. *Anticancer Res.* 37, 6893–6898 (2017).
- Bayram, F., Müderris, I. I., Güven, M. & Keleştimur, F. Comparison of high-dose finasteride (5 mg/day) versus low-dose finasteride (2.5 mg/day) in the treatment of hirsutism. *Eur. J. Endocrinol.* 147, 467–471 (2002).
- 46. Kristal, A. R. *et al.* Associations of serum sex steroid hormone and 5α-androstane-3α,17β-diol glucuronide concentrations with prostate cancer risk among men treated with finasteride.
 Cancer Epidemiol. Biomarkers Prev. 21, 1823–1832 (2012).
- 47. Wadhwa, V. K., Weston, R. & Parr, N. J. Bicalutamide monotherapy preserves bone mineral density, muscle strength and has significant health-related quality of life benefits for osteoporotic men with prostate cancer. *BJU Int.* **107**, 1923–1929 (2011).
- 48. Nguyen, D. P. *et al.* Association of Aromatase With Bladder Cancer Stage and Long-Term Survival: New Insights Into the Hormonal Paradigm in Bladder Cancer. *Clin Genitourin Cancer* 15, 256-262.e1 (2017).

- 49. Andriole, G. L. *et al.* Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* **362**, 1192–202 (2010).
- Thompson, I. M. *et al.* The Influence of Finasteride on the Development of Prostate Cancer. New England Journal of Medicine 349, 215–224 (2003).

Figure 1. **A**. Expression of AR in non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC) by sex. Data derived from immunohistochemistry staining for AR441 clone as described¹⁸. **B**. Comparison of the percentage of AR expressing tumors in two published studies using immunohistochemistry of tissue sections for both NMIBC and MIBC^{18,30}. Pathologic stage T4 tumors were excluded as none were reported in the series by Boorjian et al³⁰.



Figure 2. Flow chart detailing article selection.

