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DOI:
10.1016/j.euf.2020.10.002

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

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

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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 outcomes[1–4]. 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 men[14]. Interestingly, a pan-cancer TCGA analysis identified relatively few genes with significant expression differences between the genders in bladder cancers when compared to other cancers[15]; however, in terms of epigenetic methylation, there was a relatively large number of genes with gender differences compared to other cancers[15]. 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 females[16]. In terms of tumoral AR protein expression, a meta-analysis found no gender-based differences[17]. 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 outcomes[18] 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 rats[19]. 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 cancer[20]. Similar studies have demonstrated that castration also reduces bladder cancer incidence in mice[21]. This has been confirmed with urothelial-specific AR depletion studies, which suggest AR signalling may contribute to DNA damage via the p53 pathway[22]. 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 cancer[23].

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 tumors[17], a lack of AR expression was associated with a higher recurrence rate[17]. 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 results[31]. 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 French-language 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) tool[32], 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 cancer[38–42], with one study consisting of patients with both prostate cancer and bladder cancer[38]. One study re-evaluated data from a clinical trial of finasteride for lower urinary tract symptoms[43]. 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 use[43]. 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 tumors[41]. 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 patients[35], and one included all patients with bladder cancer[37]. 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 mechanism[38].

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 therapy[34]. 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 cancer[42]. 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 both[37]. 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 comparisons[36]. 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 AR[38], 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-androgens[47]. 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 ERα or ERβ in bladder tumors does not associate with response to androgen suppression in men[38], 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.

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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 described[18]. **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 al[30].

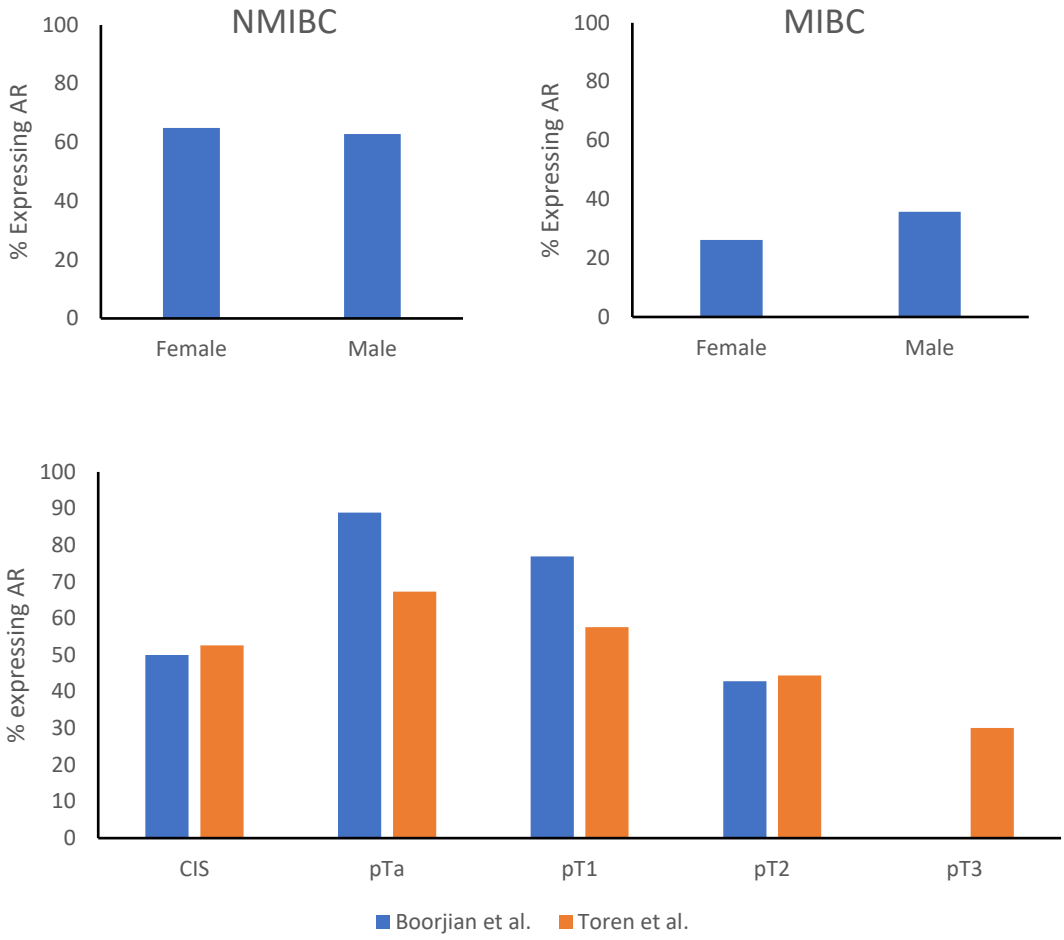

Figure 2. Flow chart detailing article selection.