Testosterone replacement therapy and bladder cancer

Mikael F. Kanaan[1], Rodney H. Breau[1,2], Luke T. Lavallée[1,2], Daniel I. McIsaac[1,2], Luke Witherspoon[1, 2]

[1]University of Ottawa, Ottawa, ON, Canada; [2]Division of Urology, The Ottawa Hospital and Ottawa Hospital Research Institute, Ottawa, ON, Canada

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Corresponding author: Dr. Luke Witherspoon, Division of Urology, The Ottawa Hospital, Ottawa, ON, Canada; lwitherspoon@ohri.ca

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ABSTRACT

KEY MESSAGES

Preoperative testosterone may prevent surgery-related:

- Muscle atrophy
- Strength loss
- Need for blood transfusion
- Hypogonadism

Muscle-invasive bladder cancer is a common malignancy, and its standard of care treatment often involves neoadjuvant chemotherapy and radical cystectomy. These treatments are invasive and associated with significant mortality and morbidity. Neoadjuvant chemotherapy is associated with skeletal muscle atrophy and reduced body mass, while radical cystectomy is associated with high-risk blood loss necessitating blood transfusion. Despite an established relationship between androgens and prostate cancer, it is unclear whether androgens impact other types of cancer, including bladder cancer. In fact, decades of research on the relationship between anti-androgens and cancer prevention/treatment have provided conflicting or inconclusive results. Preoperative testosterone could prevent surgery-related skeletal muscle atrophy and help maintain normal hematocrit levels. Preoperative testosterone is an inexpensive and feasible intervention and seems to improve postoperative recovery with minimal adverse effects in different patient populations. To date, no clinical trial has been conducted evaluating preoperative testosterone in bladder cancer patients. In this

review, we present a rationale for the use of preoperative testosterone in bladder cancer patients, which we believe may serve as the basis for the development of a future clinical trial.

INTRODUCTION

Bladder cancer annually affects an estimated 550 000 patients globally with a male to female ratio of 4 to 1 [1,2]. Although many patients can be managed endoscopically, patients presenting with muscle invasive disease typically undergo neoadjuvant chemotherapy (NAC) followed by a radical cystectomy (RC) for disease control. While these treatments are often necessary to achieve cure, they are associated with considerable morbidity and mortality [3]. Patients undergoing prolonged and invasive surgery should ideally arrive at their procedure in as optimized health as possible to improve surgical outcomes and reduce complications [4]. Unfortunately, bladder cancer patients who receive several months of systemic neoadjuvant chemotherapy may not be in optimal fitness prior to surgery. NAC is associated with low preoperative muscle mass and anemia, both of which are associated with worse oncological outcomes and increased mortality risk [5–7]. Given that bladder cancer is more common in the elderly (≥65 years old), the expected stress that RC itself can engender in terms of blood loss and extended convalescence puts these patients at a high risk of complications [8].

There have been significant efforts to preoperatively optimize patients ahead of surgery through dietary, exercise and risk factor management interventions [9,10]. However, these interventions can be energy intensive on the part of both the treating team and patient to gain any benefit. Moreover, these interventions are often of short duration (2-4 weeks and sometimes as short as 7 days) and do not always lead to improved postoperative outcomes [11]. What continues to elude the medical community is a medication/treatment that does not rely on patient motivation or energy, that is easily administered and that would physically prepare the patients for the stresses of invasive surgery. One possible treatment that is easy to administer and has not been well studied is testosterone supplementation. Exogenous testosterone is an established anabolic medication capable of improving many of the challenges commonly faced by patients ahead of a cystectomy (ex: sarcopenia, anemia, etc) [12,13]. Preoperative testosterone supplementation is not an entirely new concept with some investigation into its use in non-oncologic procedures [14,15]. However, little is known about testosterone in oncologic surgeries. Given the anabolic properties of testosterone and its known effects on other genitourinary cancers (prostate), the safety of testosterone supplementation in bladder cancer should first be established. This paper will review current understanding of how exogenous testosterone administration affects preoperative fitness for surgery, and bladder cancer specifically, and its potential use as a preoperative tool to improve surgical outcomes.

NEOADJUVANT CHEMOTHERAPY

It has been well documented that patients arriving to cystectomy following NAC have reduced body mass. **S**ignificant reductions in both lumbar muscle cross-sectional area and skeletal muscle mass index (SMI - cm^2/m^2) have been observed following NAC in patients diagnosed with

muscle-invasive urothelial carcinoma [7]. In addition, a ~10% increase in the incidence of sarcopenia was noted across the whole sample after NAC as defined by a SMI <55 cm^2/m^2 for men and <38.5 cm^2/m^2 for women. Similarly, significant reductions in body mass index (BMI) as well as psoas muscle volume (~5%) have been observed in patients following NAC [16]. This is cause for concern since low preoperative SMI in cancer patients is associated with reduced overall survival and worse cancer-specific survival [17]. In addition, NAC has been identified as an independent predictor of preoperative anemia which could increase the need for blood transfusion during RC [6]. Although the effect of NAC on hypogonadism in this specific scenario remains unstudied, based on the effects of chemotherapy in almost any other cancer, we would suspect that rates of hypogonadism to be high. In fact, the presence of cancer itself is associated with hypogonadism which can be worsened by cytotoxic chemotherapy. Chemotherapy can cause testicular damage as indicated by high levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) reported in cancer patients after the procedure [18]. An observational study on men with testicular cancer reported linear decreases in total testosterone levels (TT) correlating with the number of chemotherapy cycles. In the latter, TT prior to chemotherapy averaged ~12.8 nmol/L and was reduced to ~5.1 nmol/L after the 4th chemotherapy cycle [19]. Similar findings were previously reported in a cross-sectional study on men treated for malignant lymphomas [20]. In that study, patients treated with chemotherapy, independent of the dose, had significantly elevated odd ratios for the occurrence of exocrine hypogonadism compared to patients treated with radiotherapy only. Moreover, 79% of patients treated with radiotherapy only, remained eugonadal after the procedure. Contrarily, only 16% of patients treated for non-Hodgkins's lymphoma and 8% of patients treated for Hodgkin's lymphoma with high-dose chemotherapy remained eugonadal after the procedure [20]. Despite not having been extensively studied, chemotherapy could also cause hypothalamic and pituitary damage which would result in traits of secondary hypogonadism [21,22]. In such instances, reduced LH and FSH would be expected resulting in reduced testosterone production. Of note, not all chemotherapy regimens are associated with hypogonadism and more clinical evidence is needed to confirm whether common chemotherapy regimens used for bladder cancer lead to gonadal toxicity [23]. However, cisplatin-based chemotherapies are commonly used for bladder cancer treatment and have been associated with hypogonadism along with radiation therapies and alkylating agents [24,25]. Lastly, it is unclear whether testosterone levels would return to normal after recovery from NAC. A recent retrospective study on testicular cancer survivors who underwent chemotherapy reported that 38.5% (189 patients) of its cohort met the criteria for hypogonadism [26]. However, hypogonadism in the latter study was also associated with multiple variables including age and body mass.

RADICAL CYSTECTOMY

In addition to the important stress imposed on bladder cancer patients undergoing NAC, RC itself is associated with considerable side effects. Reductions in body mass as well as significant blood loss are to be expected with RC creating a difficult path for patients to navigate while they recover from these treatments. For example, RC has been shown to result in a ~7% loss in total

body protein paralleled with a ~4 kg loss in FFM over a 14-day postoperative period in men [27]. Those results necessitate important consideration given untreated cancer itself is a major risk factor for sarcopenia [28]. Furthermore, the loss of body protein in Mathur's study was not re-established 6 months after the operation which could jeopardize the physical autonomy of the patients [27]. It was found that 6% (226/3727) of patients were hypogonadal prior to RC in a recent retrospective study [29]. Similar observations occurred in a prospective study in which hypogonadism was seen in 37% of patients prior to RC and in 94% of patients after RC [30]. In the former, hypogonadism was associated with postoperative frailty, an independent risk factor for hospital readmission [24].

Radical cystectomy for urothelial carcinoma has been ranked as the 4th surgical procedure with the highest risk for blood loss after aortic aneurysm repair, coronary artery bypass graft and cardiac valve replacement [31]. A median blood loss of 1.4 L in women and 0.5 L in men has been previously documented as a result of RC [32]. In addition, intensive care unit stay for patients who experienced complications in the latter study, were associated with the level of operative blood loss and the amount of blood transfused [32]. Therefore, any therapy that could mitigate the loss of body mass and the loss of blood associated with RC might have favorable outcomes on bladder cancer patients and their recovery.

Given what we then know about how deconditioned patients are arriving at surgery and the effect this has on recovery outcomes, we must find solutions to improve patients' health ahead of surgery. In testosterone we possess an anabolic hormone that is readily available, easily administered and could reverse or minimize several of the features seen in this patient population with minimal effort on the patients' part. Unfortunately, what is not known is the effect of androgens on bladder cancer. In the sections below, we summarize the available evidence regarding the possible efficacy of supplementing patients with testosterone during treatment for bladder cancer and the potential safety concerns.

POTENTIAL BENEFITS OF PREOPERATIVE TESTOSTERONE SUPPLEMENTATION

Preoperative hypogonadism is common amongst cancer patients and has been associated with postoperative complications in different patient groups including those undergoing radical nephrectomy and hip arthroplasty [33,34]. Despite minimal data regarding the incidence of hypogonadism in bladder cancer patients specifically, two recent observational studies show that ~6% and 37% of their respective cohort was hypogonadal prior to RC [29,30]. Nevertheless, testosterone administration prior to non-cancer related surgeries has been shown to have a favorable impact on patients' recovery. For example, the administration of 600 mg of testosterone enanthate to knee surgery patients 21, 14, 7 and 1 day prior to surgery resulted in higher preoperative hematocrit levels compared to placebo (~45% vs ~41%) and a higher functional independence measure for standing 3 days after the operation [14]. Despite being non-statistically significant, patients receiving testosterone also tended to have shorter hospital stay after the surgery. Since both NAC and RC are associated with blood loss and hypogonadism [35,36],

it is possible that exogenous testosterone administration could reduce preoperative anemia and postoperative complications related to those treatments. In addition, hypogonadism in different patient populations, such as in patients with chronic kidney disease, is associated with a greater risk for anemia compared to eugonadal patients [37]. Accordingly, transdermal testosterone therapy for 12 months has been shown to be a viable tool for the reversal of anemia in older men [38]. Therefore, re-establishing eugonadal levels of testosterone in bladder cancer patients prior to surgery may be useful in the prevention of anemia and related red blood cell transfusions ahead of surgery and during the recovery process (Figure 1).

Preoperative testosterone treatment may also be crucial to prevent surgery related losses in fat-free mass (FFM) and strength. However, little to no research has been completed into this therapeutic avenue beyond limited research suggesting that low preoperative levels of testosterone are associated with greater weight loss following cystectomy [36]. This presents an avenue for further exploration, especially since low body weight and frailty are associated with postoperative complications [33]. Accordingly, preoperative testosterone treatment has been shown to preserve FFM in patients undergoing non-cancer related surgeries. For example, the administration of 200 mg of testosterone cypionate to men scheduled for an ACL surgery 2 weeks prior to the operation and for 6 weeks after the operation resulted in significant increases in lean mass 6 weeks post surgery compared to the placebo group (+2.7 kg vs -0.1 kg) [15]. It was also found that leg extension strength for the uninjured leg 12 weeks after the surgery was greater in the testosterone group, but no differences were noted for the injured leg. Moreover, there were no differences in lean mass and strength 24 weeks after the operation [15]. Hence, testosterone administration prior to surgery could at least accelerate the recovery process in the early stages after surgery and help patients regain their autonomy more rapidly. This could reduce the length of stay in the hospital and reduce the incidence of re-admission after RC which has been shown to average ~27% despite the implementation of the 'Enhanced Recovery After Surgery' (ERAS) protocol [39,40].

One interrogation that remains relates to the time course of administration to ensure favorable surgical outcomes and recovery for patients. Whilst there is no clear consensus as to how early testosterone administration should occur leading to surgery, there is evidence to suggest that some benefits may occur as early as 5 days after the administration. In fact, it was shown that a single 200 mg dose of testosterone enanthate in healthy men resulted in a net increase in muscle protein synthesis, amino acid recycling and net protein balance 5 days after the administration [41]. Whilst significant increases in muscle mass are unlikely to occur within days of administration, the maintenance of protein balance ahead of surgery may still result in a net positive for patients undergoing treatment. Additionally, it is also plausible that shorter esters such the 3-carbon propionate ester may provide those benefits even more rapidly as opposed to the 7-carbon enanthate ester, however that has yet to be investigated. It has also been found that testosterone cypionate and enanthate are more potent at increasing hematocrit than patches [42]. Therefore, intramuscular administration should be favored of other administration forms. Lastly,

increases in hematocrit have been seen with higher dosages of testosterone (600 mg) in just 4 weeks prior to surgery. Hence, starting testosterone therapy 30-5 days prior to surgery may provide the benefits in the above mentioned.

SAFETY CONCERNS WITH TESTOSTERONE AND CANCER

Testosterone and global cancer risk

The relationship between testosterone and the risk for cancer has largely focused on prostate cancer and stems back to Huggins and Hodges' work in the early 1940's (Huggins, 1941). The duo's finding that the administration of testosterone propionate to prostate cancer patients resulted in an increased serum acid phosphatase provided the basis for the next several decades of research into the use of androgen deprivation and prostate cancer. However, conflicting evidence has emerged over the subsequent years regarding testosterone and its effects on cancer development. We now understand that the tie between prostate cancer and androgens is not as binary as initially suspected. For example, recent evidence suggests that exogenous testosterone administration in hypogonadal patients does not increase the risk for prostate cancer [44]. Similarly, a recent longitudinal study found that men aged 55-67 years old using testosterone replacement therapy (TRT) were at a lower risk of developing prostate cancer than non-users [45]. Data from a 2007 prospective study suggests that lower levels of endogenous testosterone (<12.5 nmol/L) in men were associated with a greater risk of death from prostate cancer compared to higher levels (> 19.6 nmol/L) [46].

When expanding the scope beyond prostate cancer, other cancers do appear androgen sensitive. Elevated endogenous levels of androgens and estrogens correlate with an increased breast cancer risk in postmenopausal women [47], while liver tumors have long been reported in athletes who use supraphysiological dosages of anabolic-androgenic steroids (Oklobdzija & Weyrauch, 1989; Prat & Coleman, 1977). Hence, the contribution of androgens to the development of tumors might ultimately depend on the dose and duration of administration. Perhaps similar to prostate cancer the relationship between many cancers and androgens is possibly based on a saturation model of androgen receptor activity – that is beyond a certain concentration, no increased risk of cancer exists. What is certain is that as more research into the effect of androgens on different cancers emerges – our understanding of this nuanced relationship will expand like our understanding of testosterone and prostate cancer today.

Molecular mechanisms of bladder cancer progression in response to testosterone

The most common type of bladder cancer is urothelial carcinoma accounting for 90% of cases [50]. A proposed mechanism by which testosterone could induce its the development is via IGF-1 signaling. For example, both testosterone and dihydrotestosterone (DHT) have been shown to increase IGF-1 expression in a dose-dependent manner in prostatic stromal cells [51]. Accordingly, it has been proposed that the activation of the IGF-1 receptor plays a major role in the growth of tumor cells, partially because of its anti-apoptotic effects [52]. Blunted cellular apoptosis results in dysregulated proliferation which is pivotal in the initiation of cancer [53]. Moreover, IGF-1 has been demonstrated to increase VEGF expression in human colon cancer which results in cellular vascularization, ultimately promoting metastases (Akagi et al., 1998). In addition to systemic IGF-1, it has been proposed that peripheral IGF-1 and IGF-2 could stimulate cancer development

in an autocrine/paracrine manner (Bergmann et al., 1995). The extent to which testosterone affects serum as opposed peripheral levels of IGF-1 and the impact it has on bladder cancer progression remains to be fully elucidated.

Androgen sensitivity of the bladder and urothelial carcinoma

Current evidence regarding the sensitivity of the bladder to androgens is conflicting. For instance, it is suspected that the androgen receptor (AR) plays an important role in the development of different forms of cancer such as prostate and breast cancer [56]. Interestingly, AR is expressed in the urothelium despite the bladder being considered non-responsive to androgens. Accordingly, it has recently been proposed that AR signaling is associated with the progression of urothelial carcinoma [57]. However, some studies show reduced AR expression in urothelial tumors compared to normal tissue (Kashiwagi et al., 2016; Kauffman et al., 2011), whilst others suggest no difference [60]. Reduced AR expression in bladder cancer has been found to be associated with an increased risk for bladder cancer recurrence (Sanguedolce et al., 2020). Accordingly, treatment with finasteride, a 5-α-reductase inhibitor that prevents the conversion of testosterone to DHT, has not been shown to reduce the incidence of bladder cancer in men over a 6-year period [62]. A large scale 13-year retrospective observational study found a reduced risk for bladder cancer in men who reported to have used finasteride during the follow-up period [63]. However, the latter is limited to self-reported use of finasteride which cannot be confirmed by prescription analysis or pill count. Nonetheless, a retrospective cohort study found that prostate cancer patients diagnosed with bladder cancer who received androgen deprivation therapy (ADT) had significantly less cumulative recurrences of bladder cancer events over 5 years compared to their control counterparts [64]. Of note, the latter used the recurrence of bladder cancer with ADT as a primary end point rather than its incidence. Therefore, low androgen levels may not prevent the initial development of bladder cancer but could potentially reduce its recurrence over time [62,64].

Additionally, it is important to distinguish between AR expression and AR signaling because lack of expression does not necessarily imply blunted signaling. For example, and as previously stated, some studies show reduced AR expression in bladder cancer compared to healthy tissue (Kashiwagi et al., 2016; Kauffman et al., 2011). However, Tripathi & Gupta showed a positive association between AR signaling and bladder cancer progression [57]. Hence, it would be plausible to assume that androgens play a role in the development of bladder cancer through AR signaling despite reduced expression. However, it would also be plausible to assume that reduced AR expression would result in lowered AR signaling by default independently of androgen concentrations. Nonetheless, the effects of testosterone administration itself on bladder cancer remain unclear.

A recent retrospective study found a positive correlation between endogenous testosterone levels and the occurrence of bladder cancer after adjusting for confounding factors with a multivariate logistic regression [65]. However, TT did not differ significantly between bladder cancer patients and control; ~12.25 nmol/L vs ~11.52 nmol/L respectively. Therefore,

the correlation between TT and bladder cancer requires further investigation. Recent prospective evidence on 90 men with bladder cancer found that 37% had low preoperative testosterone whilst reductions to hypogonadal levels occurred in 94% of the cohort after the operation [30]. Considering the mixed evidence regarding androgens and bladder cancer development, it is unclear whether preoperative testosterone would result in detrimental outcomes in that patient population. A 15-year cohort study on TRT and the incidence of different cancers found no increased risk for bladder cancer occurrence [44]. In those regards, the benefits of preoperative testosterone administration may outweigh the potential risks.

General safety concerns

General safety concerns may arise regarding the use of exogenous testosterone in cancer patients. Because of the sensitivity of the prostate to androgens, monitoring changes in prostate specific antigen (PSA) routinely during the testosterone administration period may be of first order. However, it is important to note that recent trials on hypogonadal men without cancer report no changes in PSA with either intramuscular or transdermal testosterone administration [66,67]. Other potential side effects of testosterone administration include left ventricular hypertrophy, hepatotoxicity, infertility and psychiatric disorders. However, those effects may be more likely to occur with chronic supraphysiological doses of testosterone or its derivatives [68]. In fact, a recent retrospective study found that cardiac patients on TRT prior to surgery had no increased risk for cardiovascular events after the operation compared to non-users [69]. In addition, TRT in hypogonadal men may be beneficial in the treatment of metabolic syndrome which is associated with the development of different cancers [70,71]. Hence, preoperative testosterone administration may be a viable option to prevent anemia, skeletal muscle atrophy and strength loss in cancer patients as well as accelerate recovery without obvious concern for major adverse events.

CONCLUSIONS

Preoperative testosterone supplementation could increase bladder cancer patients' fitness ahead of cystectomy by preventing muscle atrophy and loss of strength and by increasing hematocrit which could reduce the need for blood transfusion during the procedure. Those effects have been reported in other patient populations when exogenous testosterone is administered prior to non-cancer related surgeries. However, the role of testosterone in bladder cancer development and its recurrence is still unclear. Large-scale observational studies thoroughly investigating the relationship between bladder cancer and testosterone – exogenous and endogenous – are lacking. A study as such should aim to determine whether the development of bladder cancer is likely to be potentiated by testosterone or not and could serve as the basis for a future clinical trial. Currently, the evidence does not seem to support the hypothesis that preoperative exogenous testosterone administration to bladder cancer patients would result in any adverse effects. In fact, short-term administration in the weeks leading to surgery may accelerate recovery and potentially reduce hospital stay. However, much of the currently available evidence is indirect and no clinical trial has yet to be conducted to answer that question.

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FIGURES AND TABLES

Figure 1. Potential benefits of preoperative testosterone in bladder cancer patients. Preoperative testosterone may increase hematocrit and hemoglobin, which would reduce the need for blood transfusion during radical cystectomy. Testosterone may also allow bladder cancer patients to maintain their muscle mass and strength as they undergo neoadjuvant chemotherapy and radical cystectomy. The maintenance of muscle mass and strength could facilitate the recovery process and potentially reduce hospital stay. Plus sign (+) indicates an increase in hematocrit, hemoglobin, muscle mass and strength as a result of exogenous testosterone administration. Minus sign (-) indicates a reduced need for blood transfusion and reduced hospital stay. Created in *https://BioRender.com*.