Perioperative hypogonadism in men undergoing radical cystoprostatectomy for bladder cancer

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STUDY PROTOCOL

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Principal Investigator: **Jeffrey Holzbeierlein, MD, FACS**
Chairman
Dept. of Urologic Surgery
ph: 913-599-7564 | e-mail: jholzbeierlein@kumc.edu

Co-investigator: **Woodson Smelser, MD**
Dept. of Urologic Surgery
ph: 913-588-7571| e-mail: wsmelser@kumc.edu

Jessie Gills, MD
Dept. of Urologic Surgery
Ph: 913-588-7571

Collaborator: **Eugene Lee, MD**
Dept. of Urologic Surgery
ph: 913-588-7564 | e-mail: elee@kumc.edu

Collaborator: **Moben Mirza, MD**
Dept. of Urologic Surgery
ph: 913-588-7564 | e-mail: mmirza@kumc.edu

Collaborator: **Ajay Nangia, MBBS**
Dept. of Urologic Surgery
ph: 913-588-0799 | e-mail: anangia@kumc.edu

Collaborator: **Hadley Wyre, MD**
Dept. of Urologic Surgery
ph: 913-588-6152 | e-mail: hwyre@kumc.edu

Medical Monitor: **Joshua Broghammer, MD**
Dept. of Urologic Surgery
ph: 913-588-6982 | e-mail: jbroghammer@kumc.edu

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BACKGROUND/LITERATURE REVIEW & SIGNIFICANCE

Radical cystectomy is a morbid operation. Bladder cancer is the sixth-most prevalent malignancy in the United States.[i] The current standard treatment for invasive bladder cancer is neoadjuvant chemotherapy followed by radical cystectomy (RC), a complex operation that requires bladder excision and urinary tract reconstruction using a segment of the terminal ileum.[ii,iii] This surgery is associated with significant morbidity, with 90-day readmission rates at approximately 26% and with infections accounting for 25% of complications at 30 and 90 days.[iv] Furthermore, the estimated mortality rate at 90 days has been reported at 7% in a previous series from a high volume center.[4]

The stress response to surgery and its effect on testosterone. Surgery evokes a cascade of hormonal and metabolic changes known as the stress response, and this can be seen with trauma, burns, severe infection, or strenuous exercise.[v] This series of changes includes an increase in pituitary hormones and activation of the sympathetic nervous system. These changes likely evolved to aid in survival in a more primitive environment by mobilizing substrates to provide energy, limit tissue damage, attack infectious organisms, and activate repair mechanisms.[5] Furthermore, several studies have noted men develop temporary hypogonadism with decreased testosterone levels in response to surgery.[vi,vii,viii] This decrease in serum testosterone level does not appear to be due to reduced sex hormone-binding capacity, although the exact pathophysiology is not known.[6] On a similar note, levels of luteinizing hormone (LH) will rise in response to surgery as levels of testosterone decrease, suggesting that suppression of testosterone results in compensatory elevation of LH.[7] This suppression of testosterone levels can be found during and up to seven days following major surgery and general anesthesia.[8]

Loss of lean body mass is a common side effect of Radical Cystectomy. Loss of body weight is a common postoperative observation, even in patients without nutritional deficiencies. A 5% loss of body weight and a 7% loss of body protein at postoperative day 14 was reported in a small observational study of 11 men undergoing RC[ix]. Body fat remained unchanged; body protein did not fully recover at 6 months post-surgery[9]. This data suggests that even patients without nutritional deficiencies are at risk of weight and body protein losses after RC.

Hypogonadism and Cancer. Low testosterone levels are common in male patients with cancer, and up to two thirds of men with advanced or metastatic cancer have hypogonadism.[x,xi,xii] The cause of hypogonadism in cancer patients is multifactorial and includes inflammation, comorbidities, opioids, weight abnormalities, or chemotherapy.[xiii] Despite the high prevalence of the association between hypogonadism and cancer, there are no clear studies delineating how extensive the hypogonadism is and how long does it persist after surgery, especially in bladder cancer.

Testosterone use Testosterone use has been studied extensively in hypogonadal men with other chronic medical conditions. Specifically, several studies have shown

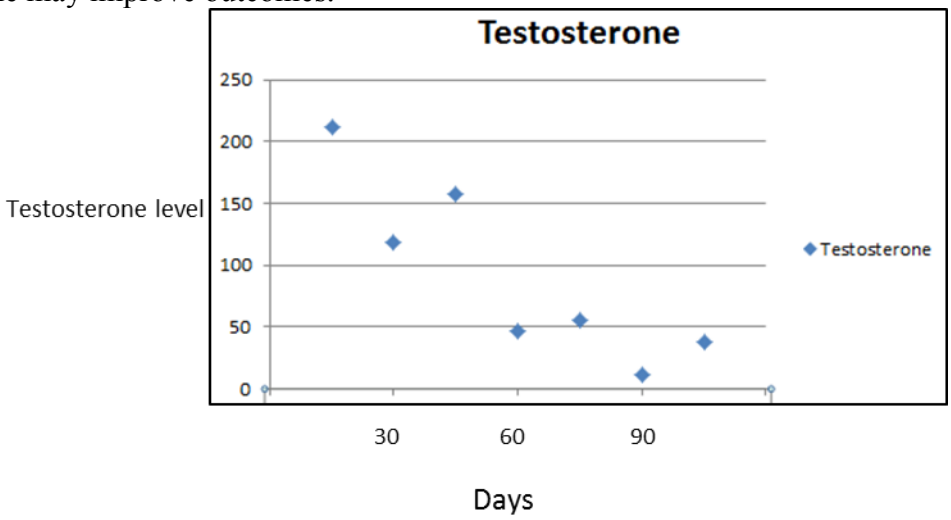
improvement in energy levels, body proportions, obesity parameters, and health related quality of life with respect to hypogonadism, diabetes, metabolic syndrome, and COPD.[xiv,xv,xvi,xvii] While these studies do not directly relate to bladder cancer or post-operative outcomes, they suggest that testosterone therapy can improve fitness outcomes, energy levels, and a patient's self-perception of their health status. These improvements would be a welcome addition to the post-operative course after radical cystectomy, as it is typically associated with decreased quality of life and significant morbidity. Furthermore, testosterone analogs have been used in the burn population, a setting of intense surgical stress, to restore weight loss and muscle mass.[xviii,xix] A randomized prospective study utilizing oxandrolone, a testosterone analog, found that testosterone replacement decreases weight loss and increases healing without side effects, compared to a control substance and human growth hormone.[18] Knowing whether hypogonadism st persists status post RC may provide a rationale for treating these patients with testosterone.

Significance. Radical cystectomy (RC) is a major urologic surgery involving bladder excision and urinary tract reconstruction utilizing a portion of the terminal ileum. Surgical stress leads to a catabolic state and temporary hypogonadism with decreased testosterone levels, both of which contribute to morbidity and mortality. The results of this study will lead to a better understanding of the stress response to RC surgery with specific emphasis on the hypogonadal state and how long this state lasts. If this hypogonadal persists or worsens at 90 days post RC then this may provide a rationale to provide testosterone supplementation to patients that are status post RC.

PRELIMINARY DATA

This project addresses an emerging need in a patient population at high risk for significant surgical morbidity and mortality. Hypogonadism is highly prevalent among patients with malignancy and is also surgically induced. Furthermore, previous literature shows that hypogonadism is present in many other chronic medical conditions and replacement of testosterone may improve outcomes.

Within our own institution, we have noted that hypogonadism is found within the radical cystectomy population to a high degree, even to castrate levels (<50 ng/dl) in patients not undergoing any therapy for androgen deprivation. To our knowledge, this has



not yet been reported among this population. Preliminary data highlight the clinical relevance of this project. We identified patients in the University of Kansas Hospital health system with urothelial bladder cancer that underwent RC over the last five months and had record of postoperative testosterone level. Seven patients met inclusion criteria, with a mean age of 76 years. The mean postoperative testosterone level for these patients was 92ng/dl (normal 270-1070 ng/dl). The mean time from RC until obtaining a postoperative testosterone level was 27 days (range 2 – 119 days).

AIM:

Aim 1: To perform a prospective observational study to determine the prevalence of hypogonadism in bladder cancer patients pre-operatively, immediately post- operatively, and at 30 and 90 days post-radical cystectomy.

There is no hypothesis testing involved in this study as it is strictly observational to determine prevalence

METHODS

Study design.

The study team will conduct a prospective, observational study in 25 male patients who are scheduled to undergo radical cystectomy for bladder cancer. Men who choose to participate will have a total and free testosterone level, as well as a serum luteinizing hormone level drawn at a preoperative visit.

The patient's will then undergo scheduled radical cystectomy. We will then repeat total and free testosterone as well as luteinizing hormone on post-operative days 2 and 3 to evaluate acute changes in serum testosterone and luteinizing hormone in the acute post-surgical period in order to quantify the suspected further decrease in the levels of these hormones in patients undergoing RC. We will then repeat laboratory analysis of these hormones at the 30 and 90 day post-operative marks. If hypogonadism is confirmed, this will serve as a proof of concept study that not only are patients hypogonadal preoperatively, but that hypogonadism is maintained postoperatively. This will aid in hypothesis generation for future studies. All patients will continue to receive routine post-cystectomy monitoring and guidance consistent with the current surgical standard of care. Daily weights, hospital length of stay, coronary events, deep venous thromboemboli, cardiovascular emboli (CVA), infections, and readmission rates will be measured as part of our normal radical cystectomy database collection methodology.

Participants.

The University of Kansas Hospital (KUH) performs an average of 80 RC procedures each year. Our recruitment goal is to recruit 25 patients in approximately 6 months,

which should be readily feasible. Participants will be recruited from the KUH Urology Clinic, KUH Cancer Center, or during their KUH inpatient hospitalization. Eligible participants are adult men undergoing RC for primary bladder cancer. Patients with evidence of advanced metastatic disease, patients undergoing cystectomy for non-bladder primary malignancy or bladder cancer type other than urothelial cell, or patients with a history of breast or prostate cancer will be excluded. Other contraindications include polycythemia, cardiovascular thromboembolism, untreated obstructive sleep apnea, uncontrolled heart failure, or acute coronary event in the past six months.

Surgical procedure.
Candidates for RC typically do not have evidence of metastatic disease and the majority will receive neoadjuvant chemotherapy. The primary tumor will have been resected prior to RC and this will ensure pathologic confirmation of urothelial cell carcinoma. RC may be performed open through a low midline incision or with robotic-assisted laparoscopic assistance using the *da Vinci* Surgical System©. Ileal conduit using terminal ileum (10-15 cm segment) or ileal neobladder (60 cm segment) will be performed for urinary diversion. All patients will receive enoxaparin therapy for DVT prophylaxis postoperatively in accordance with the current surgical standard of care.

Study calendar.

Study plan:	**Visit 1**	**Date of Surgery**	**Post-Operative Inpatient Stay**	**Visit 2**	**Visit 3**
Timeline:	Prior to Study	Radical Cystectomy	Post-Op Days 2 & 3	30 days post-op	90 days post-op
Data to collect	Introduction Consent Testosterone measurement (total/free); LH level	N/A	Testosterone measurement (total/free); LH level	Testosterone measurement (total/free); LH level	Testosterone measurement (total/free); LH level

Outcomes.

Postoperative Patient Outcomes. Complications will be recorded and defined as early (≤30 days) versus late (31-90 days) and graded according to the Clavien-Dindo scheme per our current radical cystectomy database collection methodology[xx]. Complications will be further categorized into infectious or non-infectious, and the specific location will be defined (urinary tract, wound, abdominal, etc.). Readmission, whether to KUMC or an outside facility, will be defined as admission to any hospital after discharge home up until 90 days after surgery. The reason for readmission will be recorded. Hospital length of stay will be defined as day of admission through day of discharge. Age, gender, smoking history, comorbidities, and pathological information pertaining to participants' perioperative and postoperative courses will be recorded. Severity of comorbid disease will be graded according to the Charlson Comorbidity Index, the most widely used index in oncology[xxi]. Again, these data are currently collected on all radical cystectomy patient as part of our existing bladder cancer database and do not constitute additional measures or considerations beyond our current standard.

Statistical analyses.

This is a prospective, observational study with the goal of determining prevalence of hypogonadism in bladder cancer patient's undergoing radical cystectomy. The prevalence rates will be calculated as the proportion of subjects with hypogonadism at different time points. The 95% confidence intervals will be provided. Determining prevalence will assist in hypothesis generation for future studies.

We will consider performing post-study power analysis from the data accrued from this trial for the design of potential future trials.

Potential difficulties.

Accrual. The study team does not anticipate any difficulty in recruiting for the proposed study from the patient pool at KUH. Even if accrual is slow, it should only take an additional 1-2 months to accrue the desired number of patients.

Stroke, myocardial infarction. In January of 2014 the FDA made a safety announcement regarding its investigation for the risk of stroke, heart attack and death in men taking testosterone products. The FDA did not conclude that the risk of these events was any higher for men taking testosterone but noted that the risks should be weighed against the benefits by providers. No testosterone supplementation is planned in this pilot study.

Venous blood clots. In June of 2014 the FDA required manufacturers of testosterone to include a general warning on the drug label discussing the risk of venous blood clots, or venous thromboembolism (DVT). This new warning is not related to the FDA ongoing evaluation of stroke, heart attack, or death. Furthermore, we do not definitively know if the risk of venous blood clots is increased for the RC population specifically. No testosterone supplementation is planned in this pilot trial.

Evaluation of hypogonadism. If patients are found to be hypogonadal postoperatively, then they will be referred for follow up with a fellowship trained urologist in Andrology. As part of the study they will not receive any testosterone replacement up to the 90 day post-operative mark. At this point, if they remain hypogonadal, they may receive testosterone supplementation outside of the confines of the study. This data would not be used for the current study, but may be used for any future studies.

PROTECTION OF HUMAN SUBJECTS

Informed consent process. Potential subjects will be approached by their urologic surgeon and informed about the possibility of research participation. Patients who are interested learning more about participation will be introduced to a member of the study team who will then explain the study in detail. The potential subjects will have the opportunity to read the consent form in the absence of the PI and study team. It will be explained to the subjects that the study is voluntary and that they may discontinue at any time without prejudice. Subjects will have the opportunity to ask questions before signing the consent form. Subjects who agree to participate will be consented according to HSC guidelines and in a private closed door setting.

Risks of participation. Given that RC an abdominal incision and visceral manipulation, post-operative care can lead to abdominal cramps or distention, diarrhea, or vomiting. Participants will be provided intravenous or epidural analgesia for pain control as well as anti-emetics as needed. Blood will be drawn by a trained phlebotomist or nurse and could result in a small bruise, a minor risk. Furthermore, patients that undergo a major operation for underlying malignancy have an elevated risk for DVT. Patients are

routinely started on subcutaneous heparin or enoxaparin for anticoagulation prior to the operation, and this is continued until hospital discharge.

Protection against risk. All questions that potentially eligible subjects have will be addressed. Participants will sign a consent form approved by the Human Subjects Committee (HSC). All RC participants will be followed and managed by their surgeon according to standard guidelines. All personnel will complete training for ethical research and human subjects' privacy and protection. Only persons directly involved with the study will have access to data identifying individuals. Records and forms will be kept in locked file cabinets when not in use. Names will not be stored on computer files for data analysis. No individual will be identified in the study's results. Participation in the study is voluntary and participants may withdraw at any time without a change in the normal flow of post-operative care.

Potential benefits of the proposed research. Participants may not have direct benefit from the study. The subjects and society in general will benefit from the knowledge gained about managing bladder cancer, with future benefits of improved patient outcomes.

Safety Monitoring/Medical Monitor. Serious side effects or other problems during this study will be reported to PI, Dr. Jeffery Holzbeierlein MD and Medical Monitor, Dr. Joshua Broghammer MD.

More specifically, the medical monitor will be responsible for reviewing:

1. Monitoring for the impact of independent scientific investigations (other trials) on the trial being monitored, as well as recommending changes based on those external results.

2. Requests for data from sponsoring organizations or any other party. This includes requests for preliminary data for planning ancillary studies. The research team may consult the medical monitor on other issues thereafter, such as appropriate action for late toxicities.

3. The medical monitor will have face-to-face meetings with the research team twice per year. More frequent phone conferences will be held if deemed necessary, for an evaluation of adverse effects. Any adverse effects will be reported to the medical monitor, although as an observational pilot study this is not anticipated.

ClinicalTrials.gov Registration
The proposed pilot trial will be registered on the ClinicalTrials.gov website.

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