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Assessing genitourinary and gastrointestinal toxicities in men with localized prostate cancer post high dose rate brachytherapy boost

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Thesis

ASSESSING GENITOURINARY AND GASTROINTESTINAL TOXICITIES IN MEN WITH LOCALIZED PROSTATE CANCER POST HIGH DOSE RATE BRACHYTHERAPY BOOST

by

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ASSESSING GENITOURINARY AND GASTROINTESTINAL TOXICITIES IN MEN WITH LOCALIZED PROSTATE CANCER POST HIGH DOSE RATE BRACHYTHERAPY BOOST

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ABSTRACT

Prostate cancer (PCa) remains one of the top leading cancer in the United States, with more advanced prostate cancer cases being diagnosed. While traditional curative treatments are limited in treating these aggressive cases, advancements in technology have pioneered modern radiotherapy techniques to address this issue, specifically high-dose rate brachytherapy boost (HDR-BTb). With level 1 evidence demonstrating higher efficacy than traditional techniques, however, it remains unconvinced that this technique could be offered to this cohort and able to produce tolerable toxicity profiles based on previous parameters.

The aim of this study was to assess the incidence and extent of acute and chronic genitourinary (GU) and gastrointestinal (GI) toxicity profiles in men with high- or intermediate- unfavorable prostate cancer cases after HDR-BTb treatment in a single institution. It was found that both acute GU and GI toxicities were well tolerated, with 12.5% and 4.4% reporting CTCAE Grade 2+, respectively. In addition, reported CTCAE Grade 2+ rates for chronic GU and GI toxicities were 2.5% and 0%, respectively. Further, we found that previous factors associated with these toxicity profiles, such as increased prostate volume and baseline American Urological

Association (AUA) score, are not relevant in a clinical setting when offering this treatment option.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AJCC	American Joint Committee on Cancer
AS	Active Surveillance
AUA	American Urological Association
AUC	Area under the curve
BPH	Benign Prostatic Hyperplasia
BT	Brachytherapy
CTCAE	Common Terminology Criteria for Adverse Events
DRE	Digital Rectal Exam
EBRT	External Beam Radiation Therapy
GGG	Gleason Grade Group
GEC/ESTRO	The Groupe Europeen de Curitherapie and European Society for Radiotherapy & Oncology
GI	Gastrointestinal
GU	Genitourinary
HDR	High-Dose Rate
HDR-BT	High-Dose Rate Brachytherapy
HDR-BTb	High-Dose Rate Brachytherapy Boost
HIPAA	Health Insurance Portable and Accountability Act
IRB	Institutional Review Board
IPSS	International Prostate Symptom Score

LDR	Low-Dose Rate
LDR-BT	Low-Dose Rate Brachytherapy
LDR-BTb	Low-Dose Rate Brachytherapy Boost
LUTS	Lower Urinary Tract Symptoms
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
PCa	Prostate Cancer
PSA	Prostate Specific Antigen
ROC	Receiver Operator Curve
RP	Radical Prostatectomy
RT	Radiation Therapy
SS	Symptom Score
TNM	Tumor-Node-Metastasis
TRUS	Transrectal Ultrasound

INTRODUCTION

Prostate cancer (PCa), the most common form of cancer in men, is the second leading cause of cancer death following lung cancer in America. It is a form of cancer that occurs in the prostate gland- a walnut-sized structure found in male anatomy, that is located below the bladder and anteriorly to the rectum (Figure 1). The gland functions along with the seminal vesicles to produce nourishment for sperm in the male reproductive system. Anatomically, the prostate is subdivided into four major zones: anterior fibromuscular-, transition-, peripheral-, and central- zone; all encompassed by a fibrous layer called the prostate capsule (Figure 2). A majority of PCa cases, 80-85%, arises from the peripheral zone, 10-15% arises in the transition zone, and 5-10% from the central zone.[1]

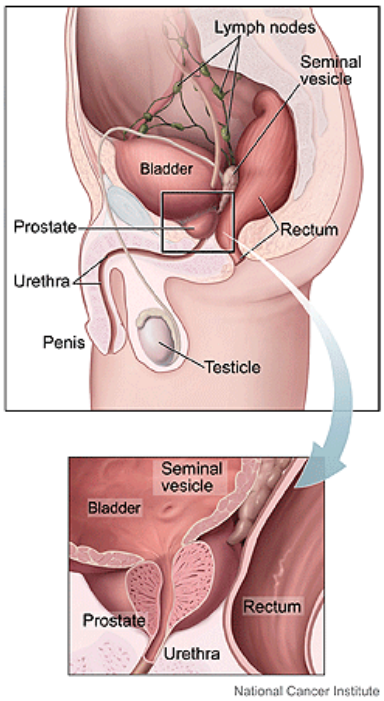

Figure 1. Anatomy of Prostate and Nearby Organs (National Cancer Institute[2])

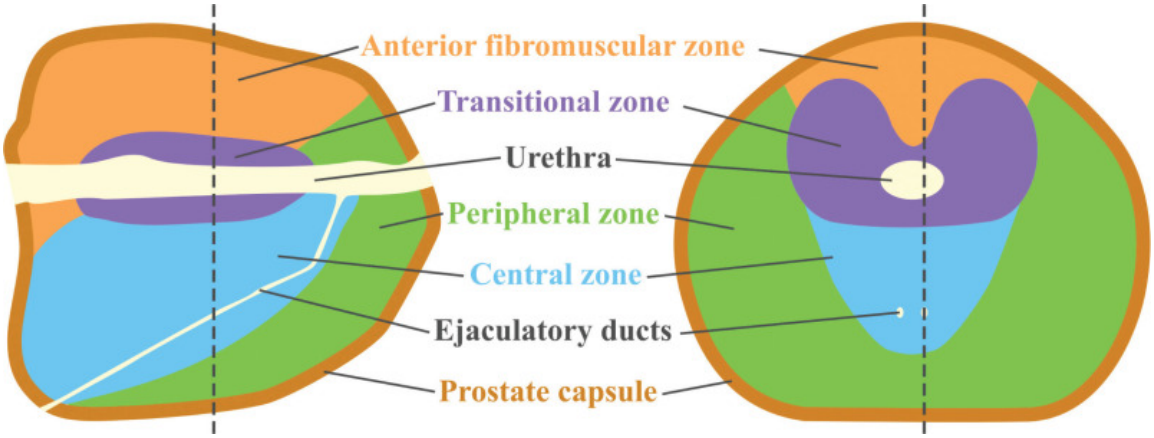

Figure 2. Zonal anatomy of the prostate. Parasagittal (left) and transverse (right) sections of the prostate, where dotted lines represent their intersection. The diagram illustrates the zonal anatomy, anterior fibromuscular zone in orange, peripheral zone in green, transitional zone in purple and central zone in blue. [3]

Age is the primary risk factor for PCa, with the average age of diagnosis being 66 years of age. Additional risk factors that increases a person's likelihood of getting prostate cancer include race, geography, family history, and lesser clear factors such as diet, obesisty, and smoking. Prostate cancer incidence rates are much higher in African-American men, with reasons associated with this disparity thought to be due to differences in genetics, social, and environmental factors.[4] Certain genetic factors, such as variants of BRCA1 or BRCA2 gene, can be inherited from parents which increase prostate cancer risk.[5] Studies have found that lifestyle habits such as dairy consumption and smoking are also associated with an increased chance of getting prostate cancer.[6]

The American Cancer Society estimates about 299,010 new cases and about 35,250 deaths will occur from prostate cancer in 2024.[7] Although prostate cancer is a serious disease, over 80% of PCa patients do not die from the disease alone, therefore preserving quality of life is key when treating PCa.

SCREENING AND DIAGNOSIS

Early detection and preventative screening remains critical in reducing overall prostate cancer burden on the individual. Though many prostate cancer cases are asymptomatic at presentation, in some cases physical symptoms manifests similarly to those of benign prostatic hyperplasia (BPH). These include lower urinary tract symptoms (LUTS) such as nocturia, increased frequency, and poor urinary stream.[8] According to American Urologic Association (AUA) panel, manifestations of LUTS should be accompanied with a screening questionnaire, to quantify a score for a person's symptoms. The series of questions asked in the form is based on the frequency of the presented symptom that is rated on a scale from 0-5, with 0 being none or not present and 5 being almost always present (Table 1).

A completed AUA form will result in a symptom score (SS), which is the total sum of all the answers. The AUA symptom score index classifies the symptoms of men with a score of 0-7 as mild, 8-19 moderate, and 20 and above as severe. Granted that the AUA questionnaire was developed and validated for measuring magnitude of urinary problems seen in those with BPH, the questionnaire remains relevant in PCa cases. A study by Lehrer et al. explored if AUA symptom score is

associated with disease stage in men with localized PCa. They concluded that there was a significant difference in AUA symptom scores and the studied disease stages. Moderate AUA symptom scores correlated with advanced disease, while mild AUA symptom scores correlated with lower tumor stage.[9] The higher the symptom score, the more concern there is for an abnormal genitourinary system and increased propensity for additional testing. The AUA questionnaire is used as an additional resource and measure that allows for tracking progression and changes of genitourinary function throughout a period of time. Specific to prostate cancer cases, information gained from this survey remains important when reporting and comparing outcomes between treatment options.

AUA Symptom Score Questionnaire

The American Urological Association (AUA) has created this symptom index to give you and your physician an understanding of the severity of your enlarged prostate symptoms.

Question	None	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
Incomplete emptying: Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
Frequency: Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5	
Intermittency: Over the past month, how often have you found that you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency: Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
Weak-stream: Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining: Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
Nocturia: Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	

Symptom Score

(Add up the points for all questions to determine the severity of your symptoms)

Total score

If you scored 8 points or higher, you should consult your physician.

Symptom Score (Severity) — 0 to 7 (Mild), 8 to 19 (Moderate), 20 to 35 (Severe)

Table 1. Example of AUA Symptom Score Questionnaire (Boston Scientific[10])

A fundamental biomarker for prostate health indication is the prostate-specific antigen (PSA), reported as nanograms of PSA per milliliter of blood (ng/mL). It is a protein that is produced by the prostate gland, with a normative

value of ≤4 ng/mL, and with anything significantly above 4 ng/mL being suspicious of PCa. According to AUA panel, PSA screening for low to average risk men should begin at 45 years of age, be offered to high-risk men starting between 40-45 year old, and be recommeneded against in men younger than 40 years of age.[11]

Continuous elevated levels of PSA would prompt a digital rectal exam (DRE), imaging tests, such as magnetic resonance imaging (MRI) or ultrasound, and lastly a prostate biopsy. A DRE is a procedure performed by a physician to physically feel the prostate gland, while an ultrasound or MRI imaging is used to anatomically visualize the prostate gland. Abnormalilities assessed by DRE and imaging results would consist of the presence of suspiscious lumps and visualize suspicious prostatatic lesions, respectively.

Convergence of these positive findings would prompt a prostate biopsy. The standard procedure, named a systematic biopsy, uses an 18-gauge needle to obtain a series of tissue cores. The number of samples taken during a prostate biopsy ranges from 6 to 24-core that extracts laterally directed cores at the base, mid-gland, and apex of the prostate with mid-lobar biopsy cores at the base and apex.[12] A meta-analysis from Eichler and colleagues concluded that the optimal prostate biopsy scheme should consists of 12-core, with no significant benefit in cancer detection taking more than 12 cores, and taking any greater than 18-core had a poor side-effect profile.[13] If cancer is detected in any of the biopsy cores, the diagnosis will be identified.

GLEASON GRADE GROUP

Diagnosed PCa cases are assigned a Gleason Grade Group (GGG), used in combination with the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system, and pre-biopsy PSA, to determine overall cancer group stage, risk grouping, and ultimately help guide treatment recommendations. The GGG assigned is determined by the sum of the two predominant patterns of cells seen in the biopsied tissue under a microscope (i.e. Pattern X + Pattern Y). Inititally, Gleason grades ranged from 1 to 5, until it was internationally recognized that Gleason score 1 and 2 are improbable, and are no longer recognized by modern standards.[14] For this reason, the lowest Gleason sum achieved is 6 (3+3), identifying as Gleason Grade Group 1. While Gleason Grade Group 2 and GGG 3 both have the same Gleason sum of 7, the difference lies in the prevelance patterns. GGG 2 has a dominant Gleason grade 3 pattern, while GGG 3 has a dominant Gleason grade 4 pattern, with prognosis favoring GGG 2 (3+4), where the primary pattern is lower than the secondary. A Gleason Grade Group 4 is a sum of 8 (4+4, 3+5, 5+3), and lastly a sum of 9 or 10 is classified as GGG 5, all summarized in Table 2. A higher GGG indicates more abnormal looking cells, and often indicates aggressive cancer.

Gleason Grade Groups	
Gleason Grade Group 1	Gleason sum <6
Gleason Grade Group 2	Gleason 3+4 = 7
Gleason Grade Group 3	Gleason 4+3 = 7
Gleason Grade Group 4	Gleason 8
Gleason Grade Group 5	Gleason 9-10

Table 2. Gleason Grade Group summarized

TNM STAGING SYSTEM

While Gleason Grade Group is determined by the pathological appearance of cells under a microscope, the TNM system gives information on spread of the tumor to locations outside the prostate. This is usually confirmed with imaging or other procedures.

According to the 8th edition of the AJCC TNM staging manual, the T category of TNM evaluation is used to describe the spread of primary tumor. Distinctions between organ confined, extension outside of the prostatic capsule, invasion to seminal vesicles (seen in Figure 3), and invasion to external sphincter, rectum, or pelvic side wall are confirmed with MRI imaging.[15] Additionally, the N category of the TNM system reveals if the cancer has spread to regional lymph nodes. Regional lymph nodes are within the pelvis, below common iliac artery bifurcation. Lastly,

the M category reveals if the cancer has metastatized and has spread outside the pelvis region (i.e. non-regional nodes, bone, lung, or liver). The TNM staging system is summarized in Table 3.

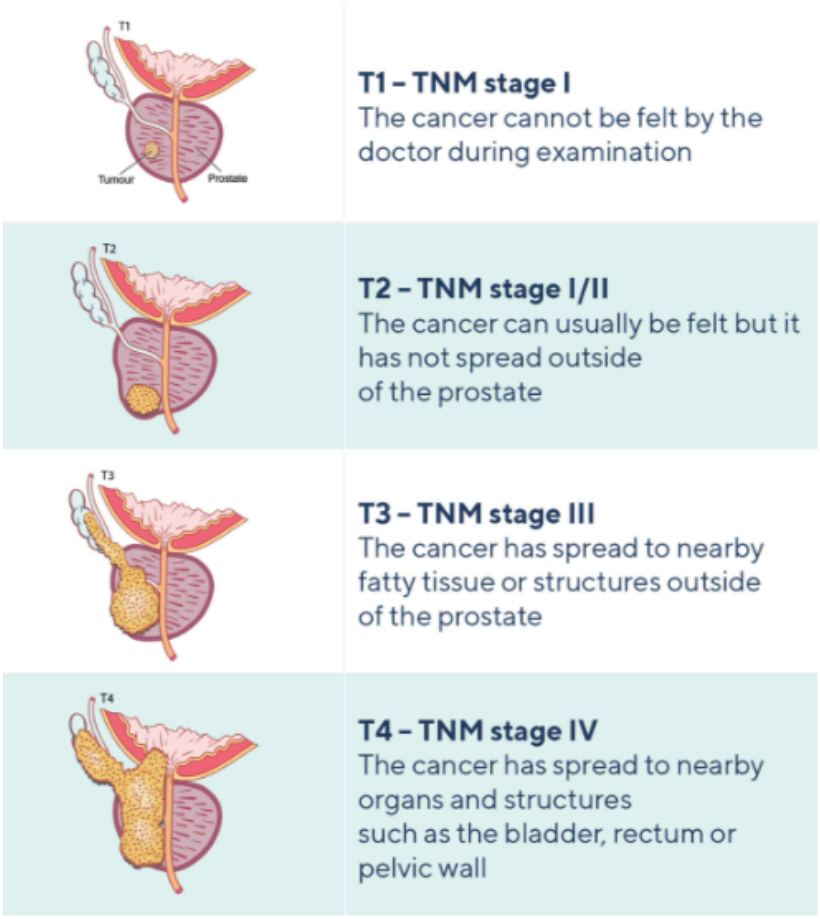

Figure 3. Tumor stage (the T in TNM)[16]

Primary Tumor	
Tx T0	Primary tumor cannot be assessed No evidence of primary tumor
T1	Clinically inapparent tumor not palpable not visible by imaging
T1a	Incidental tumor in < 5% of TUR tissue
T1b	Incidental tumor in > 5% of TUR tissue
T1c	Needle biopsy prompted by elevated PSA
T2	Organ confined
T3	Tumor extends beyond the prostatic capsule
T3a	Extracapsular, unilateral and bilateral or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicles (s)
T4	Tumor invades external sphincter, rectum, pelvic side wall
Lymph Nodes	
Nx N0	Regional nodes were not assessed No regional (below level of bifurcation of common iliac arteries) nodes
N1	Regional node metastases – including pelvic, hypogastric, obturator, iliac, sacral
Distant Metastases	
Mx M0	Regional nodes not assessed No Metastases
M1 M1a M1b M1c	No distant Non-regional lymph nodes (outside true pelvis) Bone(s) Other site(s) with or without bone disease

Table 3. 8th edition of the AJCC TNM Staging Classifications [17]

NCCN RISK GROUPING

More so, according to the National Comprehensive Cancer Network (NCCN) guidelines, Gleason score, tumor-stage, and PSA levels are used to stratify risk group of the disease. The NCCN risk-group guideline stratefies men into five groups: low-

risk, intermediate risk, high risk, and very high risk for locally advanced prostate cancer, and metastatic risk. The groups are defined as low risk: T1-T2a, Gleason score <5, and PSA <10ng/mL; intermediate risk which also subdivides into favorable and unfavorable: T2b-T2c or Gleason 7 or PSA 10-20ng/mL; high risk: T3a or GGG 4 or 5 or PSA>20 ng/mL; very high risk: T3b-T4 or primary Gleason pattern 5 or >5 cores with Gleason 8-10; and metastic risk: N1 or M1 with any T-stage[18] (Table 4).

NCCN Risk-Grouping			
Risk-Group:	**Definition**		
Low Risk	T1-T2a, Gleason score <5, PSA <10ng/mL		
Intermediate Risk	T2b-T2c, or Gleason 7, or PSA 10-20ng/mL	Favorable Intermediate	1 intermediate risk factor (IRF), <50% biopsy cores positive
		Unfavorable Intermediate	2 or 3 IRFs, ≥50% biopsy cores positive
High Risk	T3a, or Gleason 8-10, or PSA >20ng/mL		
Very High Risk	T3b-T4, or primary Gleason pattern 5 or >5 cores with Gleason 8-10		
Metastatic Risk	N1 or M1 with any T-stage		

Table 4. NCCN Risk-Grouping summarized

For patients with localized disease, the grade of the found cancer remains the strongest prognostic parameter, as well as serves an important indication for treatment options. Following curative treatment, men with Gleason sum of 6, or have a GGG 1, are reported to have a 96% likelihood of being free from PCa progression 5 years after diagnosis. As the GGG progresses from 2 to 5, the 5-year rates of being free from PCa progression decreases from 88%, 63%, 48%, and 26%, respectively.[19] Conclusively, men with less severe cancer have better outcomes when compared to those with advanced cancer progression. Fortunately, with the advancements in medicine, a range of curative treatment options for PCa include surgery, radiation, and cryotherapy and are sometimes mixed with hormone therapy, chemotherapy, and targeted therapy to further improve prognosis.

TREATMENT OPTIONS

A multitude of factors are taken into account when planning for treatment. Factors, other than stage and grade of the cancer, also includes a person's comorbidities, age, life-expectancy, and quality of life.[20] The most commonly elected options for men with prostate cancer are active surveillance (AS), surgery, or radiation therapy.[21] While both surgery and radiation therapy are offered as curative treatment stratgeies, active surveillance is not and is only indicated in patients with low or favorable intermediate risk disease.

The drawback with curative therapies are the reported adverse events (AE) which are unfavorable and unintended symptoms acquired from medical treatment

or procedure. In addition, adverse events are graded 1-5 based on severity by the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE) (Table 5). Grades 1-5 range from mild, moderate, severe, life-threating, and death. Studies have reported AEs of both surgery and radiotherapy showing similar rates of toxicities in the genitourinary system with specific outcomes regarding sexual dysfunction, urinary control, and LUTS occurring to varying individual degress across these treatment modalities, while radiotherapy toxicities have also reported gastrointestinal system such as long-term diarrhea and rectal bleeding.[22,23]

Common Terminology Criteria for Adverse Events (CTCAE) v5.0	
Grades	**Definition**
Grade 1	**Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	**Moderate**; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
Grade 3	**Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting ADL.
Grade 4	**Life-threatening** consequences; urgent intervention indicated.
Grade 5	**Death related** to AE.

Table 5. Common Terminology Criteria for Adverse Events v5.0 summarized

ACTIVE SURVEILLANCE

The purpose of active surveillance (AS) is to maintain patients' quality of life by delaying curative treatment when PCa is unlikely to cause mortality or significant morbidity. In multiple longitudinal studies comparing active surveillance, radical prostatectomy, and external-beam radiation therapy for men with localized prostate cancer, no significant difference was seen among the groups in the number of deaths from PCa, concluding that prostate-specific mortality is low irrespective of the treatment assigned.[24],[25] Active surveillance is indicated for men with localized-, low- or favorable-risk disease, but if disease progresses interventional treatment should be pursued.

Men who opt for active surveillance are not placed on any curative treatment, rather they are followed up routinely by their urologist. With this plan of care, prostate cancer progression is routinely tracked by measurements of PSA levels, prostate digital rectal exams (DRE), follow-up imaging, and prostate biopsies performed by the provider. Per the AUA advisory panel, PSA should be routinely checked no more frequently than every six months, and DRE and repeat biopsy every one to two years. [26]

SURGERY

Secondly, a common treatment option with curative intent is surgery. Men with localized PCa who opt for surgery undergo a radical prostatectomy (RP). The

option of radical prostatectomy is reserved for patients whose life expectancy is 10 years or more. [27] However, undergoing radical prostatectomy leads to increased likelihood of AEs such as erectile dysfunction and urinary incontinence. More so, according to the analysis done by Donovan et al. when comparing patient-reported outcomes after AS, RP, and radiotherapy; of the three, radical prostatectomy had the greateast negative effect on sexual function and urinary continence. [28]

In this surgical procedure, the entire prostate including the seminal vesicals are removed. There are two main ways a surgeon can perform a radical prostatectomy- open or laparaoscopic. With either type of operartion, the purpose is to remove all cancerous tissue, while minimizing both long- and short-term side effects. As with any major surgery, there poses risks with reactions to anesthesia, bleeding, or infections.

RADIATION

Lastly, a prevalent treatment option offered to men of all disease groups is radiation therapy. Studies comparing effective means of PCa treatment of radiation therapy and surgery have shown comparable cure rates and outcomes in men with localized PCa.[25] Radiation therapy encompasses a multitude of techniques including external beam radiation therapy (EBRT), using either x-ray therapy or proton therapy, brachytherapy, or a combination of both. These techniques serve the same purpose in relying on radiation to diminish cancer cells. Commonly reported AEs for

radiotherapy are changes in urinary function, sexual function, and gastrointestinal side effects.

In X-ray external beam radiation therapy (XR-EBRT), high-energy beams of x-rays, radiation produced by a machine outside the body, are carefully guided to the prostate gland over multiple treatments. Techniques are implemented to carefully guide the radiation by computer-driven machines, or image-guided techniques. Similarly, proton radiation therapy uses the same techniques, with the only difference in relying on protons instead of x-rays. Proton therapy promises a reduced likelihood of damaging nearby healthy tissues, yet cost-benefits anaylses have shown high costs with no realization of reduced toxicities. Further, limited insurance coverage has resulted in a sparcity of proton centers available in the United States.[29]

An alternative radiation technique that does not rely on the external machines delievering radiation to the targeted organ is called brachytherapy. Brachytherapy is also known as seed implantation or interstitial radiation therapy. With this technique, radioactive pellets, about the size of a grain of rice, are strategically placed into the prostate and relied on to deliver radiation. With brachytherapy, there is the possibility of permanent low-dose rate (LDR), or temporary high-dose rate (HDR) seed implantation. Furthermore, treatment options of either LDR- or HDR-brachytherapy can be combined with EBRT; named a brachytherapy boost.

HISTORY OF BRACHYTHERAPY RADIATION

Radioactive resources used to treat malignant diseases dates as far back to the early 1900s, when Marie and Pierre Currie first discovered radium. Although radium matter is not standardized for PCa brachytherapy treatment today, its first reported use in prostatic brachytherapy was in 1911. Drawbacks with using radium brachytherapy included significant toxicity in exchange for local control.[30] Following, in the 1950s, another discovery was indicated to treat prostate cancer, ^{198}Au colloid solution. While this solution proved promising with minimal morbidity, its high-energy isotope necessitated radiation safety precautions that proved more challenging. Alas, in the 1970s, colleages at Memorial Sloan-Kettering Cancer Center began using ^{125}I seeds for PCa brachytherapy. This lower energy isotope of iodine, requiring less challenging safety precautions, proved favorable in treating PCa while minimizing acute toxicities. As time progressed, ^{103}Pd and ^{192}Ir became other commonly used isotopes for low-dose rate brachytherapy (LDR-BT) to treat PCa.

Alongside its trajectory, implantation techniques used to deliver the radiation also improved with introduction of the image-guided transrectal ultrasonography (TRUS). By the late 1980s, analysis of image-based dosimetry revealed that dose coverage of LDR-BT was often lower than suggested in the preplans, yielding lower treatment efficacy. In order to overcome these limitations, high-dose rate brachytherapy boost (HDR-BTb) was introduced, before HDR-BT monotherapy. By the 1990s, multiple studies worldwide evaluated both HDR-BT

and HDR-BTb, and conclusively reported good tumor coverage and minimized dose to adjacent organs at risk.[31]

MODERN MEDICINE IN BRACHYTHERAPY FOR PCA

LOW-DOSE RATE BRACHYTHERAPY

According to ABS guidelines, low-dose rate brachytherapy (LDR-BT) is indicated for men with low-risk disease. In the LDR-BT procedure, radioactive pellets, most commonly either iodine-125 or palladium-103, are inserted via needles placed through the perineum and used to place seeds made of radioactive isotopes throughout the prostate gland. The needles are then removed, while 80-120 radioactive pellets are left inside the prostate. The radiation given off by the pellets travels a short distance and limits damage to nearby healthy tissues. Over the span of weeks to months, the prescribed radioactive dose would be completed and the isotopes decary into an inert metal.

A drawback with LDR-BT is seed migration, a common phenomenon reported in 0.7-55% of patients undergoing this treatment plan.[32] Seed migration or seed loss is the event in which the presence of one or more seeds are found away from the intended location and potentially outside the prostate gland altogether. Reasons associated with this event is thought to be due to the anatomy of the prostate region with its proximity to the urinary bladder, and surrounding plexus.[33] Although rare, it has also been reported that migrated seed(s) were found in the

lungs, pelvis, heart, mediastinum, kidney, inguinal canal, liver, and sacrum.[34] Not only is seed migration a bodily concern but early seed migration, occurring within 1st day after implantation, would severely affect postimplant dosimetry and depending on where the seed(s) migrated could have implications on adverse events. Whereas late seed migration, not clearly as defined but ranging from 6 weeks to 3 years post-implantation, have shown no significant influence on postimplant dosimetry.[32],[35] To overcome the problem of suboptimal dosimetry, and as history has stipulated, high-dose rate brachytherapy was seen as an alternative in treating men with similar-risk disease.

HIGH-DOSE RATE BRACHYTHERAPY

High-dose rate brachytherapy (HDR-BT) is indicated for men with either low- or intermediate-risk disease. Important steps for HDR-BT technique are 1) catheter placement using image guidance- TRUS 2) imaging with cathether in place 3) contouring of target(s) and organs at risk 4) dwell time optimization and planning 5) quality assurance 6) treatment delivery and 7) implant removal. The procedure of HDR-BT is similar to that of LDR-BT seed implantation. However with HDR-BT, the difference lies in the removal of the radioactive pellet(s) from the patient entirely with no radioactive substance retained. The needles are connected to catheters that allow for a single radioactive pellet, made of iridium-192 or cesium-137, to be placed in various regions of each needle for a few seconds, after

which the pellet moves to a new area and so on until the entirety of the prostate gland has received radiation. This entire radiation process takes only around 5-15 minutes to complete, and there is no concern for seed migration in HDR-BT.

In a study comparing the radiobiological models of LDR- and HDR-brachytherapy, it was concluded that both regimens achieve similar tumor control rates in men with low-risk disease. However, HDR-brachytherapy offered opportunities of dose escalated regimens that was able to achieve higher biological effective doses of irradiation and prospectively improved outcomes.[36] As more studies compared outcomes of both, HDR-brachytherapy proved superior for both dose coverage and escalation, as well as reduced irradiation to organs at risk such as bladder, rectum, and urethra; supporting the evidence that HDR-BT reduces the likelihood of side effects.[37],[38],[39]

A PUSH TOWARDS HDR-BT BOOST

Around the same time, studies began looking at brachytherapy (BT) as a boost in addition to EBRT for treating men with unfavorable intermediate and high-risk disease. As with any radiotherapy, drawbacks of boost therapy includes potential adverse events in genitourinary (GU) and gastrointestinal (GI) systems and irradiation to nearby healthy tissues. Though, it is not uncommon for men undergoing EBRT to report GI issues, where beams of radiation enters and exits the targeted radiation field which most likely encompasses the GI tract; causing mucosal

injury and inflammation attesting to occurence of GI adverse events.[40] Similar to the adverse effects seen in prostatectomies, the likelihood of GU dysfunction remains the same.

In 2017, the ASCENDE-RT trial gained traction for their reported findings in a randomized trial between LDR-brachytherapy boost (LDR-BTb) and EBRT monotherapy. It was concluded that LDR-BTb achieved better biochemical control compared to EBRT alone, though at the cost of increased incidence in acute and late genitourinary toxicities.[41] This paper created a divide between those in support of boost therapy and those who reverted back to historical techniques.

It was not until 2021, where a study published by Yamazaki et. al was able to directly compare the outcomes of HDR-BTb and LDR-BTb. The study concluded that HDR-BTb is a strong alternative to both LDR-BT and LDR-BTb, offering equivalent efficacy and in fact, less GU toxicity.[42] All the more, a study published in 2023 by Miszczyk et al. compared the outcomes of HDR-BTb and EBRT alone; reporting that overall survival, freedom from distant metastases, and metastases-free survival were significantly higher in those receiving HDR-BTb compared to EBRT alone.[43]

Gradually more research came out in support of HDR-brachytherapy boost, driving modern medicine to recognize its advantage and thus slowly moving away from LDR-BTb in treating men with high-risk PCa disease. As the name implies, High-Dose Radiation-Brachytherapy Boost, is the radiation technique that incorporates one to three HDR-BT session(s) in conjunction with multiple rounds of XR-EBRT sessions. A single session of HDR-BT can be given prior to or after

completion of all of of the EBRT sessions. While ABS consensus guidelines for HDR-BT was unable to recommend a particular dose fractionation for HDR boost[44], the European brachytherapy group, GEC/ESTRO, published fractionation recommendations (Table 6).

GEC/ESTRO Recommendations			
EBRT Dose Fractionation Schedule	**Gy**	**Fractions**	**Length**
	45 Gy	25	5 weeks
	46 Gy	23	4.5 weeks
	35.7 Gy	13	2.5 weeks
	37.5 Gy	15	3 weeks
Combined with HDR-BTb Schedule	**Gy**	**Fractions**	**Length**
	15 Gy	3	-
	11-22 Gy	2	-
	12-15 Gy	1	-

Table 6. Dose and fractionation for HDR boost (GEC/ESTRO 2013)[45]

Regardless of updated guidelines from the National Comprehensive Cancer Network (NCCN), indicating high-dose rate brachytherapy boost (HDR-BTb) for men with either intermediate- or high-, or very high-risk PCa disease, it is still not offered to everyone. Its been stipulated that only those with prostate gland volumes smaller than 65cm^3 and mild baseline AUA scores should benefit from HDR-BTb. These indications exclude those with larger prostate gland volumes or higher baseline AUA symptom scores, suggesting worse outcomes with data in support of this derived primarily from series investigating LDR-BT. Notably, research reporting on toxicities associated with brachytherapy boost were found to be independent of

multiple patient factors, questioning these contraindications.[46] Though these contraindications are no longer absolute, we seek to understand the validity of old data and how it may or may not be revelant to HDR-BTb.

SPECIFIC AIMS

The specific aims for this study are to:

1. Assess the rates and severities of toxicities reported by patients undergoing HDR-BTb
2. Assess if historical factors associated with BT toxicities remain relevant in the setting of modern BT techniques and use of HDR procedures
3. Investigate if there are novel cutoffs for baseline urinary symptoms or prostate size that more accurately predict post-BT toxicity outcomes to guide future clinical consideration and decision making

METHODS

The following study was approved by University of Nebraska Medical Center institutional review board (IRB; protocol 398-17-EP). From April 2019 to May 2023, 160 patients with intermediate- to very-high-risk PCa underwent high-dose-rate brachytherapy boost (HDR-BTb) treatment at a single-site. Under the protocol, data was prospectively collected and followed HIPAA protocols. For this project, patients' information were deidentified and data was retrospectively analyzed.

PROCEDURE

Patients underwent a single 15 Gy HDR-BT boost session prior to their daily EBRT sessions. After receiving a single boost session, 46 Gy of EBRT was delievered over 23 fractions with fractionations 2 Gy per weekday.

DATA COLLECTION AND ANALYSIS

Data was organized and analyzed using Microsoft Excel. In the master sheet, clinical, volumetric, and dosimetric data were collected. This included demographics, plan parameters, bladder-, urethra-, rectum- target volume, prostate volume, AUA symptom scores before and after treatment, both GU and GI acute and chronic toxicities, as well as the CTCAE extent were recorded.

Descriptive statistics were compiled to summarize demographic variables such as age, PSA before treatment, Gleason Grade Group, and NCCN risk group. In addition, the highest acute and chronic GU and GI toxicities were recorded and

graded from 1-5 according to CTCAE. Acute toxicities were designated as toxicities that occurred during the radiation treatment course or within 6 months of radiation completion. Chronic toxicities were designated as those occurring more than 6 months after radiation treatment was completed.

Analytical statistics using Microsoft Excel's ROC Curve and Classification Table created by Charles Zalontz and paired t-tests were performed to examine the relationship or association between variables, such as CTV volume and AUA scores, and GI and GU toxicities and CTCAE extent.

RESULTS

DEMOGRAPHIC AND ONCOLOGICAL CHARACTERISTICS

Demographic characteristics such as age, pre-treatment PSA, race, and prostate volume, were recorded in Table 7. Age, pre-treatment PSA, and prostate volume, were analyzed for mean values and standard deviation, while race was not. Mean (SD) participant age was 66.6 years (6.5); pre-treatment PSA was 14ng/mL, (18.2); and prostate volume was 36.0cc, (14.5) (Table 7). Of the 160 participants, a majority (N=142, 89%) were Caucasian. Oncological characteristics of participants are summarized and presented in Table 8.

Table 7. Demographic Characteristics

	Average (Range)
Age (yrs)	66.6 (49 - 80)
Pre-Treatment PSA (ng/mL)	14.0 (1.14 - 115)
Prostate Volume (cc)	36.0 (14.4 - 99.5)
Race	N (%)
White	142 (88.8%)
Black/African-American	15 (9.4%)
Other	3 (1.9%)

Table 8. Oncological Characteristics

	N (%)
Gleason Grade Group	
GGG 1	0 (0%)
GGG 2	38 (23.8%)
GGG 3	45 (28.1%)
GGG 4	30 (18.8%)
GGG 5	47 (29.4%)
T-stage	
1c	60 (37.5%)
2a	11 (6.9%)
2b	9 (5.6%)
2c	5 (3.1%)
3a	42 (26.3%)
3b	33 (20.6%)
N-stage	
Yes	14 (8.8%)
No	146 (91.2%)
NCCN Risk Group	
Favorable Intermediate	7 (4.4%)
Unfavorable intermediate	50 (31.3%)
High	37 (23.1%)
Very High	52 (32.5%)
Regional Metastasis	14 (8.8%)
Distant Metastasis	0 (0%)

ASSESSING ACUTE AND CHRONIC TOXICITY

Both acute and chronic genitourinary and gastrointestinal toxicities are listed in Table 9 and 10, and stratified by CTCAE extent. Of the 160 patients, 67% reported acute GU toxicities, and 21% reported chronic GU toxicities; though 12.5% and 2.5% were CTCAE Grade 2+ or clinically relevant, respectively. The most reported GU

toxicities were changes in frequency (49.4%; 9.4% Grade 2+) and dysuria (21.9%; 0% Grade 2+). In comparison, presenting at a much lower rate, 40% (4.4% Grade 2+) indicated acute GI toxicity, while 11% (0% Grade 2+) indicated chronic GI toxicity, with most reported GI toxicities being diarrhea (33.8%; 0-3.8% Grade 2+). However, in both GU and GI toxicities, acute and chronic are not mutually exclusive. No patients in this study reported any toxicity of CTCAE grade of 3+.

Table 9. GU Toxicity

Genitourinary Toxicity	CTCAE Grade	Acute	Chronic
Spasms	1	4 (2.5%)	1 (0.6%)
	2	3 (1.9%)	1 (0.6%)
	3	0	0
	4-5	0	0
Cystitis	1	10 (6.3%)	4 (2.5%)
	2	1 (0.6%)	0
	3	0	0
	4-5	0	0
Frequency	1	79 (49.4%)	20 (12.5%)
	2	15 (9.4%)	3 (1.9%)
	3	0	0
	4-5	0	0
Urgency	1	26 (16.3%)	13 (8.1%)
	2	1 (0.6%)	0
	3	0	0
	4-5	0	0
Dysuria	1	35 (21.9%)	3 (1.9%)
	2	0	0
	3	0	0
	4-5	0	0
	Total:	**107 (67%)**	**33 (21%)**

Table 10. GI Toxicity

Gastrointestinal Toxicity	CTCAE Grade	Acute	Chronic
Diarrhea	1	54 (33.8%)	9 (5.6%)
	2	6 (3.8%)	0
	3	0	0
	4-5	0	0
Fecal Incontinence	1	1 (0.6%)	4 (2.5%)
	2	0	0
	3	0	0
	4-5	0	0
Flatulence	1	0	0
	2	0	0
	3	0	0
	4-5	0	0
Naseau	1	3 (1.9%)	0
	2	1 (0.6%)	0
	3	0	0
	4-5	0	0
Rectal Hemorrhage	1	0	0
	2	0	0
	3	0	0
	4-5	0	0
Rectal Mucositis	1	0	0
	2	0	0
	3	0	0
	4-5	0	0
Rectal Pain	1	2 (1.3%)	4 (2.5%)
	2	0	0
	3	0	0
	4-5	0	0
	Total:	**64 (40%)**	**17 (11%)**

ASSESSING RELEVANCY OF OLD INDICATIONS

Previously established factors impacting brachytherapy candidacy, including prostate volume and baseline AUA symptom scores, were closely examined in Tables 11 and 12, respectively. In Table 11, acute and chronic GU toxicities outcomes were stratified between those with prostate volume of ≤65 cubic centimeters (cc) and >65cc. Data analysis concluded that acute GU toxicities were more likely than chronic, regardless of prostate volume. More so, the rates of acute and chronic GU toxicities were actually lower in men with prostate volumes of >65cc (67.3% vs 57.1%, and 20.9% vs 14.3%), p-value = <0.0001. In addition, extent and severity of symptoms were reported in the bottom half of the table, under CTCAE extent. Of the 7 patients with larger prostate volumes of >65cc, only 2 patients reported GU symptoms of CTCAE>1.

Shown in Table 12 is the reported acute and chronic GU toxicities outcomes stratified between those with baseline AUA symptom score of ≤15 and >15. In a similar manner as the previous table, CTCAE extent of GU symptoms is shown in the bottom half of the table. Patients with baseline AUA SS of ≤15 showed a decreased rate of acute GU toxicities than those with baseline AUA SS of >15, p-value = <0.0001.

Table 11. Prostate Volume

Prostate Volume (cc)	≤65 (N=153)		>65 (N=7)	
	Acute	**Chronic**	**Acute**	**Chronic**
GU				
CTCAE Spasms	7 (4.6%)	2 (1.3%)	0	0
CTCAE Cystitis	11 (7.2%)	4 (2.6%)	0	0
CTCAE Frequency	91 (59.5%)	23 (15%)	3 (75%)	0
CTCAE Urgency	26 (16.7%)	12 (7.8%)	1 (25%)	1 (100%)
CTCAE Dysuria	33 (21.6%)	3 (2%)	2 (50%)	0
Total:	**103 (67.3%)**	**32 (20.9%)**	**4 (57.1%)**	**1 (14.3%)**
CTCAE >1				
CTCAE Spasms	3 (2%)	1 (0.6%)	0	0
CTCAE Cystitis	1 (0.6%)	0	0	0
CTCAE Frequency	18 (11.8%)	4 (2.6%)	1 (14.3%)	0
CTCAE Urgency	5 (3.3%)	0	0	0
CTCAE Dysuria	5 (3.3%)	0	1 (14.3%)	0
Total:	**32 (20.%)**	**5 (3.3%)**	**2 (28.6%)**	**0 (0%)**

Table 12. Baseline AUA

Baseline AUA	≤15 (N=81)		>15 (N=17)	
	Acute	**Chronic**	**Acute**	**Chronic**
GU				
CTCAE Spasms	2 (2.5%)	2 (2%)	2 (11.8%)	0 (0%)
CTCAE Cystitis	5 (6%)	3 (4%)	1 (6%)	0 (0%)
CTCAE Frequency	45 (56%)	12 (15%)	11 (65%)	3 (18%)
CTCAE Urgency	15 (19%)	9 (11%)	3 (18%)	1 (6%)
CTCAE Dysuria	18 (22%)	1 (1%)	3 (18%)	0 (0%)
Total:	**N=45 (55.6%)**	**N=20 (24.7%)**	**N=11 (64.7%)**	**N=3 (17.6%)**
CTCAE >1				
CTCAE Spasms	1 (1%)	1 (1%)	1 (6%)	0 (0%)
CTCAE Cystitis	1 (1%)	0 (0%)	0 (0%)	0 (0%)
CTCAE Frequency	13 (16%)	2 (2%)	1 (6%)	0 (0%)
CTCAE Urgency	3 (4%)	0 (0%)	1 (6%)	0 (0%)
CTCAE Dysuria	5 (6%)	0 (0%)	0 (0%)	0 (0%)
Total:	**23 (28.4%)**	**3 (3.7%)**	**3 (17.6%)**	**0 (0%)**

ROC CURVES

As our data would suggest that previously designated cutoffs for prostate size and baseline AUA scores are not representative of ture increased risk of toxicities with HDR-BTb, we sought to investigate if different cutoffs could be established that would help to inform post-HDR-BTb toxicity outcomes using a receiver operator characteristic (ROC) curve. The ROC curve illustrates the true positive and false positive rates to distinguish or single out an optimal cut-off point. By graphing the frequencies of true and false positives, a reciprocal relation can be visualized. When

true positive rate increases, by default false positive rates will decrease. A perfect test will show a curve favoring the Y-axis near the upper left corner and converging horizontally to the right. Done statistically to quantify the result, the area under the curve (AUC) is calculated and the value gives insight to accuracy of tests. As general knowledge, AUCs between 0.50 and 0.70 is low; between 0.70-0.90 is moderate; and values over 0.90 suggests high test accuracy.

Displayed in Figure 4 and 5, baseline AUA score vs acute or chronic GU toxicities were graphed to deteremine if there was any correlation. With the displayed curve, the area under the curve was found to be 0.56 and 0.53, respectively, which can be interpreted as a failed test. Relevant to this study, a failed test would indicate zero significance in predicting toxicity.

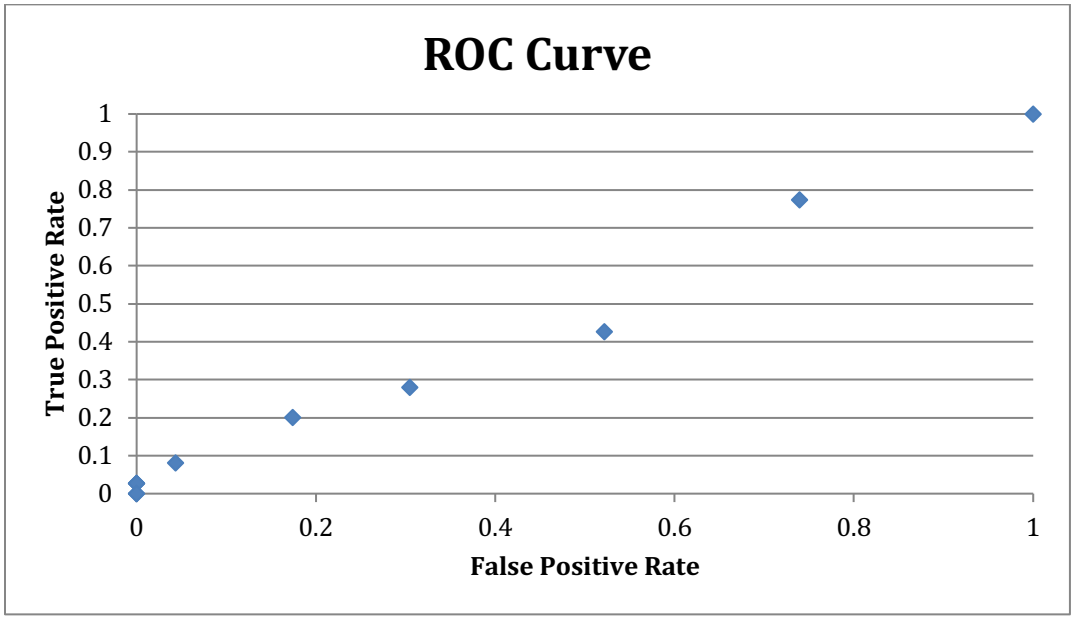

Figure 4. ROC Curve- AUA baseline score vs Acute GU Toxicity (AUC: 0.561)

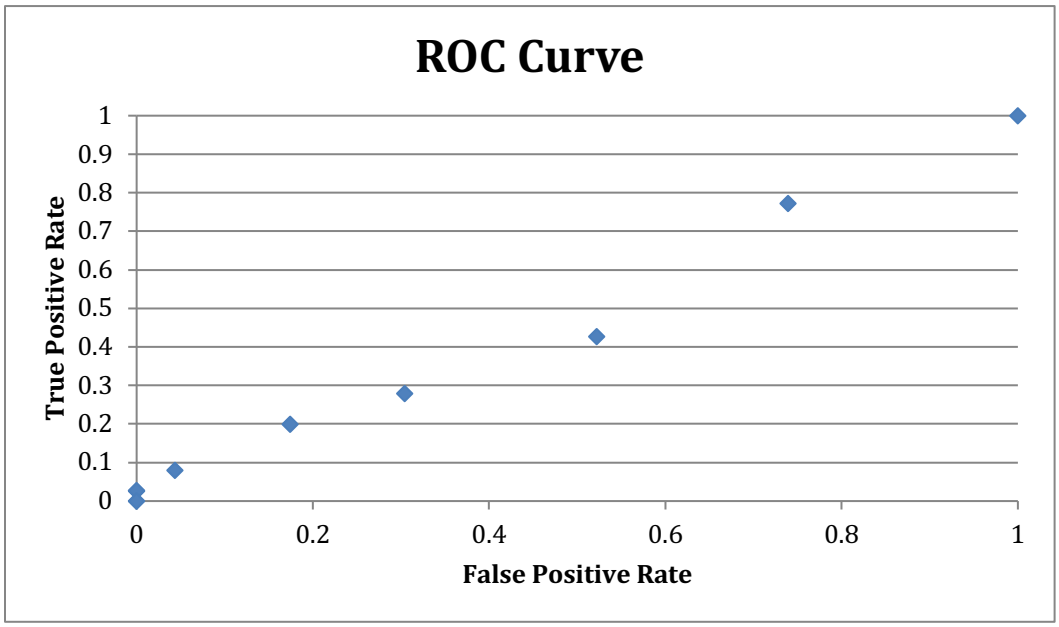

Figure 5. ROC Curve- AUA baseline score vs Chronic GU Toxicity (AUC: 0.528)

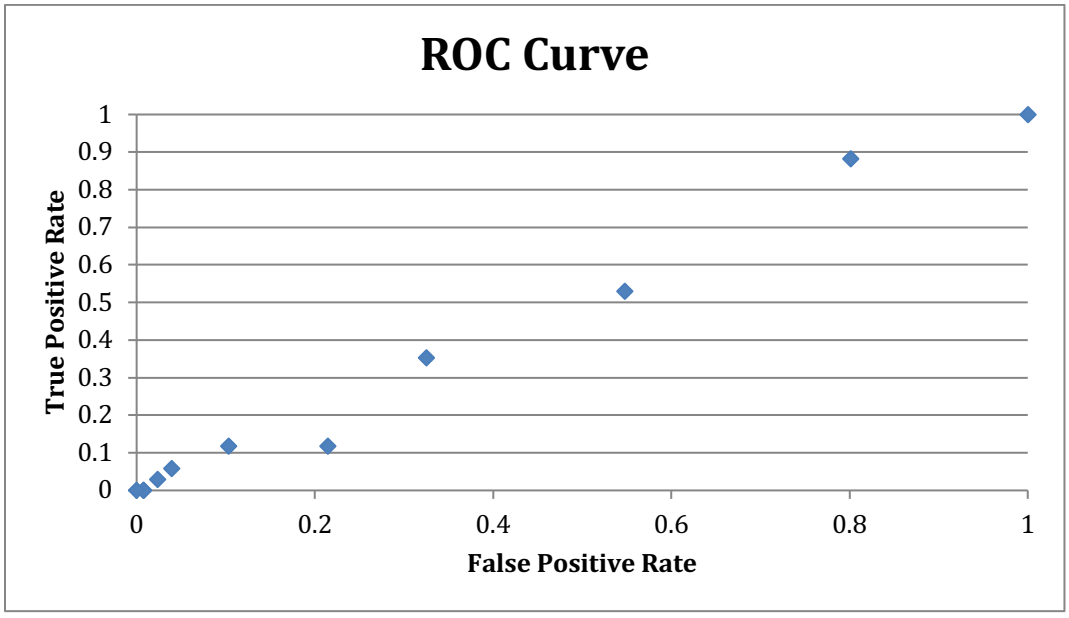

Figure 6. ROC Curve- Prostate Volume vs Acute GU Toxicity (AUC: 0.601)

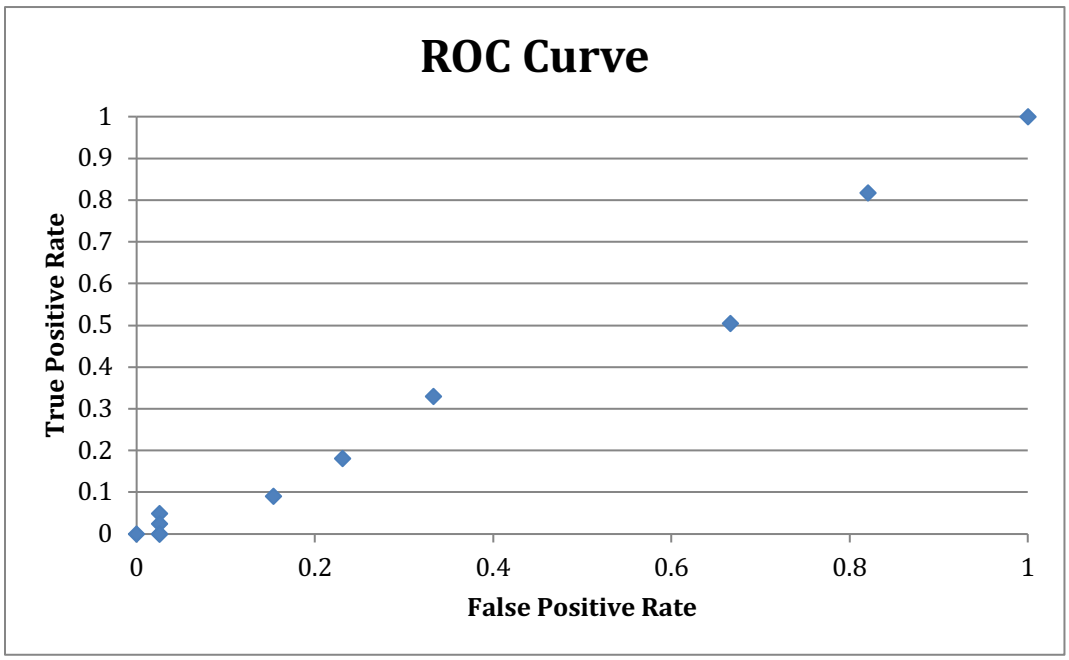

Figure 7. ROC Curve- Prostate Volume vs Chronic GU Toxicity (AUC: 0.517)

In addition, prostate volume was also looked at. Figures 6 and 7 demostrates the ROC curve of prostate volume vs acute or chronic GU toxicities. Reported AUC values were 0.601 and 0.517, respectively; similar to AUC values seen with AUA baseline score, indicating a poor correlation of prostate volume with acute or chronic GU toxicity. Conclusively, these results show no impact of these variables on predicting toxicities.

DISCUSSION/CONCLUSION

Over the past two decades, radiation has become increasingly popular for treating PCa of all stages due to its biochemical control and favorable patient outcomes, with increasing support in brachytherapy. Advantages of brachytherapy includes comparable long-term survival, minimal irradiation to adjacent organs, and the most favorable toxicity profiles. Both permanent and temporary brachytherapies, LDR and HDR-BT, respectively, are used to treat mainly low risk group. However, studies have conclusively shown better reported toxicities (i.e. urethra and rectum) and effective potential for dose escalation in HDR-BT alone. With these promises, in addition to level 1 data demonstrating higher cure rates over EBRT alone, men with intermediate- to very high-risk localized prostate cancer diseases can benefit from combining brachytherapy and EBRT together, named a brachytherapy boost, with the most favorable outcomes seen with HDR-BTb. HBR-BTb has been established as an effective means in treating unfavorable intermediate-, high-, or very-high-risk PCa disease.

Regardless of the intervention chosen and as radiotherapy history has depicted, adverse events are inevitable and prove challenging to control. Adverse events commonly reported among men undergoing curative treatment for PCa are disruptions in urinary, bowel, and sexual functioning. While weighing the cost-benefit analysis with different radiotherapy techniques, maintaining and managing quality of life for these men remains of greatest importance when deciding on treatment options. Our study aimed to prove that HDR-BTb is an effective and well

tolerated procedure that can be safely provided to patients regardless of prostate size or baseline AUA score; encouraging more research to be done in this field.

Our study evaluated the incidence of GU and GI toxicities primarily in unfavorable intermediate-, high-, or very-high-risk men after HDR-BTb treatment. We found that both acute (67%) and chronic (21%) genitourinary toxicities were more common amongst these men in comparison to gastrointestinal toxicities; though with 12.5% and 2.5% having clinically significany grade 2+ GU and GI toxicities, respectively. Furthermore, rare to no CTCAE 3-5 toxicities were reported. The most to least commonly reported GU symptoms were frequency (49.4%) > dysuria (21.9%) > urgency (16.3%) > cystitis (6.3%) > spasms (2.5%). Nonetheless, these urinary patterns follow a predictable course; occurring acutely within the first 6 months after treatment and typically resolve within 1 year. Compared to discussed outcomes of LDR-BT, GU side effects occur less frequently with HDR-BT and HDR-BTb. This favorable profile is credited to the dose-escalation technique, specific to HDR-BT, and lack of migratory seeds seen in LDR-BT. With this difference, activity of the radiosource throughout the pelvic region to surrounding normal tissues is minimized and thus reducing side effects.

Similarly, reported gastrointestinal toxicities seen in HDR-BTb were more evident in the acute term (40%), and than 11% develop into a chronic problem . The most commonly reported GI symptoms with grade 2 CTCAE out of the seven listed were diarrhea (3.8%) and nausea (0.6%). There were no incidences of grade 3 or higher acute or late GI toxicities. With an even lower rate of toxicity compared to the

GU toxicity profile, it seems that GI adverse events are well tolerated and do not pose a serious concern in HDR-BTb. All the more, according to a national population-based study comparing the impact of LDR-BTb and HDR-BTb on toxicity by Parry et al., it was also concluded that HDR-BTb has achieved signicantly lower GI toxicity rates when compared with LDR-BTb, with 16.7% and 32.3% respectively.[47] Other than the predictable toxicity profiles as seen in similar brachytherapy techniques, HDR-BTb offers a better trade-off than historical radiotherapies and should be considered during treatment planning.

In addition to assessing our toxicity data, we also assessed if historical contraindications for LDR-BT were applicable to modern HDR-BTb. Previous studies on brachytherapy have concluded that larger prostate size correlate with increased acute toxicity, and those with a prostate volume of ≥65 cubic centimeters (cc) should not be considered for brachytherapy procedures. More so, rare studies have looked at toxicity reports in men with large glands undergoing HDR-BTb. Recognizing this scarcity, our study compared the differences in the toxicity profiles between men undergoing HDR-BTb with gland size ≤65cc (N=153) and those with gland size >65cc (N=7). Based on our data analysis and performed t-test, we found similar toxicities profiles in both groups, opposing what literature has published when LDR techniques are employed – men with gland size >65cc do not have higher rates of acute and chronic GU toxicities.

However, with a relatively small cohort of men with with gland size >65cc, we were only able to speculate that men with larger gland size do not have higher

acute toxicities. As a supplement, we examined to see if prostate volume of any size were predictive of acute or chronic GU toxicity profiles using a receiver operator characteristic (ROC) curve. In our study, the false and positive rates were indistinguishable, concluding that prostate volume of any size is not predictive of acute or chronic GU toxicity. These findings conclude that these specific parameters are not relevant to candidacy selection when considering HDR-BTb.

In addition to looking at prostate gland volume as a parameter model for acute GU toxicities, we also looked at baseline AUA score. Previous research reporting on urinary outcomes in men, following other radiotherapies, have conclusively found an increase in acute GU toxicities with high baseline International Prostate Symtom Scores (IPSS) and AUA symptom scores. However, little to rare research has been reported to see if this is also applicable following HDR-BTb. In our study, we used the established AUA symptom score of 15 as our cutoff point. Using the same procedure as prostate volume, we compared GU toxicity profiles of those with baseline AUA SS ≤15 (N=81) and those with AUA SS >15 (N=17). Our study concluded that those with a baseline AUA SS >15 have an increase in acute GU toxicities (64.7%) when compared with those with baseline AUA SS ≤15 (55.6%), p-value = <0.0001. However, those reporting a CTCAE grade 2+ with acute GU toxicities with a baseline AUA SS >15 compared to those with baseline AUA SS ≤15 were 17.6% and 28.4%, respectively. Our data corresponds to the established research that those who reported baseline AUA SS >15 have an increased risk of acute GU toxicities than those who reported baseline AUA <15,

though upon further investigation baseline AUA SS >15 is not clinically revelant. With the addition of the ROC curve data, we concluded that baseline AUA symptom score could not be used as a predictive model for acute GU toxicity. Displayed in Figures 4-7, our data has concluded that both large prostate volume and high baseline AUA symptom score may be disregarded as a contraindication for HDR-BTb procedure.

Recognizing the scarcity of research published on HDR-BTb parameters, there is further reason to expand and encourage studies to do so. While our study was limited to a single institution, our study is reproducible on a multi-institution scale, in which data can be retrospectively analyzed as well as prospectively analyzed with new encounters. We also recognized that our study demographics were majority Caucasian men, with little racial diversity, thus limiting extrapolation to other demographics. To better conclusively discuss these findings, increased effort in international studies should be ensued.

From a procedural standpoint, our findings were limited to ultrasound imaging without the additional planning of CT- or MRI-based real time imaging. Though with advancements in imaging technology, other parameters could be studied: evidence of a median lobe, measuring the distance between rectal wall and posterior catheter placement, specific location of the urethral in other zones of the prostate gland, and measurement of prostate width. Ultimately, these anatomic details of the pelvic region may be significant in the planning process and needle

placements during operation and influence expected outcomes and thereby favorability of offering this treatment to specific patients.

Discerning that the standard parameters indicated for LDR-BT does not apply to HDR-BTb remains relevant and should be considered when deciding treatment options in prostate cancer patients. By doing so, we widen the candidacy selection pool and offer patients with a more individualized treatment option.

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