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A Phase II Study Evaluating Bone Marrow-Sparing, Image-Guided Pelvic Intensity-Modulated Radiotherapy (IMRT) with Cesium-131 Brachytherapy Boost, Adjuvant Chemotherapy, and Long-Term Hormonal Ablation in Patients with High Risk, Non-Metastatic Prostate Cancer

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Abstract

Purpose/Objective(s): Management of localized high-risk prostate cancer remains challenging. At our institution we performed a prospective Phase II study of 2 years of androgen deprivation therapy (ADT), pelvic radiation, Cesium (Cs)-131 brachytherapy boost, and adjuvant docetaxel in high risk, localized prostate cancer with a primary endpoint of 3-year disease-free survival.

Materials/Methods: Acute/chronic hematologic, gastrointestinal (GI) and genitourinary (GU) toxicities were scored based on the CTCAE v3.0/RTOG-EORTC criteria, respectively. Actuarial biochemical recurrence free survival (bRFS), bRFSdisease free survival (DFS) and overall survival (OS) were calculated. Patients had a median age of 62 years (range 45–82), median Gleason score 8 (74% Gleason 8–10), median PSA of 11.2 (range 2.8–96), and 47% cT2-T3a stage disease. Androgen deprivation was given for two years, 45 Gy whole-pelvis IMRT was followed by an 85 Gy Cs-131 boost to the prostate gland, and adjuvant docetaxel was given for 4 cycles.

Results: Thirty eight patients enrolled from 2006–2014, with 82% completing protocol specified treatment, and 84.2% completing 4 cycles of docetaxel. Median follow-up for the entire and alive cohorts were 44 months and 58 months (range 3.4–118), respectively. Acute grade 2 GI and GU toxicity rates were 18.4% and 23.7%, respectively. Chronic grade 2 GI and GU toxicity rates were 2.6% and 2.6%, respectively. Twelve patients (31.6%) developed grade 4 hematologic toxicity, with no grade 5 toxicity. The 5-year DFS, bRFS and OS rates were 74.1%, 86.0% and 80.0%, respectively.

Conclusion: This aggressive pilot multi-modal approach appears to be safe and well-tolerated, providing disease control in a significant proportion of patients with particularly high risk prostate cancer.

Keywords

Prostate cancer; high risk; brachytherapy; Cs-131; external beam radiotherapy; docetaxel; chemotherapy

Introduction

High risk prostate cancer remains a challenging entity to treat. The standard of care at the time of trial development typically included radiation therapy, given entirely as external beam radiation therapy (EBRT) or EBRT with a brachytherapy boost, along with long-term neoadjuvant, concurrent, and adjuvant androgen deprivation therapy (ADT). Even with these therapies, many patients still suffer a biochemical recurrence.

Prior retrospective and prospective trials demonstrate improved relapse-free survival rates with dose-escalated approaches, as well as improved dosimetric and clinical outcomes among patients using conformal techniques that have progressed from 3D conformal radiation therapy (3DCRT) to intensity-modulated radiation therapy (IMRT).^{1,2} Recently, data have been emerging regarding further improvements in patients with high-risk prostate cancer. Specifically, the ASCENDE-RT trial randomized patients with intermediate- or high-risk prostate cancer to 12 months of ADT (8 months neoadjuvant) followed by 46 Gy whole pelvis EBRT in both arms, followed by dose-escalated EBRT with an additional 32 Gy boost or 115 Gy I-125 low dose rate (LDR) brachytherapy boost. At a median follow up of 6.5 years, those receiving dose-escalated EBRT had a hazard ratio of 2.04 (95% CI 1.25–3.33, $p=0.004$) on multivariable analysis with regard to biochemical relapse compared to those receiving LDR brachytherapy boost.^{3,4} Additionally, a recent retrospective analysis has shown a distant metastasis and prostate cancer-specific mortality benefits to external radiation with brachytherapy boost over definitive external radiation or prostatectomy specifically in Gleason 9–10 disease.⁵

Recent clinical trials evaluating the efficacy of docetaxel chemotherapy with ADT have shown mixed reviews, with one study showing no improvement in overall survival,⁶ one showing improvements in overall survival in select patients with locally advanced and metastatic castration sensitive and high risk locally advanced prostate cancer (i.e. those with high volume metastatic disease)⁷, and finally the STAMPEDE data showed the largest magnitude of benefit in those patients with high-risk metastatic disease, with improvements in failure-free survival and prognosis, but not overall survival in the high-risk non-metastatic patients.⁸ Given the concern for micro-metastatic disease in high-risk prostate cancer patients at diagnosis, an important consideration is to evaluate the potential benefit of integrating docetaxel with radiation in the management of such patients. A trial, RTOG 0521, has been reported in abstract-only form showing a disease-free and small (4% over 4 years) overall survival benefit among high risk prostate cancer patients undergoing ADT, RT and docetaxel therapy compared to ADT and RT alone.⁹

Originally described in 1965,¹⁰ Cesium-131 (Cs-131) as a prostate brachytherapy source has been thought to offer many theoretical advantages over the traditional Palladium-103 (Pd-103) and Iodine-125 (I-125) sources, including a shorter half-life (9.7 days) that may translate into a faster resolution of associated urinary side-effects as well as increased dose rate that could offer a theoretical radiobiological advantage.¹¹ At the time of trial conception, this was the isotope chosen for low-dose-rate prostate brachytherapy implantation.

The primary endpoint of this study is the efficacy as defined by 3-year DFS in localized high-risk prostate cancer patients treated with a combination of bone marrow sparing IMRT, long-term ADT, Cs-131 LDR brachytherapy boost, and adjuvant docetaxel chemotherapy at a single institution. We additionally evaluated acute and chronic rectal and urinary toxicity.

Methods and Materials:

After approval by our Institutional Review Board, patients were accrued and treated at the University of Maryland Medical Center between the years of 2006 to 2014. All patients were required to have histologically confirmed adenocarcinoma of the prostate within 180 days prior to enrollment and to meet one of the following high-risk criteria: Gleason score 8, PSA ≥ 20 (but < 150), clinical T3 disease, or at least 2 of the following: Gleason 7 score, PSA 15–20, or clinical T2c disease.

To ensure adequate candidacy for the brachytherapy portion of the study, eligible patients also had to meet the following criteria: no pubic arch interference; prostate size < 60 grams; IPSS score ≤ 15 and no documentation of urethral strictures; no significant prostate defect in patients with previous TURP; no T4 disease, no common iliac or para-aortic nodal involvement, no distant metastasis on MRI, CT or bone scans; no prior prostatectomy or pelvic radiation; initiation of hormonal therapy ≥ 90 days prior to enrollment; no previous or concurrent cancers other than superficial basal or squamous cell skin carcinoma unless disease free for at least five years; no previous chemotherapy > 5 years prior to enrollment; WBC $> 3000/\text{mm}^3$, absolute granulocyte count $> 1500/\text{mm}^3$, platelets $> 100,000/\text{mm}^3$, transaminases (AST and/or ALT) up to 2.5 x institutional upper limit of normal (ULN) if alkaline phosphatase was $< \text{ULN}$, or alkaline phosphatase up to 4 x ULN if transaminases are $< \text{ULN}$; no uncontrolled or severe cardiovascular disease including recent MI (< 6 mos), CHF, or angina pectoris; no current scleroderma or inflammatory bowel disease; no current or pre-existing peripheral neuropathy ($> \text{grade } 1$); no other serious medical or psychiatric illness; Karnofsky performance status ≥ 70 and life expectancy > 2 years; and patient age ≥ 18 years.

Before enrollment, patients underwent history and physical examination, including a digital rectal exam. To rule out metastatic disease, a computed tomography (CT) scan of the abdomen/pelvis and a bone scan were performed in all patients. Within 30 days prior to enrollment, comprehensive blood work, including PSA, CBC, chemistries, and liver function tests, were also obtained. Transrectal MRIs were performed at the discretion of the treating physician. Patients were enrolled only after multidisciplinary evaluation by a medical oncologist, urologist, and radiation oncologist.

Radiation Treatment

Patients were simulated supine with high resolution computed tomography imaging at 3 mm intervals extending from 2 cm superior to the level of the aortic-common iliac bifurcation (approximately L4 through the entire pelvis (below the lesser trochanter of the femur)). All patients were immobilized with a Vac-loc, alpha cradle or equivalent immobilization device. A pubic arch interference study was performed after the urethrogram simulation in lithotomy position. Bone marrow-sparing Intensity-Modulated Radiotherapy (IMRT) was used for all patients for the entire course of radiotherapy. Megavoltage (6 MV photons) equipment was used. Gross tumor volume (GTV) was defined as the prostate; clinical target volume (CTV) included the prostate, seminal vesicles and regional lymph nodes (including perirectal, internal iliac, external iliac, presacral down to S2/S3, and obturator) with superior border at L5/S1; planning target volumes (PTV) were up to physician preference with guidance of a range of 0.5–1.0 cm for prostate and seminal vesicles, and 1.0–1.5 cm around the regional lymph nodes with final block margin approximately 0.5 cm further to ensure 95% isodose line coverage of the PTV. Small bowel dose constraint was 1/3 volume < 40 Gy, and bone marrow mean dose < 15 Gy. Radiation was delivered via external beam to a total dose of 45 Gy in 1.8 Gy/fraction for a total of 25 treatments with daily image guidance at physician discretion (BAT ultrasound, electronic portal imaging detector or cone-beam CT). Following a 2–8 week break, patients proceeded to an 85 Gy Cs-131 brachytherapy boost. Dose volume histogram (DVH) constraints included: prostate V100 >90%, prostate D90 >100%, urethra V150 <50%. The treatment schema is shown in Table 1. Acute toxicity was scored according to the common terminology criteria for adverse events version 3.0 (CTCAE v3.0) and late toxicity was scored according to modifications from the radiation therapy oncology group (RTOG) and late effects normal tissue task force (LENT).^{12–14}

Androgen deprivation therapy and chemotherapy treatment:

Luteinizing hormonal releasing hormone (LHRH) agonists (i.e. leuprolide, goserelin, buserelin, triptorelin) were administered by subcutaneous injection for a total duration of 24 months starting on day 1 of EBRT (patients were eligible if started no longer than 60 days prior to EBRT). Anti-androgen therapy (e.g. flutamide, bicalutamide) was administered for 28 days starting concurrently with LHRH agonist administration.

Four to six weeks after brachytherapy completion, adjuvant docetaxel was administered at 75 mg/m² IV q21 days for 4 cycles along with prednisone 10 mg PO QD from day 1 of docetaxel administration until 21 days after final docetaxel infusion.

Endpoints and Statistical analysis

The primary end point was the disease-free survival (DFS) rate at 3.0 years. DFS in our trial was defined as time from registration to disease recurrence or death from any cause, whichever occurs first. Date of disease recurrence was determined using the Phoenix definition of PSA nadir + 2 ng/mL. Patients alive without a recurrence were censored at the date of last contact. Our target accrual was 40 patients, and as designed in the protocol, if a true disease-free survival rate at 3.0 years was found to be at least 74%, the protocol therapy would be considered effective in this patient population. If the true disease-free survival rate at 3.0 years was 50% or below, then the suggested treatment would not be considered

promising. We planned to follow all patients for at least 3 years. Under these assumptions, with 40 eligible patients, the study had minimum 90% power to detect a 24% improvement in the proportion of patients surviving and being disease-free at 3.0 years. The sample size calculations assumed exponential survival and a one-sided exact test at a significance level of 0.05.

Patients were seen every 3 months for the first 3 years after the completion of chemotherapy, then every 6 months. At each follow up visit, a history and physical and PSA value were obtained, and the toxicity was assessed by the physician and research coordinator. Furthermore, the patients completed a battery of toxicity questionnaires that included the International Index of Erectile Function (IIEF) and International Prostate Symptom Score (IPSS) at each visit. Bone and CT scans were obtained in follow-up if clinically indicated.

Results

Patient and tumor characteristics

From June 2006 to April 2014, 38 patients with high-risk localized prostate cancer were accrued to this Phase II study. The median follow-up for the entire and alive cohorts were 44 months and 58 months (range 3.4–118), respectively. A summary of all patient and treatment characteristics is shown in Table 2. Fifteen patients (39%) were categorized as very high risk based on either T3b-4 disease, a primary Gleason pattern of 5, or >4 cores of Gleason 8–10 disease. Six patients did not complete the study according to the pre-specified criteria: One patient withdrew consent, two patients refused chemotherapy and were removed due to noncompliance, one patient developed Stevens-Johnson like syndrome after cycle 1 of docetaxel and two patients received 3 of a planned 4 cycles of chemotherapy, for a total of 84.2% (32/38) completing all courses of chemotherapy per protocol. A total of 86.7% (33/38) patients completed a full two year course of androgen deprivation therapy.

Efficacy

At a median follow up of 44 months for the entire cohort, and 58 months for the surviving cohort, the three-year DFS was 74.1% (Figure 1), the 5-year freedom from PSA recurrence (bRFS) rate was 86% (Figure 2) and 5-year prostate-cancer specific survival (PCSS) was 92% (Figure 3) for our entire cohort. There were four biochemical failures noted among the entire cohort. Details of these failures are outlined in Table 3. Median time to PSA failure was 22 months (range 11–34). There were 8 total deaths, of which 4 were prostate cancer related (all preceded by an elevation in PSA failure) and 4 due to other causes.

Failure Patterns:

Five patients developed distant metastases, most commonly in the thoracic spine (n=4), lumbar spine (n=1), rib (n=1), liver (n=1), and pelvic lymph nodes (n=1). One patient was found to have metastatic disease from a lung cancer primary and did not have prostate recurrence at the time of lung cancer diagnosis. Treatment at the time of metastatic disease consisted of Lupron monotherapy (n=1), palliative radiation and enzalutamide (n=1), cabazitaxel and abiraterone (n=1), and one patient sought treatment at an outside facility (records unavailable at time of censoring).

Toxicity

During the course of treatment the most common acute toxicity was genitourinary (GU) followed by gastrointestinal (GI). Acute grade 2 GU and GI toxicities were 23.7% and 18.4%, respectively (Table 4). Chronic grade 2 GU and GI toxicities were 2.6% for both. One grade 4 GI complication occurred, with the patient developing a rectovesical fistula requiring creation of a colostomy for management of recurrent abscess. During chemotherapy, the most common toxicities were lymphopenia followed by afebrile neutropenia (Table 5). 23 patients (60.5%) developed grade 3 or 4 lymphopenia, and 13 (34.2%) patients developed grade 3 or 4 afebrile neutropenia. There were no grade 5 toxicities. All other toxicities are summarized in Table 5.

Discussion

In our phase II clinical trial of high-risk, localized prostate cancer patients treated with long-term ADT, 45 Gy whole pelvis EBRT, Cs-131 brachytherapy boost, and 4 cycles of docetaxel chemotherapy we noted both 3- and 5-year DFS of 74.1%, 5 year bRFS of 86%, and 5 year PCSS of 92%. These results are promising in high-risk prostate cancer patients, especially for those with predominantly very-high risk features as our trial had a significant amount of these patients (Table 1). While acute GU toxicities (23.7%) and GI toxicities (18.7%) were not uncommon during treatment, chronic GU and GI toxicities were quite low (2.6% for GI and 2.6% for GU, for a total rate of 5.2% late GI/GU complications), and longer term follow up will be needed for cumulative chronic toxicity numbers.

To minimize irradiated bone marrow in the setting of chemotherapy administration, given that approximately 25% of the bone marrow reserve is located within the pelvis, we additionally evaluated bone marrow-sparing IMRT in our cohort. This has been shown to decrease hematologic toxicity in the gynecologic literature.¹⁵ When comparing hematologic toxicity in this study to our prior study of ADT, EBRT (via 4-field box technique), brachytherapy boost and 3 cycles of adjuvant docetaxel,¹⁶ hematologic toxicity in the current trial appeared to be higher in terms of leukopenia (18.4% vs 2.4% grade 4) and neutropenia (13.2% vs 0% grade 4). This could in part be related to the 4 vs 3 cycles of docetaxel in our current study but also suggests no apparent benefit to bone marrow-sparing IMRT in this patient population.

Androgen deprivation therapy (ADT) has been studied in multiple trials in combination with radiation therapy in intermediate and high-risk prostate cancer patients,^{17–21} showing improvements not only in biochemical recurrence free survival (bRFS), local control (LC), distant metastases (DM) and cause-specific survival (CSS) but also overall survival. Further efforts to determine optimal duration of ADT evaluated 28–36 months of ADT relative to 4–6 months of ADT in prior studies; improved overall survival has been observed among patients receiving 2–3 years of ADT, particularly those with higher risk disease features.^{22,23} Importantly, all of these studies were performed prior to the current era of radiation dose escalation.

Multiple other studies have also evaluated the use of radiation dose escalation, which have shown improvements in biochemical progression-free survival, but not overall survival.^{24–28}

It is important to note that the majority of these studies were done without the addition of androgen deprivation therapy (ADT), with the notable exception of the MRC RT01 trial²⁵ which mandated neoadjuvant and concurrent ADT for a total of 3–6 months, and the Dutch trial²⁶ which allowed for ADT (only 22% of men actually received ADT on this trial, however). The MRC RT01 trial demonstrated an improvement in 10-year biochemical progression-free survival from 43% to 55% with the addition of ADT ($p=0.0003$) but no difference in overall survival. None of these trials utilized hormonal ablation, brachytherapy boost, chemotherapy, or pelvic IMRT. Our study is among the first to build on the collective experience of some of the earlier trials in high risk patients by attempting to integrate radiation dose escalation via brachytherapy boost, long term ADT and systemic chemotherapy in an effort to not only assess feasibility of such a multi-modal approach but also potentially improve outcomes in this challenging disease setting.

Brachytherapy allows for dose escalation while minimizing toxicity to nearby critical organs. A systematic review by the Prostate Cancer Results Study Group suggested that combination therapy including external beam radiation therapy (EBRT) and brachytherapy with or without ADT was superior to more localized treatments such as seed implant alone, surgery or EBRT²⁹. A randomized trial of patients with clinically localized T2–3N0M0 prostate adenocarcinoma who were staged with pelvic lymphadenectomy were randomized to 66 Gy EBRT alone or 35 Gy iridium implant followed by EBRT of 40 Gy in 20 fractions; this trial showed improved biochemical control in the brachytherapy dose-escalated arm.³⁰ Hoskin et al. showed similar findings in patients randomized to 55 Gy in 20 fractions EBRT vs 35.75 Gy in 13 fractions plus 2×8.5 Gy HDR brachytherapy given over 24 hours.³¹ A major criticism of these trials is that the EBRT dose was inadequate by modern standards. ASCENDE-RT addressed this by performing dose escalation to 78 Gy in the EBRT alone arm, compared to 46 Gy to the whole pelvis plus at least 115 Gy I-125 brachytherapy boost with 12 months of ADT;⁴ this trial showed bPFS of 89% at five years in the brachytherapy boost arm, similar to 86% bRFS rate at five years in our study but with higher toxicity (18.4% vs 0% and 6.3% vs 2.6% for chronic GU and GI toxicity, respectively).³²

Given concerns for micrometastatic disease in high risk patients, adjuvant docetaxel has been evaluated in a phase III trial of ADT with EBRT to a total dose of 72–75.6 Gy vs ADT with EBRT to a total dose of 72–75.6 Gy followed by 6 cycles of adjuvant docetaxel and prednisone (RTOG 0521).⁹ To date, the results of this study have been presented in abstract form only, and show 4 year OS rates of 89% for the ADT+EBRT arm compared to 93% for the ADT+EBRT+docetaxel arm (1 sided $p=0.03$). We anxiously await final publication of these results to see the magnitude of benefit with long-term follow up. Although our study is a limited pilot trial, the results among our cohort are in concordance with the RTOG 0521 study (5-year DFS of 73% with docetaxel in RTOG 0521 compared with 74.1% in our cohort). Similar to RTOG 0521, many of the patients in our study had Gleason 9–10 disease. Unfortunately, 2 possibly/probably related grade 5 AE's were reported in the RTOG trial. No grade 5 events occurred in our cohort, although the number of patients evaluated in the current trial is small, and the duration of follow up is shorter. This study, taken together with the ASCENDE-RT data, show that escalation of therapy, both locally and systemically, may lead to much needed improvements in this high-risk cohort. Whether 6 cycles of docetaxel rather than the 4 cycles used in the current study would further enhance treatment outcomes

and/or alter the safety profile is not clear. A larger randomized study will be required to more clearly establish the role of adjuvant docetaxel chemotherapy in the context of brachytherapy boost and ADT to define the role of such a multi-modality approach in patients with high risk prostate cancer. Given the positive results of the ASCENDE-RT trial with respect to brachytherapy boost and the RTOG 0521 trial with respect to chemotherapy, our study potentially provides a framework to further build upon these trials where brachytherapy boost, ADT and chemotherapy could be integrated as a next step to evaluate in a randomized setting in high risk prostate cancer.

This study does have some weaknesses. First, this study was designed in 2006 and best bNED estimates were used based on the available data at that point in time, and may not be the best trial design in the present day. We do acknowledge that the ASCENDE-RT trial was presented in 2015 after our trial design was completed. However, based on the benefit of LDR brachytherapy boost in that setting, we feel that the overall design of our trial is still very progressive and relevant in the management of high-risk prostate cancer today. Additionally, direct comparison between the ASCENDE-RT trial and our trial are not possible because of the differences in duration of ADT (12 mo in ASCENDE-RT vs. 24 mo in our study), as well as the shorter-term follow up in our study. More than 75% of our patient had Gleason 8–10 disease, while 40% of those enrolled in ASCENDE-RT had the same Gleason score, which makes our results relevant and hypothesis generating.

Conclusion

Our study demonstrates the efficacy and tolerability of a treatment strategy integrating long-term androgen deprivation therapy, EBRT, brachytherapy boost, and 4 cycles of adjuvant docetaxel chemotherapy achieves a high level of disease control with relatively short follow up and with acceptable acute and low chronic toxicity side effects among high-risk, localized prostate cancer patients. We await the full results of the RTOG 0521 trial, but this phase II trial taken together with ASCENDE-RT and the preliminary results of RTOG 0521, warrant aggressive therapy in appropriately selected high risk prostate cancer patients. Longer-term follow up is planned to assess further biochemical control and chronic toxicity.

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Figure 1:
Kaplan Meier: 3-year Disease Free Survival (DFS)

Figure 2:
Kaplan-Meier: 5 year Freedom from PSA Failure

Figure 3:
Kaplan-Meier: 5 year Overall Survival (OS)

Table 1.

Treatment schema

Day 1	Day 1	2–8 weeks after EBRT	4–6 weeks after Brachy
LHRH [*] + Anti-androgen ^{**} →	EBRT [∇] →	Cesium-131 Brachy [#] →	Adjuvant chemotherapy ◀

^{*} LHRH (luteinizing hormone-releasing hormone) agonist (e.g., goserelin, leuprolide, etc) given for 24 months total starting Day#1 of EBRT (patients are eligible if LHRH was started within 60 days prior to EBRT).

^{**} Anti-androgen (e.g., flutamide, bicalutamide, etc) will be given for the first 28 days at the start of LHRH agonist (patients are eligible if anti-androgen was started within 90 days prior to EBRT).

[∇] EBRT (External Beam Radiation Therapy) delivered at 1.8 Gy daily fractions, 5 days/week, for a total of 45 Gy to the pelvis. Bone marrow-sparing pelvic Intensity-Modulated Radiation Therapy (IMRT) technique is mandatory for the entire course of EBRT.

[#] Brachy (Brachytherapy): Brachytherapy boost with Cesium-131 sources to a dose of 85 Gy.

◀ Adjuvant docetaxel will be administered at 75mg/m² IV Q 21 days (plus or minus 2 to 3 days) for 4 cycles along with prednisone 10mg PO QD (from Day#1 of adjuvant docetaxel until 21 days after last docetaxel cycle infusion)

Table 2.**Patient and Tumor Characteristics (N=38)**

Characteristic		N (%)
Median age at diagnosis (range)		64 y (range 45–82)
Follow up		
	Entire Cohort	44 mo (range 3.4–118)
	Alive	58 mo (range 3.4–118)
Median Baseline IPSS		7 (range 0–20)
Median Follow Up IPSS *		9 (range 0–21)
Stage (AJCC 6 th Edition)		
	T1c	17 (44.7)
	T2a	8 (21.1)
	T2b	4 (10.5)
	T2c	8 (21.1)
	T3	1 (2.6)
Gleason Score		
	3+4=7	2 (5.3)
	4+3=7	7 (18.4)
	8	11 (28.9)
	4+5=9	10 (26.3)
	5+4=9	4 (10.5)
	10	4 (10.5)
Pre-treatment PSA		
	<10 ng/mL	18 (47.4)
	10–20 ng/mL	6 (15.8)
	>20 ng/mL	14 (36.8)
Risk grouping [#]		
	High risk	23 (60.5)
	Very high risk	15 (39.5)

* Follow up > 1 year,

[#]: high risk grouping based upon T3a disease OR Gleason score 8 or Gleason score 4+5=9 OR PSA>20 ng/mL. Very high risk grouping defined as T3b-4 disease OR primary Gleason pattern 5 OR >4 cores with Gleason score 8–10.

Table 3:

Characteristics Associated with Biochemical Failure

Patient Age	Gleason Score	Pre-Tx PSA	Clinical Stage	Completed RT?	Completed chemotherapy?	Specific Locations of metastases (if known)	Time to failure (mo)
48	4+5=9	96	T2c	Yes	Yes	None	30
62	5+5=10	15	T2c	Yes	Yes	T4, iliac LN	32
64	4+4=8	6	T2a	Yes	Yes	T9 and L5, 9 th rib	9
69	4+5=9	31.9	T1c	Yes	No	Thoracic Spine	15

Table 4.

Patients with Grade 2 acute and chronic GI and GU toxicities

Toxicity grade					
Group	2	3	4	5	
GI complications					
Acute	7	0	0	0	
Late	0	0	1	0	
GU complications					
Acute	7	1	1	0	
Late	1	0	0	0	

Acute toxicities are measured by Common Terminology Criteria for Adverse Events (CTCAE v3.0), chronic toxicities were assessed with the RTOG/EORTC Late Radiation Morbidity Scoring Schema; chronic toxicities were reported as cumulative events, and a given patient may have had more than one event.

Abbreviations: GI = gastrointestinal; GU = genitourinary

Table 5.**Worst Acute Treatment Related Toxicity ***

Toxicity		2	3	4	5
Dermatologic					
	Radiation Dermatitis	0	0	0	0
	Hyperpigmentation	0	0	0	0
	Induration/Fibrosis	0	0	0	0
GI					
	Diarrhea	2	0	0	0
	Rectal Bleeding	2	0	0	0
	Incontinence	0	0	0	0
GU					
	Urgency/frequency	9	3	0	0
	Hematuria	1	0	0	0
	Erectile impotence	10	3	1	0
	Ejaculatory dysfunction	7	1	1	0
	Libido	9	0	0	0
Chemotherapy related					
	Febrile neutropenia (ANC<1.0)	0	0	0	0
	Afebrile neutropenia (ANC<1.0)	7	8	5	0
	Lymphopenia	12	16	7	0
	Anemia	9	0	0	0
	Thrombocytopenia	0	0	0	0
Other					
	Fatigue	6	0	0	0
	Pain	1	0	0	0
	Hot flashes	10	1	0	0
	Dehydration	1	0	0	0
	Toxicity NOS	0	0	0	0

* Complications are listed by worst grade experienced by a given patient according to CTCAEv3

Abbreviations: GI = gastrointestinal; GU = genitourinary; ANC = Absolute neutrophil count; NOS= not otherwise specified