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A Prospective Phase II Trial of Trans-perineal Ultrasound-Guided Brachytherapy for Locally Recurrent Prostate Cancer after External Beam Radiotherapy (NRG Oncology/RTOG -0526)

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Abstract

Purpose: Only retrospective data is available for low dose rate (LDR) salvage prostate brachytherapy for local recurrence after external beam radiotherapy (EBRT). The primary objective of this prospective Phase II trial (NCT00450411) was to evaluate late gastrointestinal and genitourinary adverse events (AEs) after salvage LDR brachytherapy.

Materials/Methods: Eligible patients had low/intermediate risk prostate cancer prior to EBRT and biopsy-proven recurrence >30 months after EBRT, with PSA <10 ng/mL and no regional/distant disease. The primary endpoint was grade 3 or higher late treatment-related GI/GU AEs occurring 9-24 months after brachytherapy. These were projected to be ≤10%, with ≥20% considered unacceptable. All events were graded with CTCAE V3.0. Multivariate analyses investigated associations of pre-treatment or treatment variables with AEs.

Results: From May 2007 to January 2014, 100 patients were registered from 20 centers. 92 analyzable patients had a median follow-up of 54 months (range: 4-97) and median age 70 (IQR: 65-74). Initial Gleason score was 7 in 48%. Median dose of EBRT was 74 Gy (IQR: 70-76) at a median interval of 85 months previously (IQR: 60-119). Only 16% had androgen deprivation at study entry. Twelve patients (14%) had late grade 3 GI/GU AEs with no treatment-related grade 4 or 5 AEs. No pre-treatment variable predicted late AEs, including prior EBRT dose and elapsed interval. Higher V100 (% of prostate enclosed by prescription isodose) predicted both occurrence of late AEs (OR=1.24; 95% CI: 1.02-1.52; p=0.03) and earlier time to first occurrence (HR=1.18; 95% CI: 1.03-1.34; p=0.02).

Conclusions: This prospective multicenter trial reports outcomes of salvage LDR brachytherapy for post EBRT recurrence. The rate of late grade 3 AEs did not exceed the unacceptable threshold. The only factor predictive of late AEs was implant dosimetry reflected by V100. Efficacy outcomes will be reported at a minimum of 5-yr follow-up.

Summary

We report the primary endpoint of the phase 2 NRG/RTOG 0526 trial of salvage low dose rate prostate brachytherapy for locally recurrent prostate cancer following prior external beam radiotherapy (EBRT). Eligible patients initially presented with favorable or intermediate risk prostate cancer. At a median follow up of 54 months, 12 of 92 analyzable patients (14%) had late grade 3 gastrointestinal or genitourinary adverse events, which did not exceed the previously set threshold for unacceptable toxicity.

Keywords

Prostate cancer; Salvage low dose rate brachytherapy; external beam radiotherapy failure

Introduction

External beam radiotherapy (EBRT) is the most frequently used non-surgical option for primary management of localized prostate cancer. It is widely available throughout the developed world, and has the advantage of being non-invasive and safe. However, even with

modern dose escalation, and conformal techniques, biochemical failure occurs in up to 15% of low or intermediate risk disease within 5 years, and by 10 years in 20-50%(1-8). Correlation of multi-parametric magnetic resonance imaging (MRI) and salvage prostatectomy pathology has demonstrated that failures most commonly occur at the site of the original dominant intraprostatic lesion and many patients may initially have an isolated local recurrence(9). Despite numerous options for local salvage, fewer than 5% of patients are offered potentially curative second-line treatment, with the majority being observed or managed with palliative androgen deprivation therapy (ADT)(10). Although this may be appropriate due to advanced age, comorbidities or concerns about toxicity, a significant proportion of these patients could benefit from curative treatment, especially since locally persistent tumor serves as a source of subsequent distant dissemination(11). Furthermore, long-term ADT is associated with specific morbidity and perhaps even mortality(12).

As single center reports demonstrated efficacy of salvage LDR brachytherapy, the Radiation Therapy Oncology Group (RTOG) undertook a prospective Phase II trial in 2005 to investigate late toxicity(13,14). The trial was supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), and from the National Cancer Institute. The Clinicaltrials.gov registry number is NCT00450411. We report the primary endpoint: treatment-related, grade 3 or higher, late gastrointestinal (GI) or genitourinary (GU) adverse events (AEs).

Materials and methods

Patient Eligibility

Eligible patients had low or intermediate risk prostate cancer prior to EBRT, and biopsy-proven local recurrence at an interval >30 months after EBRT, administered in doses up to 78 Gy/39 fractions or 81 Gy/45 fractions. At study entry, prostate-specific antigen (PSA) was <10 ng/mL and systemic staging with Tc99 bone scan and abdominal/pelvic computed tomography (CT) showed no regional or distant disease. Post EBRT prostate biopsies were required within 180 days of trial entry and were centrally reviewed prior to registration (MA). Prostate volume from transrectal ultrasound (TRUS) was ≤45 cc and International Prostate Symptom Score (IPSS) was ≤15. Eligible patients could not have residual EBRT-related grade ≥2 GI or GU toxicity.

Brachytherapy

All participating centers were credentialed in prostate LDR brachytherapy by the RTOG. Implants were planned and executed under TRUS visualization using transperineal template-guidance with either I-125 (prescribed minimum target dose 140 Gy), or Pd-103 (dose 120 Gy). Preplan dosimetric parameters were specified to avoid regions of high dose inhomogeneity; for I-125 V150 <45% and V200 <10% and for Pd-103 V150 <55% and V200 <15%. No dosimetric parameters were specified for the urethra or rectum. It was felt that the conservative V150 would keep the urethral dose within acceptable limits, and the rectal dose cannot be predicted from the preplan. Partial prostate implants to the biopsy-proven site of recurrence identified with metabolic imaging were allowed.

Post implant dosimetry was assessed by CT scan 30 days after implant. The Evaluation Target Volume (ETV) was the CT-contoured prostate with no margin. Calculated dosimetric parameters included V100 (percentage of prostate receiving minimum of 100% of prescription dose; a measure of implant quality) and similarly, V150 and V200 (measures of implant homogeneity). In addition, the isodose enclosing 90% of the prostate volume (D90) was reported to indicate the magnitude of delivered dose. The ETV for partial prostate implants was the whole prostate, but the V100 was required to be > 60%.

Endpoints

The primary objective for this single-arm phase II trial was to evaluate late treatment-related GI and GU AEs after salvage LDR brachytherapy for local recurrence following EBRT. Late AEs, with an attribution of definitely, probably, or possibly related to treatment, were evaluated between 9 and 24 months from implant, using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Statistics

Late grade ≥3 treatment-related GI/GU AEs were projected to occur in ≤10% of patients under protocol treatment (alternative hypothesis) while ≥20% would be considered unacceptable (null hypothesis). To detect this effect size with a one-sided significance level of 0.05 and 85% statistical power, 87 analyzable patients were required based on Fleming's multiple testing procedure with two interim analyses and one final analysis(15). Adjusting by 10% for ineligibility or lost to follow-up, 96 patients were required for accrual.

Analyzable patients received protocol treatment and had at least 23 months follow-up from implant. Patients experiencing an AE of interest during the specified time frame but without 23 months follow-up were included, but those lost to follow-up or deceased before 23 months without experiencing an AE of interest were not analyzable for the primary endpoint. For the final analysis, the null hypothesis would be rejected if the number of late grade ≥3 treatment- related GI/GU AEs was ≤10, and the treatment would be deemed tolerable.

Multivariate analyses were performed to investigate the effect of pretreatment characteristics, such as T-stage, PSA, Gleason, and age, as well as treatment delivery parameters. Multivariate logistic regression was used to analyze the occurrence of late grade ≥3 treatment-related GI/GU AEs. Time to the first occurrence since implantation was analyzed using Gray's method. Death without experiencing an AE of interest was treated as the competing risk. The Fine-Gray method was used to model the time to first occurrence with pretreatment characteristics and treatment delivery parameters as covariates.

Secondary endpoints included early treatment-related GI/GU AEs, clinical outcomes (overall, disease-free, and disease-specific survival; local, distant and biochemical failure), and the post-brachytherapy dosimetric parameters. The analysis of clinical outcomes is planned when a minimum of 5-year follow-up is reached.

Early AEs were defined as occurring ≤ 9 months from implantation. Patients experiencing a grade ≥3 treatment-related AE during this time frame but without required follow-up were

included in the analysis, but those lost to follow-up or deceased before 9 months without experiencing an AE of interest were not analyzable. Similar to the primary endpoint analysis, the occurrence of early grade ≥3 treatment-related GI/GU AEs and time to first occurrence were analyzed using logistic regression and the competing risk approach, respectively. Descriptive statistics for each dosimetric parameter were calculated.

Results

From May 2007 to January 2014, 100 patients were registered from 20 centers. Eight patients were excluded (Table 1). Table 2 shows the distributions of pretreatment characteristics for the 92 eligible patients. Median age was 70 years; 48% had Gleason score 7 (52% 2-6), and 84% had PSA ≤10 ng/mL at initial diagnosis. Recurrent disease was not palpable in 74% and < half of one lobe in 16%.

Treatment Delivery

Brachytherapy was delivered using I-125 for 85 patients (92%), with 7 implanted using Pd-103 (Table 2). Reviews of ETV and organs at risk were either per protocol or with acceptable variation for 90% of reviewed patients. Submitted post plans show the median prostate volume was 29cc (Interquartile range (IQR): 24-37cc). The median minimum dose covering 90% of the ETV (D90) was 109% (IQR: 101-116%).

Test for the Primary Endpoint

All AEs were graded with CTCAE version 3.0. At a median follow-up of 54 months, 87 of 92 eligible patients (95%) were evaluable for the primary endpoint. Twelve of these 87 (14%; 95% CI: 6%-21%) experienced late grade 3 treatment-related GI/GU AEs (Table 3), with no grade 4 or 5 reported. Table 4 shows results from multivariate analysis using logistic regression on the occurrence of late grade ≥3 treatment-related GI/GU AEs. None of the pretreatment characteristics had a significant effect, including prostate size, dose of prior EBRT (median=74 Gy; IQR: 70-76 Gy) and interval from EBRT to salvage (median=85 months; IQR: 60-119). There was a considerable range reported in dosimetric parameters, the lowest values being due to the 2 partial prostate implants (Table 2). The median ETV percentage covered by 100% of the prescribed dose (V100) was 94% (IQR: 91-96%). Median V150 was 50% (IQR: 43-59). Median D90 was 109% (IQR: 101-116). Only V100 as a continuous variable was predictive of late treatment-related GI/GU AEs with an odds ratio (OR) of 1.24 (95% CI: 1.02-1.52; p=0.03 in favor of lower percentages). Table 5 shows the multivariate analyses of time to first occurrence since implantation of late grade ≥3 treatment-related GI/GU AEs. V100 is again significant, with a hazard ratio (HR) of 1.18 (95% CI: 1.03-1.34; p=0.02).

Separate logistic regression modeling was performed for the association of V150 and V200 (percentage of prostate volume covered by 150% and 200% of prescription) as continuous variables with the occurrence of late AEs, and Fine-Gray modeling for time to first occurrence, but neither of these dosimetric parameters was associated with late AEs. D90 was examined as both a continuous variable and dichotomized at the median. Although not

statistically significant, there were 4 AEs below the median D90 (109%) and 8 AEs above the median with an OR=3.23 (95% CI: 0.78-13.40; p=0.11).

Results for Secondary Endpoints

Immediate post-implant urinary catheterization occurred in 4% (2/85 I-125; 2/7 Pd-103). Twelve of 88 patients (14%; 95% CI: 6-21%) experienced early grade 3 treatment-related GI/GU AEs, with no grade 4 or 5 reported. Six of these 12 subsequently developed late grade 3 treatment-related GI/GU AEs. Table 6 lists these AEs with information on the grade, attribution to protocol treatment and weeks from implantation. Multivariate analysis showed that PSA at initial diagnosis was predictive of both the occurrence of early grade ≥3 treatment-related GI/GU AE's (p=0.04) and time to first occurrence (p=0.02).The interval since prior EBRT showed a trend to significance for occurrence (p=0.08), and the dose of EBRT a trend for time to first occurrence of early AEs (p=0.06).

Discussion

Local recurrence is not uncommon after EBRT, depending on radiation dose, technique, initial stage and Gleason score, and on investigations at the time of biochemical failure(1,16). Nichol et al reported on a prospective study of 140 patients with non-high risk prostate cancer treated with 3D conformal radiation and daily fiducial image-guidance. Three-year post EBRT biopsies were positive in 51% and 5-year biochemical failure free survival (BFFS) was 55%(1). Dose escalation to 78-80 Gy is associated with encouraging 5-year BFFS of 78-84%(4,8) but with steady attrition between 5 and 10 years(3,5,8). Over 2 decades ago, Fuks et al showed that uncontrolled local disease was associated with 24% 15-year freedom from metastases compared to 77% for patients with local control(17). The fact that dose escalation studies show a dose response relationship, at least in terms of biochemical failure, indicates that many biochemical failures are at least initially of local origin(2,4,18-20). Imaging studies and salvage RP results show that failure is usually at the site of the dominant intraprostatic lesion(9,21). As an optimal dose of EBRT has yet to be achieved(22), it is likely that few local recurrences are completely radioresistant. In selecting the optimal form of re-irradiation, brachytherapy has the important advantage of being a tightly conformal internal application with rapid dose fall-off to maximally spare adjacent organs already exposed to EBRT.

Despite the fact that uncontrolled local tumor is a source for subsequent dissemination and prostate cancer specific mortality, fewer than 5% of biochemical failures after EBRT receive local salvage(10). There are a number of factors contributing to this low utilization, including advancing patient age, co-morbidities that shorten life expectancy and obviate the need for intervention, and fear of toxicity in a patient who is otherwise asymptomatic. Thus, the most common approach is palliative ADT, which is not without significant impact on quality of life with a myriad of systemic side effects including weight gain, adiposity, anemia, changes in lipid profiles, loss of muscle mass, decreased bone density, altered glucose metabolism, depression, and possible cognitive decline and increased risk of cardiac events(12). For these reasons, delayed hormonal intervention(23) or an intermittent approach have been explored(24). However, the median duration of hormonal sensitivity is about 3

years(25) with ultimate progression to castrate resistance (CRPC). With the advent of effective chemotherapy and newer hormonally-based agents, life with CRPC can be prolonged but at great cost to the health care system. These end-of-life palliative drugs cost upward of $500,000 per patient in the USA(26) and $150,000 per patient in Canada(27).

Prior studies on salvage LDR brachytherapy have been limited by retrospective reporting and non-uniform selection criteria and dose prescription. Nonetheless, for selected patients reported BFFS is 84% at 3 years(28), 70% at 5 years(29,30) and 50% by 10 years(31). RTOG set out to investigate the safety of this salvage option in uniformly selected patients who had minimal morbidity after previous EBRT, a curable presentation at diagnosis, and biopsy proven recurrence ≥30 months after EBRT.

Selection for efficacy

The goal of selection is to choose patients for radical salvage who are most likely to benefit, while minimizing the risk of severe toxicity. The first requirement is to have biopsy proven recurrence at least 30 months after EBRT. Crook et al showed that histologic resolution can take up to 30 months, with earlier biopsies often showing indeterminant remnants of prostate cancer of uncertain viability(32). Such pathology can be difficult to interpret and should be reviewed cautiously. In addition, biochemical failure before 30 months is often associated with co-existing metastatic disease and such patients will not benefit from aggressive salvage(33,34). Additional indicators of co-existing systemic disease are the PSA at salvage, which should be ≤10 ng/mL (as per RTOG 0526) or preferably ≤6 ng/mL(30). Although PSA doubling time was not a criterion in this trial, a doubling time ≤6 months is indicative of higher likelihood of co-existing metastases(35-37).

Risk group at initial presentation is also an important consideration. As initial favorable or intermediate risk disease is potentially more curable, high-risk patients were excluded from RTOG 0526. However, recent studies indicate that as few as 10% of high-risk patients have co-existent metastases(8,38,39). Thus, if all other criteria are favorable, including the interval since EBRT and the PSA doubling time, salvage for these patients is not unreasonable. Rose et al reported on salvage LDR brachytherapy for 18 patients, 9 of whom were initially high-risk and 2 of whom had CRPC at salvage. Five of these 9 were free of biochemical failure at 3 years (40).

All patients considered for local salvage should have negative traditional systemic staging including a Tc99 bone scan and abdominal/pelvic CT, although these have limited sensitivity at PSA <10 ng/ml. The utility of PSMA Ga68 PET scanning or other more sensitive PET-based scanning has not been reported in this population but will play a prominent role in the future. Scan positivity is seen in 50-60% of cases with PSA 0.5 ng/ml(41) and up to 90% for PSA 2-3 ng/mL(42,43). The higher sensitivity for detecting extra-prostatic disease at these PSA levels compared to the traditional testing will benefit patient selection.

Selection for minimizing toxicity

Complication rates following salvage brachytherapy vary widely in the literature due to many contributing factors. In early reports from the 1990’s a uniform loading seed pattern resulted in substantial dose heterogeneity, with higher urethral doses than peripherally. This

may have contributed to incontinence in 24% and the need for transurethral resection in 15% (13,14).

Patients with persistent late GI/GU EBRT grade ≥2 AEs should not be considered for further salvage radiation. RTOG 0526 also placed a prostate size constraint of 45cc and IPSS ≤15.

The interval since prior EBRT is also important; Nguyen et al reported a strong association between toxicity and early salvage in a prospective study of 25 men. Grade 3 or 4 GI/GU AEs occurred in 30% at 4 years (HR=12; p=0.02)(30) and recto-prostatic fistulae in 13% (HR=25; p=0.04), associated with salvage at an interval <4.5 years. RTOG 0526 required a minimum interval of 3 years for more reliable biopsy interpretation and to reduce inclusion of early biochemical failures due to systemic disease. The median interval was actually 7 years (IQR: 5-10), sufficiently long to minimize time-sensitive cumulative toxicity. Nonetheless, even with this conservative timing, *early* grade 3 AEs were still less frequent with longer intervals since EBRT (p=0.08).

This study did not identify prior EBRT dose as a factor influencing the incidence of late grade ≥3 treatment-related GI/GU AEs. In the study population the median dose was 74 Gy with an IQR of 70-76 Gy, although doses up to 78 Gy/39 or 81 Gy/45 were accepted. Again, *early* AEs showed a trend to increase with higher prior dose (p=0.06). There is no experience with salvage brachytherapy after hypofractionated regimens.

The delivered dose to the ETV is important. Pre-implant guidelines were designed to minimize dose heterogeneity, with V150 <45% for I-125 and <55% for Pd-103. All participating investigators were credentialed for prostate brachytherapy. Although, as expected in LDR brachytherapy, the delivered dose showed considerable range, the IQRs for each dosimetric parameter were quite narrow, showing adherence to the prescription guidelines. This contrasts with Moman et al where a median V150 of 74% and D90 of 196 Gy resulted in 26% grade 3 GI/GU AEs(44).

In the dosimetric analysis, the only factor associated with late grade 3 GI/GU AEs was V100, which was associated with both the incidence (OR=1.24; p=0.03) and time to first occurrence (HR=1.18; p=0.02). However, V100 is constrained at 100% and therefore cannot determine which implants with excellent coverage may be “too hot” for a salvage scenario. The median V100 was 94% and the IQR 90-96%. In the range of V100 values >90%, the prostate region that is most often lacking complete coverage is the anterior base. Thus, implants that fail to cover 5-10% of the prostate generally are deficient in this area. As all but one of the 12 late AEs was urinary, V100 may be a surrogate for bladder neck dose, suggesting that avoidance of full dose in this region in a salvage setting may be desirable.

D90 has no upper limit and can differentiate the range of delivered dose in those implants with near complete coverage. However, D90 analyzed both as a continuous variable and dichotomized at the median, was not predictive of late GI/GU AEs. There were twice as many AEs above the median as below, but this was not statistically significant and it appears that absolute dose is less important than where the dose is delivered. In contrast, Rose et al found the median D90 for those with grade 3 to 4 toxicity was 155 Gy compared to 132 Gy (p=0.03) for those without(40).

In the analysis of early GI/GU AEs, baseline PSA (at initial diagnosis) was significantly associated with both occurrence of early AEs (p=0.04) and time to occurrence (p=0.02). Although this association was observed, we do not know if this is spurious or a surrogate for some unmeasured variable. Perhaps future studies in this area will also assess this relationship. It is of interest to note that higher baseline PSA has been a factor in predicting post EBRT impotence(45).

Conclusions:

LDR brachytherapy delivered at the investigated dose level has acceptable tolerance for patients with local tumor recurrence following EBRT for clinically localized prostate cancer. Although the 14% grade 3 or higher late treatment-related GI/GU AEs was greater than the 10% threshold to reject the null hypothesis, it is well below the 20% limit set as intolerable. Furthermore, there was no grade 4 or 5 late toxicity observed. Provided that subsequent analysis of efficacy, scheduled for 2019, is compatible with the published literature for similarly selected patients, the role for salvage LDR brachytherapy will be more secure. Given the association of late grade 3 GI/GU AEs with V100, sparing of the anterior prostate base should be considered when possible. Advanced imaging to identify the site of recurrence followed by a partial prostate focal salvage implant can be considered as a future means of reducing toxicity.

Clinical outcomes will be evaluated when all patients have a minimum of 5 years' follow-up.

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Table 1:

Reasons for exclusion

Reason	n (%)
PSA not within protocol criteria	3 (37.5%)
No protocol treatment	2 (25.0%)
No recurrent tumor in specimen submitted for central review	1 (12.5%)
Recurrence diagnosed <30 months post RT	1 (12.5%)
Treated prior to pathology eligibility results	1 (12.5%)

Table 2:

Patient, prior treatment and implant dosimetry characteristics

Characteristic	Median	Range	IQR
Prostate volume cc	26	14-44	22-31
Months from EBRT to BT	85	39-199	60-119
Dose EBRT (Gy)	74	45-81	70-76
Age	70	55-82	66-74
PSA @ study entry (ng/ml)	4.1	0.4-9.7	2.8-5.7
ADT at recurrence	No: 84%	Continuing: 5%	Prior: 11%
Seed activity I125 (n=85) (U)	0.43	0.33-0.51	0.42-0.46
Seed activity Pd103 (n=7) (U)	2.07	1.81-2.47	1.86-2.22
V100	94%	62-100%	91-96%
V150	50%	18-90%	43-59%
V200	21%	5-69%	17-28%
D90	109%	46-149%	101-116%

Table 3:

Nature and timing of Late Grade 3 or higher Treatment-related GI/GU AEs (9-24 months or 38-104 weeks)

Type	# of Patients	Attribution	Grade	Time since Implant (weeks)
Frequency/incontinence	1	Probably	3	68/68
Fistula	1	Probably	3	63
Cystitis	1	Possibly	3	45
Retention	2	Definitely	3	52, 70
Frequency/incontinence/retention	1	Definitely	3	57/57/61
Frequency	1	Definitely	3	45
Cystitis/obstruction/incontinence	1	Definitely	3	78/61/78
Incontinence	1	Definitely	3	57
Frequency/retention/obstruction	1	Definitely	3	45/45/103
Cystitis/retention	1	Possibly/definitely	3	39/39
Proctitis	1	Probably	3	84

Table 4:

Multivariate Analysis using Logistic Regression Modelling the Occurrence of Late Grade 3 or Higher Treatment-related GI/GU AEs

Parameter	Comparison	Group 1 AE/Total	Group 2 AE/Total	OR (95% CI)	p-value
T-Stage	T1 (RL) vs. T2	4 / 42	8 / 45	1.79 (0.40, 8.03)	0.45
Gleason	3-6 (RL) vs. 7	5 / 46	7 / 41	1.20 (0.27, 5.38)	0.82
Zubrod	0 (RL) vs. 1	10 / 80	2 / 7	1.70 (0.17, 16.7)	0.65
Age	Continuous	-	-	0.94 (0.84, 1.06)	0.30
Baseline PSA	Continuous	-	-	0.90 (0.73, 1.11)	0.31
V100	Continuous	-	-	1.24 (1.02, 1.52)	0.03
Time from EBRT to BT (mos)	Continuous			0.98 (0.96, 1.01)	0.18
EBRT dose (Gy)	Continuous	-	-	1.06 (0.92, 1.21)	0.43

RL = Reference Level; OR = Odds Ratio; CI = Confidence Interval

Table 5:

Fine-Gray Model of Time to the First Occurrence of Protocol-Specified Late Treatment-related GI/GU AE
All Patients Observed at Least 9 Months Post-Implant

Parameter	Comparison	Group 1 AE/Total	Group 2 AE/T4tal	HR (95% CI)	p-value
T-Stage	T1 (RL) vs.T2	4 / 42	8 / 45	1.40 (0.29, 6.74)	0.68
Gleason	3–6 (RL) vs.7	5 / 46	7 / 40	1.23 (0.26, 5.91)	0.79
Zubrod	0 (RL) vs. 1	10 / 80	2 / 6	1.92 (0.49, 7.47)	0.35
Age	Continuous	-	-	0.95 (0.85, 1.07)	0.40
Baseline PSA	Continuous	-	-	0.93 (0.85, 1.03)	0.17
V100	Continuous	-	-	1.18 (1.03, 1.34)	0.02
Time from EBRT to BT (mos)	Continuous			0.99 (0.96, 1.01)	0.17
EBRT dose (Gy)	Continuous	-	-	1.04 (0.96, 1.12)	0.34
TRUS volume(cc)	Continuous	-	-	0.95 (0.86,1.04)	0.25

RL = Reference Level; HR = Hazard Ratio; CI = Confidence Interval

Table 6:

Early Grade 3 or higher Treatment-related GI/GU AEs occurring 9 months (39 weeks) or less from treatment.

Type	# of Patients	Attribution	Grade	Time since Implant (weeks)
Rectal bleed	1	Definitely	3	32
Rectal pain	2	Possibly	3	26, 17
Retention	2	Definitely	3	7, 6
Frequency	3	Possibly, definitely, probably	3	4, 11, 14
Frequency/retention	1	Definitely	3	8/8
Urethral stricture	1	Probably	3	36
Frequency/retention/obstruction	1	Definitely	3	1/1/1
Incontinence	1	Probably	3	30