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Long-Term Results of NRG Oncology/Radiation Therapy Oncology Group 0321: A Phase 2 Trial of Combined High-Dose-Rate Brachytherapy and External Beam Radiation Therapy for Adenocarcinoma of the Prostate

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Abstract

Purpose: To report the long-term outcome of patients with prostate cancer treated with external beam radiation therapy and prostate high-dose-rate brachytherapy from a prospective multi-institutional trial conducted by NRG Oncology/RTOG.

Methods and Materials: Patients with clinically localized (T1c-T3b) prostate cancer without prior history of transurethral resection of prostate or hip prosthesis were eligible for this study. All patients were treated with a combination of 45 Gy in 25 fractions from external beam radiation

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therapy and one high-dose-rate implant delivering 19 Gy in 2 fractions. Adverse events (AE) were collected using Common Toxicity Criteria for Adverse Events, version 3. Cumulative incidence was used to estimate time to severe late gastrointestinal (GI)/genitourinary (GU) toxicity, biochemical failure, disease-specific mortality, local failure, and distant failure. Overall survival was estimated using the Kaplan-Meier method.

Results: One hundred and twenty-nine patients were enrolled from July 2004 to May 2006. AE data was available for 115 patients. All patients were National Comprehensive Cancer Network intermediate to very high risk. The median age was 68, T1c-T2c 91%, T3a-T3b 9%, prostate-specific antigen (PSA) ≤10 (70%), PSA >10 to ≤20 (30%), GS 6 (10%), GS 7 (72%), and GS 8 to 10 (18%). Forty-three percent of patients received hormonal therapy. At a median follow-up time of 10 years, there were 6 (5%) patients with grade 3 GI and GU treatment-related AEs, and no late grade 4 to 5 GI and GU AEs. At 5 and 10 years, the rate of late grade 3 gastrointestinal and genitourinary AEs was 4% and 5%, respectively. Five- and 10-year overall survival rates were 95% and 76%. Biochemical failure rates per Phoenix definition at 5 and 10 years were 14% and 23%. The 10-year rate of disease-specific mortality was 6%. At 5 and 10 years, the rates of distant failure were 4% and 8%, respectively. The rates of local failure at 5 and 10 years were 2% at both time points.

Conclusions: Combined modality treatment using high-dose-rate prostate brachytherapy leads to excellent long-term clinical outcomes.

Introduction

Numerous single institutional studies have demonstrated that high-dose-rate (HDR) brachytherapy combined with external beam radiation therapy (EBRT) is a highly effective treatment for localized prostate cancer.[1–4] In 2004, NRG Oncology/RTOG developed a phase 2, prospective, multi-institutional study to further investigate this combined modality approach. The primary goal of the study is to estimate the rate of treatment-related toxicity and overall efficacy. An HDR prostate brachytherapy credentialing and a quality assurance process were designed and implemented with support from the Image Guided Therapy Center in St Louis and the Radiological Physics Center in Houston. This study met its accrual in 2006 and was first reported in 2010.[5] This is an update on the results at 10-year median follow-up.

Since the completion of this trial, the results from 2 randomized clinical trials comparing EBRT with and without brachytherapy boost have been reported.[6,7] Both studies have demonstrated a superior biochemical control rate with brachytherapy boost compared with EBRT alone. The HDR study conducted by Hoskin et al[6] showed similar incidences of late genitourinary (GU) and gastrointestinal (GI) morbidity between study arms. The more recent ASCENDE-RT, however, showed that the low-dose-rate (LDR) brachytherapy boost arm had a higher rate of GU morbidity compared with EBRT alone. Despite improved biochemical control with this combined modality approach, there is concern for increased late toxicity. It is in this context that we would like to update the long-term outcome of this HDR brachytherapy study.

Methods and Materials

Patient eligibility

The preliminary report of this study was published in 2010.[5] For ease of reference, the details of the 2010 study design are set forth below.

The study enrolled patients with histologically confirmed adenocarcinoma of the prostate. All patients were staged using the American Joint Committee on Cancer Staging manual, 6th edition. All patients were National Comprehensive Cancer Network (NCCN) intermediate to very high risk. All eligible patients have one of the following combinations of factors: (1) clinical stage T1c to T2c, Gleason score 2 to 6 and PSA >10 but ≤ 20; (2) clinical stage T3a to T3b, Gleason score 2 to 6 and PSA ≤20; (3) clinical stage T1c to T3b, Gleason score 7 to 10, and PSA ≤20. All patients had clinical negative nodes by imagining and no evidence of distant metastatic disease. Zubrod performance status of 0 to 1 was required. Additionally, patients were ineligible if they have a prior history of any of the following: transurethral resection of prostate, pelvic or prostate radiation therapy, chemotherapy for prostate cancer, induction hormonal therapy begun more than 120 days before study registration, invasive malignancy (except for nonmelanomatous skin cancer) unless the patient has been disease free for a minimum of 3 years, and hip prosthesis.

All patients completed informed consent before study entry. Only institutions that completed precredentialing were able to enroll patients in the study. The credentialing process was completed by the Radiological Physic Center. To ensure that the study truly represents a multi-institutional experience, no single institution could enroll more than 20 patients.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Treatment

All patients were treated with a combination of external beam radiation therapy and HDR prostate brachytherapy. External beam radiation therapy was delivered with effective photon energies of ≥6 MV. A minimum of 4 fields was required. Perineal boost and IMRT were not allowed. The clinical target volume (CTV) for the EBRT was the prostate and seminal vesicles or the whole pelvis, depending on the lymphatic risk. If 2/3 PSA + [(GS-6) x 10] is >15%, whole pelvis radiation was required. For the whole pelvis field, the superior border was at L5/S1; the lateral borders were 2 cm lateral to the pelvic brim; and the inferior border was either at the inferior border of the ischial tuberosity or at least 2 cm below the most inferior aspect of the prostate, or 1.5 cm below apex of the urethrogram. The lateral fields included internal and external iliac lymph node below L5, the S2 vertebral body, pubic symphysis, and the posterior extension of seminal vesicles. For both the whole pelvic and the prostate field, the planning target volume (PTV) is a 1- to 1.5-cm margin around the prostate and seminal vesicles. A total of 45 Gy was delivered in 25 daily fractions.

HDR brachytherapy may be performed before or after the EBRT. The overall treatment course (EBRT and HDR boost) was limited to less than 8 weeks. To eliminate CT imaging artifacts, only nonmetallic brachytherapy catheters were allowed. All implant catheters were inserted under transrectal ultrasound guidance. A minimum of 14 catheters were inserted in the clinical target volume to ensure adequate target coverage without excessive hot spots. Flexible cystoscopy evaluation of the insertion depth was recommended to avoid leaving the catheter crossing the mucosa and accidental over treatment of the urethral or bladder mucosa.

Computer tomography (CT) based brachytherapy treatment planning was required. For T1c to T2b, the brachytherapy CTV includes only the prostate. For T3a to T3b, the brachytherapy CTV included the prostate and the region of known extracapsular extension. The brachytherapy PTV was identical to the CTV. The outer border of the bladder and rectum was contoured and the outer surface of the Foley catheter was contoured for dose calculation of organ at risk. To take full advantage of the image guided brachytherapy capability of HDR brachytherapy, all forms of dwell time optimization, such as inverse optimization, geometric optimization, and manual optimization were allowed. A total of 19 Gy was delivered in 2 fractions within 24 hours, with at least 6 hours between each fraction. The goals of brachytherapy planning were to deliver the prescription dose to at least 90% of the PTV while keeping the volume of bladder and rectum receiving 75% of the prescription dose to less than 1 mL and the volume of urethra receiving 125% of the prescription dose to less than 1 mL. To minimize the effect of catheter movement, visual inspections or imaging of the implant before each fraction was required. If significant catheter displacement was found, the treatment physician may reposition the catheter, replan, or postponed the treatment until a satisfactory implant was done.

Androgen suppression was permitted on study, if it is clinically indicated. It must begin less than 120 days before registration to this study and must not continue more than 2 years from completion of radiation therapy.

Follow-up evaluation

All patients were seen weekly during the external beam radiation therapy for treatment of side effects. Posttreatment follow-up evaluation were done at 3, 6, 9, and 12 months from start of treatment, then every 6 months for 3 years, and annually thereafter. A history and physical examination (including digital rectal examination), PSA, and toxicity evaluation were done at each follow-up evaluation. All adverse events (AEs) were scored using the Common Toxicity Criteria for Adverse Events, version 3.

Statistical analysis and study design

The primary endpoint of this study is to estimate the rate of late grade 3 to 5 GU and GI toxicity after treatment with EBRT and HDR prostate brachytherapy. The study was designed to test whether the 18-month late GU and GI adverse events (AEs) from the start of protocol treatment was >10% (0.012/mo). The sample size was determined such that the probability of rejecting the treatment due to excessive late AEs was 90% if the true late AE rate was 20% (0.025/mo). A total of 98 patients were required to be accrued within 1 year

and followed up for an additional 18 months to have a statistical power of 90% with a one-sided significance level of 0.05. Assuming 10% of the cases were ineligible or lacked data, the total sample size needed for the study was determined to be 110 patients. The study met its accrual and follow up goals and the result was published in 2010.[5] The secondary endpoints included estimation of the rates of GU and GI toxicity, biochemical failure, overall survival, disease-specific survival, and clinical progression, including local, regional, and distant relapse. Here, the focus is on secondary endpoints.

The time to occurrence of severe late GI and GU toxicity was defined as the time interval from the 10th month after start of protocol treatment to the date of onset of grade 3 to 5 GI and GU toxicity. All time to event endpoints were measured from the date of registration to the date of the event. Patients who did not experience the event were censored at their last known visit.

The American Society for Radiation Oncology (ASTRO) definition of PSA failure (BF-ASTRO) was used for protocol.[8] PSA failure based on the Phoenix definition or a PSA rise of 2 ng/mL above the posttreatment nadir (BF-Phoenix) is also calculated in this study.[9] Distant failure required documentation of regional nodal recurrence or distant disease relapse. Biopsies were strongly recommended for patients without evidence of distant failure to assist in accurately determining the “true” local control rate. In the absence of a biopsy, patients were considered local failure if their examination was abnormal. If their examination was normal or if they were post orchiectomy, then they were censored at the last point in time they were considered locally controlled and considered “unevaluable” for further assessment of local control. Disease-specific deaths included those due to prostate cancer, other causes with active malignancy (clinical or biochemical progression), and complications from treatment.

Cumulative incidence was used to estimate time to severe late GI and GU toxicity, biochemical failure, disease-specific mortality, local failure, and distant failure. Competing risks were death without an event. Overall survival was estimated using the Kaplan-Meier method.

Results

Patient pretreatment characteristics

One hundred twenty-nine patients were enrolled from July 30, 2004 to May 26, 2006 at a rate of almost 6 patients per month. This analysis included all data received as of February 23, 2017.

Only one patient was ineligible due to his PSA with t-stage and Gleason score. Five patients withdrew consent and 3 were excluded due to not receiving protocol treatment. Of a total of 125 eligible patients, follow-up information was available for 115 patients. The median of follow-up of all patients was 9.9 years (range, 1.9–11.9). The median follow-up for living patients was 10.0 (2.4–11.9).

The pretreatment characteristics of 125 eligible patients are listed in Table 1. The median age was 68 years (range, 48–80) with most patients being white (69%), not Hispanic or Latino (79%), of Zubrod 0 (97%), had an entry PSA ≤10 (70%), had a Gleason score of 7 (72%), had T1c to T2c disease (91%), and did not receive hormone therapy (57%).

Late toxicity

Table 2 summarizes the grade 3 to 5 late GI and GU toxicities. There were 6 patients with grade 3 GI and GU AEs, and no late grade 4 to 5 GI and GU treatment-related AEs. The single grade 3 GI AE was proctitis. The grade 3 GU AEs were cystitis (n = 1), pollakiuria (n = 1), renal and genitourinary, other (n = 1), urethral stricture (n = 1), urinary incontinence (n = 1), and urinary retention (n = 2). At 5 and 10 years, the rate of late grade 3 to 5 GI and GU AEs was 4% and 5%. As depicted in Figure 1, most late grade 3 to 5 GI and GU AEs occurred between 1 and 2.5 years.

Efficacy

Five- and 10-year overall survival rates were 95% (95% confidence interval [CI], 91–99) and 76% (95% CI, 67–84; Fig. 2). The 5-year and 10-year rates of BF-ASTRO were 10% (95% CI, 5–16) and 15% (95% CI, 9–22). The 5-year and 10-year rates of BF-Phoenix were 14% (95% CI, 9–21) and 23% (95% CI,15–31; Fig. 3). The 10-year rate of prostate-specific mortality was 6% (95% CI, 3–13). No patients died from prostate cancer for the first 6 years. There were no patients who had an active malignancy at the time of death. At 5 and 10 years, the rates of distant failure were 4% (95% CI, 2–9) and 8% (95% CI, 4–14).

Using BF-ASTRO, there were 17 failures, 7 of which had biopsies and 2 had positive results. Using BF-Phoenix, there were 27 failures, 8 of which had biopsies with 2 having positive results. The estimated rates of local failure at 5 and 10 years were 2% (95% CI, 0.3–5) at both time points.

Discussion

Multiple studies have demonstrated improved clinical outcome by dose-escalation in prostate cancer using advanced EBRT or a combination of EBRT and brachytherapy.[6,7,10–14] Most improved clinical outcomes also resulted in a modest increase in treatment related toxicity. In the prior report of this protocol, the GI and GU grade 3 + toxicity was reported at an acceptable level of 2% at the median follow-up time of 30 month.[5] In this report, the toxicity has remained at a low level of 5% at 10 years and patients continue to have excellent local control rate, at a rate of 98%.

To illustrate its significance, the results should be examined in the context of other studies. Table 3 is a summary of contemporary multi-institutional clinical trials. This study shows that dose escalation to equivalent dose of 95 Gy to 108 Gy (prostate $\alpha/\beta = 3$ or 1.5) can be achieved with treatment related GI and GU toxicity of 5% at 10 years. More importantly, this study demonstrated that low toxicity can be achieved in combined modality treatment using external beam radiation therapy and brachytherapy. For the first time, it was demonstrated that dose escalation, hormonal therapy, and pelvic radiation therapy can all be used together safely and effectively.

There have been 4 randomized clinical trials, and all have demonstrated statistically significant improvements by adding brachytherapy to external beam radiation therapy compared with external beam radiation therapy alone. Sathya et al first demonstrated an improved biochemical control at 8 years using temporary iridium LDR brachytherapy.[15] There was increased gastrointestinal toxicity in the brachytherapy arm, but it did not reach statistical significance. Hoskin et al showed an 31% reduction in the risk of biochemical recurrence at 10 years by adding HDR brachytherapy.[6] He reported an increase in the prevalence of genitourinary AE, including strictures, in the brachytherapy arm, and an increase in gastrointestinal AE in the EBRT arm. However, these observed increases in prevalence did not lead to a statistical difference in AE between the arms of the study. Recently, results from multi-institutional studies were reported. ASCENDE-RT was designed specifically to test if adding LDR brachytherapy improves outcome compared with dose-escalated EBRT. They reported a 50% reduction in risk of biochemical failure at 6.5 years in the LDR brachytherapy arm.[7]

However, there was a significant increased incidence of GU grade 3 + AE in the brachytherapy arm compared with dose-escalated EBRT (18.4% vs 5.2% at 5 years).[16] Furthermore, 8.5% in the brachytherapy arm developed urethral stricture requiring dilatation, 2% required transurethral resection of the prostate, and 3% developed severe urinary incontinence. The long-term outcome of TROG 03.4 RADAR trial was recently published. It was a randomized study designed to study the effects of androgen suppression duration, dose escalated radiation therapy, and zoledronic acid.[17] HDR brachytherapy boost was included but the patients were not randomly assigned between the study arms. In fact, more patients with high-risk features, such as higher T stage and Gleason score, were treated with HDR brachytherapy than with EBRT.[18] In the subset analysis of this randomized study, they reported a significant reduction in distant disease progression using HDR brachytherapy compared with 70 Gy EBRT (hazard ratio 0.68 [95% CI, 0.57–0.80]; $P < .0001$) independently of androgen suppression duration.[19] There was also a statistically significant increase in urinary dysfunction for patients treated with HDR brachytherapy measured using EORTC PR 25 instruments at 18 and 36 months.[18] A decrease in protopathic symptoms were also observed in HDR patients; however, this was not statistically significant.

The results of these randomized studies suggest there may be clinical benefit of adding brachytherapy but at the expense of increase urinary toxicity. It is in this context, the result from this study is significant and relevant. Unlike the other studies, this trial's primary objective is to measure the rate of toxicity from HDR brachytherapy, and its design reflects this goal. For example, steps were taken to maximize the number of participating institutions by capping the maximum number of patients each institution can enroll to 20. As the result, 14 institutions participated in this study, which is much higher than other studies. Because more institutions participated in this study, one can argue this is likely a more accurate and robust measurement of toxicity. Procedural and technical details of this protocol may have contributed to the favorable outcome. In TROG 03.4 RADAR's post hoc analysis, the investigator concluded that catheter slippage may have been the cause of HDR induced strictures. Because the risk of catheter migration increases with time from the implant, this study used the lowest number of HDR fractions to minimize time between implant and treatment, a minimum that was tested and proven safe at the time of trial design.[4] To

minimize unintended injury to the urethra, a flexible cystoscopy was required as a part of the implant procedure to ensure implant catheter was not left in the urethra or bladder mucosa. This was the first Radiation Therapy Oncology Group/NRG study that required 3-dimensional imaging and 3-dimensional planning for brachytherapy. The technology was so new at the time, the study opening was postponed over a year until a digital quality assurance (QA) infrastructure was ready. Beside digital planning and QA, efforts were made to improve the CT image quality so the investigator can see the target volume during planning, including requirement to use plastic implant catheters, and the removal of radiopaque catheter markers before CT to minimize imaging artifacts. To ensure good dosimetry, a minimum of 14 implanted catheters was required and volume metric dose calculations were required instead of just point dose calculations for QA. These design details were included specifically because this was a multi-institutional study, and there was a need ensure treatment quality across the board. It is unclear if any of above factors, or other yet unknown factors, may have contributed to the favorable outcome observed in this study. Nevertheless, this study showed HDR prostate brachytherapy can be done effectively in a multi-institutional setting. Physicians interested in treatment should be able to reproduce the result by using the protocol and published dosimetry data from this study.[20]

This study reported the lowest rate of G3 + AE in Table 3. The late GI toxicity was 1% at 10 years. This is likely due to steep dose gradient from brachytherapy. Also, no additional margins were added to the brachytherapy CTV. This further reduced dose to the rectum. This is a unique advantage of using brachytherapy. The late GU toxicity also compared favorably with prior studies. The urethral stricture rate in the current study was <1%. Prior randomized studies have reported urethral stricture rate at 7 year of 2% and 8% for EBRT and EBRT + HDR boost, respectively.[6] There have been concerns raised around the issue of urethral stricture. The TROG 03.4 RADAR investigators made a detailed post hoc analysis and found, beside the presenting symptoms of nocturia (22%), strictures that occur after HDR brachytherapy tend to cause frequency (50%), which is different from strictures that occur after EBRT, which tend to cause urgency (45%) and incontinence (30%).[18] The time to diagnosis of stricture after HDR was earlier with median time of diagnosis 1.2 year after treatment versus 3.6 years after EBRT. The post hoc analysis was performed because this complication was not anticipated a priori. In this study, documentation based on the Common Terminology Criteria for Adverse Events, version 3, was collected prospectively at each follow-up visit. Under the renal and genitourinary category, a grade 1 stricture is asymptomatic; grade 2 is symptomatic but not requiring dilation, stent, or endoscopic repair, and grade 3 if the stricture is symptomatic and require operative intervention. It is conceivable that asymptomatic strictures were not recorded or symptomatic strictures were classified under other grade 2 urinary symptoms. This issue was not unique to this study because the same methodology was used in other studies from the era, including the Radiation Therapy Oncology Group/NRG studies listed in Table 3. Furthermore, given TROG 03.4 RADAR's finding regarding the timing of HDR related stricture, evidence for strictures should have been detected long before this update. It is also reassuring to see the AEs appear to have plateaued after 2.5 years. The secondary analysis of data from this trial demonstrated an association between the maximum urethral dose and late G2 + GU toxicity.[20] Using image-guided dose optimization, it is possible to further reduce the urethra dose.[21]

As a result, it may be possible to further reduce treatment acute toxicity using HDR brachytherapy.

The BF-Phoenix rates of 86% and 77% at 5 and 10 years, respectively, are in the expected range for NCCN intermediate- to high-risk patients, as well as the 10-year overall survival rate of 76% and prostate-specific survival rate of 94%. The limitation of this study is that it is not randomized so it is unclear if its efficacy is significantly better than standard of care.

Conclusions

This study found an estimated local control rate of 98% at 10 years. Other studies have reported similar, low rate of local failure after combined HDR brachytherapy and EBRT. In a prospective study reported by Borghede et al, all patients were treated with HDR boost without hormonal therapy.[2] Forty-nine out of 50 (98%) patients were biopsied at 6- to 24-month posttreatment, and 48 out of 50 (96%) had negative biopsy. Because post radiation therapy biopsies have been associated with complication risks, this study like others, did not perform posttreatment biopsy on all patients. There is also limited data on interpretation of posttreatment biopsy. However, 2 large studies reported by Crook et al and Krauss et al both showed positive biopsies post treatment were associated worse clinical outcomes.[22,23] Because this study was not designed or powered to test efficacy, it cannot demonstrate superiority or equivalency compared with other treatments. However, the local control rate observed is in line with the past HDR study.

There is a trend toward clinical application of shorter course radiation therapy treatment. Beside the combinations of EBRT and HDR fractionations tested in this study, there are other HDR boost combinations that appear to be able to further reduce overall treatment time.[6,24] In NRG Oncology/RTOG prostate trials designed after the current study, such as 0815 and 0924, a single fraction HDR brachytherapy boost of 15 Gy was used. We hope the positive result from this study will lead to future randomized studies to compare the efficacy of this approach with other short course treatments. Is there a possibility for further dose escalation using HDR brachy-therapy? Other institutional studies have used higher doses.[1,4] But with an estimated local failure rate of 2%, it would be difficult to demonstrate further therapeutic gain. A partial or targeted dose escalation, however, may be a practical approach to take advantage of dose modulation capability of HDR brachytherapy.[25–28]

Excellent long-term outcomes were demonstrated in this study using the combined modality approach. This effective combined modality approach should be available to intermediate to patients with high-risk prostate cancer.

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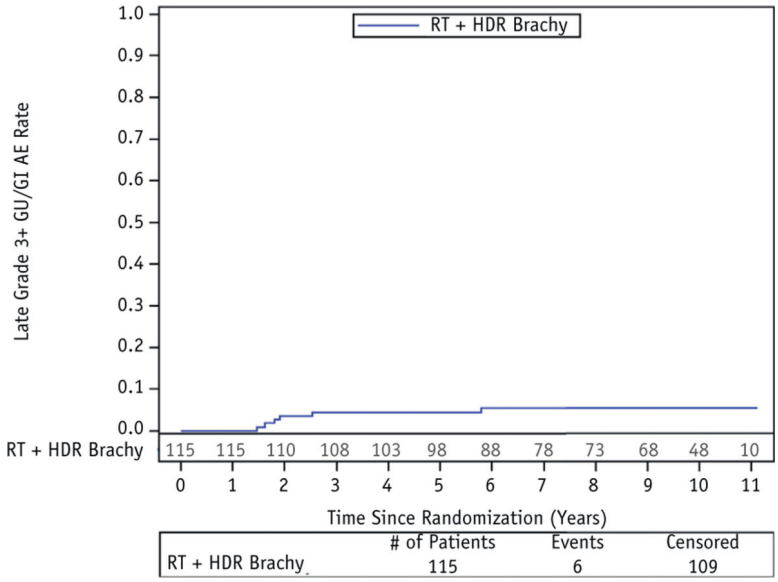

Fig. 1.

Time to late G3 + gastrointestinal (GI)/gastrointestinal (GU) adverse events. *Abbreviations:* HDR = high-dose-rate; RT = radiation therapy.

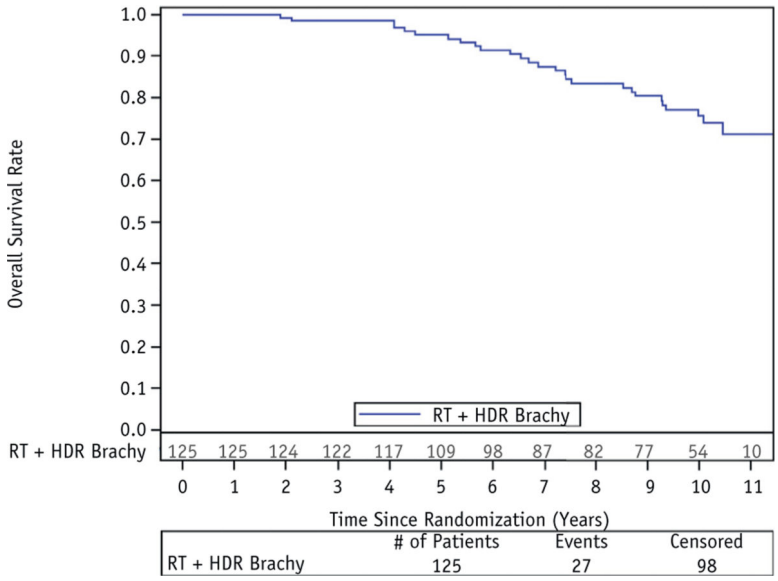

Fig. 2.

Overall survival. *Abbreviations:* HDR = high-dose-rate; RT = radiation therapy.

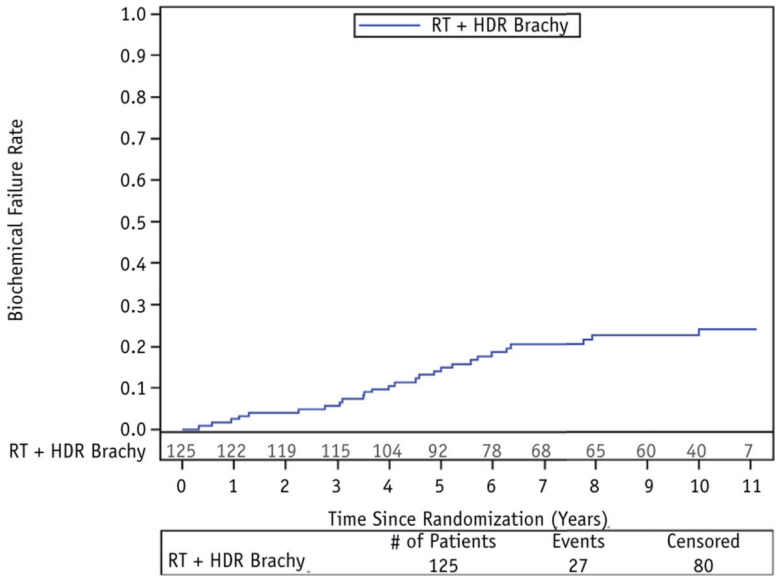

Fig. 3.

Biochemical failure, Phoenix definition. *Abbreviations*: HDR = high-dose-rate; RT = radiation therapy.

Table 1

Pretreatment characteristics (N = 125)

Age (y)		
Median	68	
Range	48–80	
Race		
White	86	69%
Black or African-American	32	26%
Asian	2	2%
>1 race	2	2%
Unknown or not reported	2	2%
American Indian/Alaska Native	1	1%
Ethnicity		
Not Hispanic or Latino	99	79%
Unknown or not reported	23	18%
Hispanic or Latino	3	2%
Zubrod		
0	121	97%
1	4	3%
PSA		
≤10	87	70%
10–20	38	30%
Median	7.54	
Range	0.85–19.3	
Gleason score (institutional)		
6	13	10%
7 (3 + 4)	66	53%
7 (4 + 3)	24	19%
8	15	12%
9–10	7	6%
T stage		
T1c-T2c	114	91%
T3a	7	6%
T3b	4	3%
HDR brachytherapy PTV		
Median, mL	54	
Range, mL	19–130	
Hormone therapy *		
No	71	57%
Yes	54	43%
NCCN risk group v2.2020 †		
Intermediate	95	76%

High	20	16%
Very high risk	10	8%

Abbreviations: HDR = high-dose-rate; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; PTV = planning target volume.

* The maximum duration of any hormonal therapy was <2 years from the time of completion of radiation therapy.

† This is an estimation since percentage of positive biopsy was not available on all subjects.

Table 2

Number of patients with late GI/GU adverse event by category, term and grade possibly, probably, or definitely related to protocol treatment (n = 115)

Category	Grade				
Term	1	2	3	4	5
Gastrointestinal	17	7	1	0	0
Abdominal distention	0	1	0	0	0
Constipation	3	0	0	0	0
Diarrhea NOS	10	1	0	0	0
Dyspepsia	1	0	0	0	0
Fecal incontinence	1	1	0	0	0
Flatulence	2	1	0	0	0
Gastrointestinal, other	2	0	0	0	0
Hemorrhoids	2	0	0	0	0
Proctitis NOS	4	3	1	0	0
Renal/genitourinary	37	46	5	0	0
Cystitis NOS	0	7	1	0	0
Pollakiuria	41	36	1	0	0
Renal/genitourinary, other	5	3	1	0	0
Urethral obstruction	7	2	0	0	0
Urethral stricture	0	6	1	0	0
Urinary incontinence	16	6	1	0	0
Urinary retention	20	5	2	0	0

Abbreviations: GI Z gastrointestinal; GU Z genitourinary.

Adverse events were graded with Common Toxicity Criteria for Adverse Events, version 3.0.

Table 3

Summary of prospective multi-institutional studies

Study name and modalities	Patient eligibility NCCN group	GI/GU G3+ AE rate	Biochemical failure rate (Phoenix definition)
Present NRG/RTOG 0321	Int mcd to very high risk	5% at 10 y	23% at 10 y
EBRT + HDR ± HT			
RTOG 0019[29]	Int med risk	14% at 8 y	18% at 8 y
EBRT + LDR			
NRG/RTOG 0126[10]	Int med risk	8% at 8 y	20% at 8 y
EBRT 79.2 Gy arm			
ASCENDE-RT[7]	Int med and high risk *	27% at 7 y	17% at 9 y
EBRT + LDR + HT arm			
TROG 03.4 RADAR[17]	Int mcd and high risk †	1 % at 3 y (12.7% stricture at 7.4 y) †	18AS 34% at 10 y
EBRT + HDR + HT arm			6AS 45.9% at 10 y

Abbreviations: 18AS = 18 monili of androgen suppression; 6AS = 6 month of androgen suppression: EBRT = external beam radiation therapy; IIDR = high-dose-rate: HT = hormonal therapy; Int Med = intermediate risk; LDR = low-dose-rate.

Rates are based on cumulative incidence.

* T3b excluded.

† Retrospectively collected data.