



Favorable long-term toxicity for salvage low-dose rate prostate brachytherapy for recurrent prostate cancer after external beam radiotherapy from a phase II prospective trial (NRG Oncology/ RTOG 0526)

Randall J. Brennen¹, Edward Soffen², Hiram A. Gay¹, Peter F. Orio III^{3,4}, John P. Christodouleas⁵, John C. Baumann², Brian C. Baumann^{1,6}

¹Department of Radiation Oncology, Washington University in St. Louis, St. Louis, MO, USA; ²Princeton Radiation Oncology, Princeton, NJ, USA;

³Department of Radiation Oncology, Dana-Farber Cancer Institute, and Brigham and Women's Hospital, Boston, MA, USA; ⁴Harvard Medical School, Boston, MA, USA; ⁵Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA, USA; ⁶Leonard Davis Institute of Healthcare Economics, University of Pennsylvania, Philadelphia, PA, USA

Correspondence to: Brian C. Baumann, MD. Washington University in St. Louis, St. Louis, MO, USA. Email: brian.baumann@wustl.edu.

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External beam radiotherapy (EBRT) is the most commonly employed non-surgical treatment for prostate cancer in the modern era (1). Local recurrence of prostate cancer after EBRT occurs in up to 15% of patients (2-4). Local recurrence is not only common and often symptomatic, but is also a risk factor for developing distant disease. Dose-escalated EBRT reduced local recurrence risk and need for salvage local therapy in a large Phase III trial (5); however, local recurrence after EBRT remains an important problem. The morbidity and mortality associated with local failure suggests a possible role for local salvage therapies for appropriately selected patients (6,7).

Multiple local salvage treatments are available, including radical prostatectomy, low-dose rate (LDR) and high-dose rate (HDR) brachytherapy, cryotherapy, high-intensity focused ultrasound, and stereotactic body radiotherapy. Currently, there is no consensus on optimal management. A small percentage of eligible patients receive potentially curative salvage therapy, with most instead receiving palliative androgen deprivation therapy (ADT) or observation (8). Reasons for conservative management include absence of prospective studies assessing whether there is benefit for local salvage *vs.* ADT, concern about the potentially high toxicity of salvage therapy given

limited prospective data, and patient-specific factors, such as preexisting gastrointestinal (GI) or genitourinary (GU) symptoms and/or medical comorbidities that would further complicate salvage therapy (9).

Salvage whole-gland brachytherapy is a minimally invasive treatment option for biopsy-proven, locally-recurrent prostate cancer following EBRT. Brachytherapy involves intraprostatic radiation via temporary or permanent transperineal delivery of radioisotopes under transrectal ultrasound guidance. Brachytherapy is advantageous for reirradiation as it delivers highly conformal, high-dose radiation while reducing the dose to previously irradiated normal tissues, including the bladder, rectum, and urethra. LDR uses permanently implanted radioisotope-containing seeds, typically iodine (¹²⁵I), palladium (¹⁰³Pd), and now cesium (¹³¹Cs) that deliver curative doses of radiation over several months. HDR involves temporary implantation of intraprostatic catheters to deliver HDR radiation in a short time interval via temporary insertion of radioisotope, typically iridium (¹⁹²Ir). Prior series investigating salvage LDR brachytherapy demonstrated potential biochemical control rates approaching 90% at 3 years, >70% at 5 years, and >50% at 10 years in appropriately selected patients [pre-salvage prostate-specific antigen (PSA) <10 ng/mL]

(10–12). The recent Princeton Radiation Oncology salvage brachytherapy experience reported 5- and 7-year relapse-free survival of 79% and 67% respectively (13).

While efficacy data from these small, single-institution studies has been encouraging, prospective data on adverse events (AEs) is limited. Concerns about late GI/GU toxicity following re-irradiation with salvage brachytherapy has historically dampened enthusiasm for the treatment. In a small series from the Brigham and Women's Hospital with 25 patients treated with ^{125}I salvage LDR brachytherapy (137 Gy), biochemical control was very good at 70% at 4 years, but substantial late grade 3–4 GI/GU toxicity (30%) was observed (14). Toxicity was related to initiating salvage brachytherapy within 4.5 years of EBRT, suggesting that both cumulative dose and time interval between definitive and salvage treatment impacts toxicity (14). For salvage HDR, several series demonstrated efficacy comparable to salvage LDR with similar concern for late grade 3 GI/GU toxicity rates between 10–20% (12,15,16). Given the absence of data from large, multi-center trials of salvage brachytherapy, and heterogeneity in patient selection, radiation dose, and toxicity outcomes from single-institution series, it is not surprising that salvage LDR brachytherapy is not routinely recommended. Data from large, multi-center prospective trials are needed to determine the safety and efficacy of salvage brachytherapy, and to provide guidance on patient selection, radiation dose, dosimetric parameters for the implant, treatment efficacy, and acute and late AEs.

Beginning in 2007, the RTOG (now NRG Oncology) cooperative group opened RTOG 0526, a prospective, single-arm Phase II trial of whole-gland salvage LDR brachytherapy to assess both the toxicity and efficacy of salvage brachytherapy for prostate cancer. The study opened at 20 centers and enrolled 100 patients. The efficacy and late toxicity results from RTOG 0526 have been eagerly anticipated by the prostate cancer community. The late toxicity results were recently published by Crook *et al.* (17); results on treatment efficacy are expected soon once a minimum follow-up of 5 years is reached. The NRG, Dr. Juanita Crook, Dr. Howard Sandler, and the other RTOG 0526 investigators are to be commended for a well-designed trial addressing an important clinical question.

RTOG 0526 evaluated treatment-related \geq grade 3 GI/GU AEs at 9–24 months following salvage LDR using ^{125}I (140 Gy) or ^{103}Pd (120 Gy) brachytherapy at doses comparable to primary brachytherapy. Grade 3 GU AEs reported included severe urinary frequency, obstruction, incontinence, cystitis, and fistula. Grade 3 GI AEs included

severe proctitis. Secondary endpoints included early AEs ≤ 9 months from implantation, oncologic outcomes, and post-brachytherapy dosimetry. Eligible patients had low to unfavorable intermediate-risk prostate cancer (T1–T2c, Gleason score 2–7, PSA ≤ 20 ng/mL) at initial diagnosis and were treated with definitive EBRT (median dose 74 Gy, interquartile range: 70–76 Gy) as their initial therapy. All patients had biopsy-proven local recurrence >30 months from primary EBRT, a pre-salvage PSA <10 ng/mL, no clinical evidence of metastatic disease, a pre-salvage prostate volume ≤ 45 cm³, adequate baseline urinary function (IPSS ≤ 15), and no residual grade 2 or higher GI/GU toxicity attributed to their prior EBRT. ADT was permitted with initial EBRT (total duration <8 months or normal testosterone level if >8 months) and as neoadjuvant therapy with recurrence if started within 2–6 months of enrollment. Of 100 patients registered between 5/2007–1/2014, 92 received salvage brachytherapy (92% with ^{125}I), with 87 patients eligible for primary endpoint evaluation (85 whole-gland and 2 partial gland brachytherapy implants).

Late grade ≥ 3 GI/GU AEs were predicted to occur in $\leq 10\%$ of patients; a rate of $\geq 20\%$ was considered unacceptable. The authors reported a 14% (12/87) incidence of late grade 3 treatment-related GU/GI AEs, which did not exceed the prespecified study threshold for unacceptably high toxicity. There were no grade 4/5 AEs. Of the 12 grade 3 AEs, 8 (8/87=9%) were deemed “definitely” or “possibly/definitely” related to brachytherapy and 4 (4/87=5%) were deemed “possibly” or “probably” related to treatment, suggesting that $<14\%$ of AEs may be entirely attributed to salvage treatment. Most late grade 3 AEs were GU (11/12). On multivariable analysis, no pretreatment variables (prostate size, prior EBRT dose, interval from EBRT to salvage treatment) predicted late GI/GU toxicity. The authors reported detailed dosimetric data on prostate dose [e.g., D90 (minimum dose covering 90% of the prostate), V100 (percentage of the prostate by volume receiving 100% of the prescription dose), V150 and V200 (percentage of the prostate by volume receiving 150% and 200% of the prescription dose, respectively)]. In their analysis, only a higher V100 (median 94%, interquartile range: 94–100%) as a continuous variable predicted incidence [odds ratio (OR) 1.24, 95% CI: 1.02–1.52, $P=0.03$] and time to first occurrence of a grade 3 GU AE [HR 1.18, 95% CI: 1.03–1.34, $P=0.02$] on multivariable analysis.

The association of higher V100 as an independent predictor of developing late grade 3 toxicity is interesting

and requires some interpretation. The portion of the prostate that tends to receive <100% of the prescription dose is not random and is usually the anterior base, due to technical challenges of implanting sources in this location because of its proximity to the bladder (18). The anterior base is also close to the bladder neck and proximal urethra; high-dose radiation to these structures is associated with higher rates of grade 2/3 GU toxicity in definitive prostate brachytherapy series. Therefore, a higher V100 is likely a surrogate marker for increased dose to the previously irradiated bladder neck and proximal urethra, correlating with higher GU AEs.

While the V100 finding suggests that bladder neck/proximal urethra dose is important for predicting GU AEs, it begs the question of the dose threshold to these structures predictive of grade 3 GU AEs. On the RTOG 0526 protocol, urethral constraints were provided [V150 <30% (urethral volume receiving $\geq 150\%$ of the prescription dose should be <30%) and maximum urethral dose <200% of prescription] yet the recent study omits analysis of urethral dose and how it correlates with late GU toxicity. Bladder dose was tracked for each patient, per protocol, but bladder dose constraints were not provided, in part since there is no consensus on LDR prostate brachytherapy bladder dose constraints, even in the definitive setting. Retrospective data on definitive upfront LDR brachytherapy suggest that no more than 2 cc of the bladder neck should receive more than 72 Gy out of a prescription dose of 144 Gy to reduce the risk of acute and late grade ≥ 2 GU toxicity (19). Similar results were observed for focal and whole-gland salvage LDR brachytherapy in another study where >70 Gy to >2 cc of the bladder predicted late grade ≥ 3 GU toxicity (20). Data on whether GU toxicity correlates with bladder neck dose is of great interest and may appear in subsequent analyses of this trial.

Early toxicity (within 9 months of implantation) was a secondary endpoint of RTOG 0526 and occurred in 14% (12/87) of patients. Interestingly, 6 of 12 patients with early grade 3 GI/GU AEs developed late grade 3 GI/GU toxicity. On multivariable analysis, PSA at initial diagnosis predicted early toxicity ($P=0.04$) and time to first occurrence ($P=0.02$), with interval between prior EBRT and salvage suggesting an association ($P=0.08$); however, this was likely limited by the small study sample size. These results indicate that early toxicity and higher initial PSA may predict development of late toxicity in salvage brachytherapy patients, necessitating closer interval monitoring and possible cystoscopy prior to salvage brachytherapy to evaluate for subclinical bladder

neck stenosis.

RTOG 0526 provides important prospective evidence regarding development of acute and late toxicity following salvage LDR brachytherapy in the largest prospective cohort of low and intermediate-risk patients to-date. Toxicities are comparable to those reported in larger salvage HDR brachytherapy series (21). Acute and late treatment toxicities in RTOG 0526 were observed in only 14% of patients, did not exceed grade 3, and were mostly GU-related.

Although the relatively low number of late toxicities observed in RTOG 0526 are encouraging, there are several limitations to the study. The authors have not yet reported efficacy data, making it difficult to weigh the pros and cons of salvage brachytherapy compared to alternative salvage treatment options. Another limitation is that the expected toxicity of salvage brachytherapy for patients with early failure after EBRT must be interpreted cautiously from this data, as the median interval between prior EBRT and salvage brachytherapy was long (7 years) despite inclusion criteria allowing patients with a 30-month minimum interval from EBRT to recurrence on study. Severe late GU AEs are associated with a shorter time interval between EBRT and salvage brachytherapy in other series (14). While RTOG 0526 does include patients treated with EBRT in the dose-escalated era (median EBRT dose of 74 Gy), it does not report on the toxicity of salvage brachytherapy for patients previously treated with moderately hypofractionated radiation therapy (daily radiation doses of 2.5–3 Gy instead of conventionally fractionated doses of 1.8–2 Gy) or extreme hypofractionated regimens using stereotactic body radiotherapy, fractionation schemes that have become increasingly common. The study largely predated the use of hydrogel spacer injected between the prostate and the rectum to reduce rectal dose, which has become increasingly common for brachytherapy patients in the intact setting, although the low rates of late grade 3 GI toxicity in the trial are reassuring.

RTOG 0526 identified a relationship between V100, late grade 3 GU toxicity, and time to first occurrence for whole-gland salvage LDR brachytherapy, indicating that a lower volume of the prostate covered by the prescription dose reduced the probability of developing late GU AEs. Late toxicity could be further reduced by dose reduction or focal salvage brachytherapy; however, dose reduction or focal salvage may compromise disease control. Short-course ADT is now commonly employed in combination with salvage prostate bed radiotherapy, based on the GETUG

trial (22) and RTOG 0534 (SUPPORT trial) presented at ASTRO in 2018 (23). Could the addition of short-course ADT to salvage brachytherapy allow for radiation dose reduction without compromising overall efficacy, thereby decreasing the likelihood of acute and late radiation AEs?

The largest retrospective study addressing this question was by Baumann *et al.* analyzing the Princeton Radiation Oncology salvage brachytherapy experience (13). The authors found that patients treated with lower dose salvage brachytherapy [^{103}Pd LDR median dose 100 *vs.* 120 Gy on RTOG 0526 or ^{192}Ir HDR (median dose 30 Gy/6 fractions)], in combination with 4–6 months of neoadjuvant, concurrent, and adjuvant ADT had favorable relapse-free survival at 5 and 7 years (79% and 67%, respectively) compared to other series where patients did not receive ADT with salvage brachytherapy. Interestingly, the Princeton cohort had more aggressive disease compared to RTOG 0526, with 55% having high-risk disease at diagnosis (13). These results suggest that short-course ADT with dose-reduced salvage brachytherapy may be comparable to higher-dose salvage without ADT, and that ADT may effectively compensate for the reduction in radiation dose. Of note, 4 of 33 patients (12%) in the Princeton series had late grade 3 GU toxicity after salvage brachytherapy, comparable to that observed in RTOG 0526, yet most Princeton patients would be ineligible for RTOG 0526. The median time from EBRT to recurrence, an important predictor of late toxicity after salvage EBRT, was much shorter in the Princeton series (4.7 *vs.* 7 years). All other things being equal, a reduction of radiation dose, particularly to the bladder neck and urethra, would be expected to reduce late side effects. Adding ADT in the salvage setting could also allow for pre-treatment prostate cytorreduction to shrink enlarged prostates and decrease the number of catheters and sources needed, potentially further reducing acute and late AEs.

Another question of clinical interest not addressed in the present trial is the toxicity of whole-gland *vs.* focal gland salvage brachytherapy, as only a few patients were treated with the focal approach on RTOG 0526. Focal salvage brachytherapy is a promising option and could potentially reduce toxicity; however, there is no consensus on the appropriate salvage brachytherapy treatment volume in the literature (24). In our opinion, reduced-dose salvage brachytherapy to the entire gland combined with short-term ADT may be a reasonable way forward to reduce the side effects from high-dose, whole-gland salvage radiotherapy while taking advantage of the synergistic effects of radiotherapy and ADT in the salvage setting. Reduced dose

to the whole-gland could be combined with a focal boost to the dominant lesion(s) seen on multi-parametric magnetic resonance imaging (MRI) or prostate-specific positron emission tomography/computed tomography (PET/CT) (25). Whole-gland salvage brachytherapy reduces the risk of a marginal miss in the prostate, which is a greater concern when treating patients with initially high-risk disease who have failed locally, a cohort excluded from RTOG 0526.

As mentioned previously, RTOG 0526 did not investigate the role of hydrogel spacer placed between the prostate and the rectum following completion of the salvage LDR implant. We now routinely place hydrogel spacer after salvage LDR cases to ensure the lowest possible dose to the anterior rectal wall. In our experience, hydro-dissection of Denonvilliers' fascia prior to hydrogel injection is feasible after salvage LDR and often poses no greater challenge than hydro-dissection following definitive LDR brachytherapy in patients with no prior EBRT (26). However, hydrogel spacer use in the salvage LDR setting has not been rigorously studied.

RTOG 0526 demonstrates the feasibility of salvage prostate brachytherapy, with relatively low rates of significant acute and late side effects. Advances in functional imaging (e.g., multi-parametric MRI, FACBC and ^{68}Ga -PSMA PET) may facilitate focal brachytherapy, helping to reduce the volume of the prostate receiving 100% of the prescription (V100), and expand the use of salvage brachytherapy to patients with initially high-risk disease. We look forward to the efficacy data from this trial.

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Footnote

Conflicts of Interest: JP Christodouleas discloses part-time employment at Elekta AB. The other authors have no conflicts of interest to declare.

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