Editorial

Salvage prostate brachytherapy after definitive external radiation: tried and now tested

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Definitive external beam radiation therapy (EBRT) has long been one of the standard treatment modalities for prostate cancer. However, 15–75% of patients will experience a disease recurrence depending on such factors as the risk group, use and length of androgen deprivation therapy (ADT) and radiation dose (1). Approximately 25% of patients with biochemical recurrence will have local clinical disease progression within 5 years (2).

For those opting for salvage therapies, negative metastatic workup and a positive prostate biopsy must be confirmed. Aggressive local salvage therapies include radical prostatectomy, re-irradiation, cryotherapy, and high-intensity focused ultrasound (HIFU). They are associated with significant toxicities although the fistula risk is typically less than 10% (3,4). The option for re-irradiation has mainly been limited to patients initially treated with EBRT salvaged with low dose rate (LDR) or high does rate (HDR) brachytherapy, although repeat EBRT as well as salvage EBRT after brachytherapy have now been described (2,3,5-7). *Table 1* summarizes prior experiences of whole gland salvage therapies.

Unfortunately, most men with biochemically recurrent disease are managed with observation or ADT, and less than 5% of patients are offered curative-intent salvage therapies (8). This is likely from the combination of the lack of expertise and availability of salvage therapies and wanting to avoid the risk of significant toxicities in the elderly population.

RTOG 0526

Despite these challenges the first multicenter, cooperative trial of salvage brachytherapy (SBT) for recurrent prostate cancer after EBRT has now been reported (9). RTOG 0526 was a prospective phase II trial that enrolled 100 patients from 20 centers from 2007–2014. The main eligibility criteria included low- and intermediate-risk patients before EBRT, biopsy-proven disease >30 months after EBRT, prostate-specific antigen (PSA) <10 ng/mL and no nodal or distant disease. The LDR SBT entailed the standard full dose (I-125 to 140 Gy, Pd-103 to 120 Gy) to the whole gland. The primary objective was to evaluate the late gastrointestinal (GI) and genitourinary (GU) adverse events (AEs) for local recurrence after initial EBRT (median = 74 Gy; IQR: 70–76 Gy). The late grade ≥3 GI/GU AEs were projected to occur in ≤10% (alternative hypothesis) while ≥20% would be unacceptable (null hypothesis). A sample size of 96 patients was required to detect this effect size with a one-sided significance level of 0.05 and 85% statistical power.

Twelve of the evaluable 87 patients (14%) experienced late grade 3 GI/GU AEs at a median follow-up of 54 months. There were no grade 4 or 5 AEs reported. There were no pretreatment characteristics that predicted for grade 3 AEs. A much larger sample size would have been required to tease out the predictors. Only V100 as a continuous variable was predictive of late GI/GU AEs (P=0.03) and time to first occurrence of late grade ≥3 GI/GU AEs (P=0.02). Post-implant urinary catheterization occurred in 4% (4 patients). The efficacy data is scheduled to be reported later in 2019 with minimum of 5-year follow-up. The investigators should be commended for completing

Table 1 Overview of experiences of whole prostate gland salvage therapies for recurrent prostate cancer after definitive EBRT

Salvage therapies after prior RT	Urinary incontinence (%)	Other GU toxicity	Rectourethral fistula (%)	Other GI/rectal toxicity	Other toxicities
Radical prostatectomy (after prior brachytherapy or EBRT) (Nguyen *et al.*)	41	24% (stricture)	n/a	4.7%	n/a
Cryotherapy (after prior brachytherapy or EBRT) (Nguyen *et al.*)	36	17% (stricture/ retention)	2.6	n/a	Urethral sloughing, 11%; perineal pain, 36%
Brachytherapy (after prior brachytherapy or EBRT) (Nguyen *et al.*)	6	17%	3.4	5.6% (Gr 3/4)	n/a
EBRT (after prior brachytherapy only) (Rutenberg *et al.*)	36	9% (≥ Gr 2 urinary obstruction requiring TURP)	9	9% (≥ Gr 2 fecal incontinence)	0%

EBRT, external beam radiation therapy; RT, radiation therapy; GU, genitourinary; GI, gastrointestinal; Gr, grade; TURP, transurethral resection of prostate.

Table 2 Overview of experiences of focal prostate gland salvage therapies for recurrent prostate cancer after definitive EBRT

Focal salvage therapy	N	Efficacy	Rectourethral fistula (%)	Other toxicities
HIFU (Ahmed *et al.*)	39	49%; 2-year PFS	2.6	26% urinary leakage
Cryotherapy (Li *et al.*)	91	46.5%; 5-year bDFS	3.3	6.6% urinary retention
LDR brachytherapy (Hsu *et al.*)	15	62.7%; 3-year PFS	0	33% Gr 2 GU toxicities
HDR brachytherapy (Murgic *et al.*)	15	61%; 3-year PSA failure-free	0	1 patient with Gr 3 hematuria

EBRT, external beam radiation therapy; PFS, progression free survival; bDFS, biochemical disease free survival; Gr, grade; TURP, transurethral resection of prostate; HIFU, high intensity focused ultrasound; LDR, low dose rate; HDR, high does rate; PSA, prostate-specific antigen; GU, genitourinary.

such a challenging trial.

RTOG 0526 proves that SBT is feasible in the multi-institutional, cooperative setting. Furthermore, the grade 3 GI/GU AE rate of 14% with full dose to the whole gland did not exceed pre-specified unacceptable toxicity rate (grade ≥3 GI/GU AEs rate of ≥20%). This toxicity rate is well within the published literature. It has set the standard for full dose LDR SBT when treatment of the entire gland is required. Multiple whole gland HDR SBT experiences with acceptable toxicities have also been reported (10,11).

Focal SBT

While RTOG 0526 was enrolling, significant improvements in MRI-based prostate cancer imaging was occurring. Siddiqui and colleagues at the NCI enrolled 1,003 men from 2007–2014 on a prospective study of targeted prostate biopsies. This study demonstrated that a targeted MRI/ultrasound fusion biopsy was associated with increased detection of high-risk disease and decreased detection of low-risk disease compared to standard ultrasound-guided biopsy in men suspected of prostate cancer (12).

This improvement in MRI has allowed for increasing number of men being treated with focal gland ablation for newly diagnosed prostate cancer. Valerio and colleagues reviewed the literature and described 37 articles with 3,230 men treated focally with modalities such as HIFU, cryotherapy, photodynamic therapy, laser thermotherapy, brachytherapy, electroporation and radiofrequency (13). Similarly, there have been multiple reports on focal salvage therapies with modalities such as cryoablation, SBT with LDR and HDR, HIFU, and stereotactic body radiation therapy (SBRT) (10,14-18). *Table 2* summarizes the select focal salvage therapies for MRI visible tumors that have been published.

The rationale for focal salvage therapy is to decrease the toxicity risk by decreasing the prostate volume being treated. This would naturally lead to a lower radiation dose

to the urethra, anterior rectal wall and the bladder neck. Focal salvage therapy is possible since the recurrence after EBRT often involves a single focus. Leibovici and colleagues evaluated 50 consecutive salvage prostatectomy specimens after recurrent prostate cancer after radiation (19). A single cancer focus was found in 66% of patients.

The initial experience with focal cryotherapy and HIFU demonstrates a rectourethral fistula rate of 2–3%. This appears not different from whole gland cryotherapy or SBT experiences (15,16). The initial experience with focal LDR and HDR SBT on the other hand seems more encouraging. The efficacy is in line with past whole gland SBT while the toxicity rate seems much lower. Rectourethral fistula was not seen in the prospective trials by Hsu *et al.* and Murgic *et al.* (17,18). However, the numbers are small and follow-up periods relatively short.

Future questions

While whole gland therapy remains the standard in multifocal, multicentric recurrent prostate cancer after EBRT, it is hard to justify treating the whole gland in unifocal recurrences. Advancements in prostate MRI imaging has allowed accurate focal salvage therapy delivery, especially LDR and HDR SBT. However, there are many unanswered questions. What margin or volume should be treated? In the trial by Hsu, the recurrent lesion was treated with a tight margin. The whole quadrant of the prostate was treated in the trial by Murgic. In the trial by Hsu recurrences too close to the urethra or anterior rectal wall were not allowed. How close is "too close"? What would be the implications if a second recurrence were to occur close to these structures and the first recurrent focus? Would there be an overlap in SBT doses?

These questions must be answered with well-designed prospective protocols. Long-term follow-up is critical since a second, elsewhere recurrence is always possible and since GU toxicity is notoriously late. Given how difficult it was to complete the RTOG 0526, it is highly unlikely that a randomized trial comparing the different focal salvage therapies will ever be performed. However, a prospective, multi-institutional trial exploring focal LDR or HDR SBT is more feasible and is clearly the next step.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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