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Point/Counterpoint

Rebuttal to Dr. Stone

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Dr Stone has raised meritorious points regarding the treatment of intermediate-risk prostate cancer and the potential concerns of supplemental external beam radiotherapy (EBRT) (1). However, within all the arguments he posed to support the routine use of brachytherapy alone for intermediate-risk disease, there are inconsistencies. Indeed, some of his perspectives actually represent cogent reasons to support our viewpoint for adding supplemental EBRT to brachytherapy in this patient population. So for this rebuttal, let's carefully analyze Dr Stone's arguments for the use of brachytherapy alone. The following key points will be critically assessed: (*1*) benefit of further dose escalation to allow the delivery of a higher biologic effective dose (BED); (*2*) the efficacy for achieving the ''trifecta'' with brachytherapy alone, namely, low urinary toxicity and maintained sexual function with durable tumor control; (*3*) secondary malignancy risk with EBRT; and (*4*) theoretical financial burden of more aggressive therapy using supplemental EBRT.

Perhaps, unwittingly, Dr Stone is actually arguing in favor of supplemental EBRT by reinforcing the notion that further dose escalation improves tumor outcomes, and we could not agree more. As shown in our table 1 (2), when comparing series with ≥8-year outcomes, most implant alone reports have noted biochemical failure rates >20%, whereas combination therapy series have reported failure of approximately 10%. This is consistent with the data Dr Stone presented from Mount Sinai that reported that BED >200 Gy resulted in improved biochemical control compared with lower doses (3). Dr Stone had also reported that doses >220 Gy were associated with further improvements in biochemical control (4). To achieve these kind of dose levels with an implant alone, one would require an I-125 D_{90} coverage of approximately 210 Gy … now that is a hot implant (hotter than any of the D_{90}s even in his tables)! The addition of supplemental EBRT can readily achieve such high BEDs safely without resorting to excessive hot spots within the target and still provide the necessary dose coverage for extraprostatic disease.

A logical *concern* that Dr Stone brings forth is that the better tumor control with high BEDs may negate the ability to achieve the coveted ''trifecta'' of brachytherapy and result in greater risks for long-term toxicity. However, the concern for toxicity with such high BEDs with combination therapy has been evaluated in three multi-institutional prospective Phase II trials that did not even use intensity-modulated radiotherapy (IMRT) (let alone image-guided radiotherapy [IGRT]) and had wide >1.5-cm margins on the prostate for the EBRT component. The CALGB reported 0.0% acute gastrointestinal (GI) Grade ≥3 toxicity and 0.0% late GI Grade ≥3 (5)! The Radiation Therapy Oncology Group (RTOG) reported only 2.9% late Grade ≥3 GI toxicity Reference 10 (Lawton et al) Dr Stone cited multiple retrospective single institution studies depicting the concern for increased toxicity with supplemental EBRT (6, 7). Why use data with inherent biases from disparate study methodologies when it is clear from prospective multi-institutional trials that the excessive toxicity risk is exaggerated?

The *theoretical* risks Dr Stone touched on regarding secondary malignancies should be kept in the context of *absolute* risk. Data from one of the largest studies performed on over 122,000 men comparing RT to prostatectomy found that the radiation-associated second malignancy rates were 1 in 290 (8). Remember, this 0.3% absolute risk is radiotherapy (RT) compared with no RT. Dr Stone cited data demonstrating a *relative* 18% increased risk in second cancers from implant to combination therapy (4.7% to 5.7%); however, this would correlate to an *absolute* increased risk of only 0.05% when adding supplemental EBRT over implant alone!

Lastly, Dr Stone is correct that the *upfront* costs of supplemental EBRT are more expensive than implant alone. However, the Markov model he cited reported by Cooperberg et al. was driven by the immense increased toxicity with combination therapy and assumed a fourfold higher risk of acute GI toxicity and nearly twofold increase in GI late toxicity with the additional of

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supplemental EBRT (9). Based on prospective data from the RTOG and CALGB for combination therapy cited previously, these estimates are exaggerated (5, 10). Assuming a minimal increase in toxicity, and a conservative estimate of approximately 10% improvement in biochemical control with the addition of supplemental EBRT (Cooperberg estimated 12%), the costs of salvage therapy will dominate the overall costs of therapy. The estimated *annual* cost of a biochemical recurrence treated with ADT is $2566, one-time cost of salvage RT is $27,586, and salvage prostatectomy is $8547. With success rates of salvage therapy often less than 50%, coupled with the costs of increased chronic toxicity from salvage therapies, the benefit of supplemental EBRT likely outweighs any initial upfront cost saving of implant alone for patients with intermediate-risk disease.

In summary, dose escalation has a proven benefit for intermediate-risk prostate cancer. Further dose escalation appears to further enhance biochemical and local control, and this can readily be achieved with supplemental EBRT while providing the needed extraprostatic coverage for this cohort of patients. Supplemental EBRT is safe with very low rates of severe late toxicity, clinically minute increased risk of secondary radiation included malignancies, and likely comparable costs to implant alone. We agree that low volume intermediate-risk disease can be adequately treated with implant alone, yet for many patients with moderate or large volume disease, we believe that the addition of supplemental EBRT is paramount in achieving durable long-term tumor control and the most efficacious radiotherapeutic treatment intervention for these patients.

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