Salvage Brachytherapy After External-Beam Irradiation for Prostate Cancer

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Dr. Beyer has presented a thorough review of the current literature on salvage implant therapy following external-beam therapy failure. Although the review presents the available data clearly, I would characterize the data as preliminary and suspect. I would question conclusions drawn from these studies and would especially question guidelines for patient selection based on these conclusions. It will be necessary to improve staging at recurrence, improve pathology postradiation, and improve postimplant dosimetry before we can define the appropriate candidate for salvage therapy.

Key Questions
There are two practical clinical questions to ask at recurrence. First, which patients with local recurrence have a high probability of local-only recurrence with potential to metastasize? Salvage implants carry risk, albeit a justified risk if they prevent death. The risk is probably not justified if local control is the major goal of such therapy. Second, which patients with local-only recurrence but a threat of metastasis can be controlled with brachytherapy? The review implies that men likely to benefit are those with low-prostate-specific antigen, low-grade recurrences. Patients who require cure are those with a limited burden of intermediate-grade tumor or very limited burden of high-grade tumor without metastasis. Excluding those with higher-grade recurrence based on the current literature undermines the greater goal of preventing death through salvage therapy. What is needed to move beyond the preliminary data presented is a rigorous research approach. I would propose exhaustive "saturation biopsies" at recurrence, wherein multiple biopsies are obtained under anesthesia for analysis and research. This staging would allow percent-positive biopsies to be determined, and the relative grade to be determined. Although radiation atypia may make grading difficult, there are recurrent tumors with little or no radiation atypia that may be graded and may represent primary radiation resistance.[1,2] Tools of molecular pathology must be applied to address the challenge of grading and classifying recurrence postradiation and to develop consensus. Patients who develop a recurrence represent a remarkable opportunity to further our understanding of radiation resistance. Why they recur is a greater question to answer than how to treat recurrence.

Unknown Factors
After thorough definition of the extent and grade, it will be possible to define the full potential of salvage therapy. I would not exclude patients with limited intermediate- or high-grade tumors from experimental salvage therapy, because we don't know if such patients failed the salvage implant due to incurable locally extensive disease or inadequate implant coverage. Missing in the current analysis are the dose and response data necessary to determine the potential of brachytherapy following recurrence. Implant quality remains the greatest determinant of implant success.[3] It is difficult to interpret early results of implant salvage out of the context of postimplant dosimetry. Control rates with implants improved within the same practice by 20% following guidelines to ensure implant quality.[4] Even within his own study group, Dr. Beyer's early results reflect implant quality more than efficacy. Thus, it is premature to conclude that certain patients are beyond implant salvage until an exhaustive "saturation biopsy" assessment is combined with postimplant dosimetry. I would contend that a subset of patients exists with local-recurrence only and limited quantities of intermediate- to high-grade cancer, controllable with high-quality implants. This is the group with the greatest potential to benefit from implant salvage procedures.

Conclusions
Although the oft-repeated adage, "those who require therapy the most, benefit the least," applies to
the conclusion and guidelines offered by Dr. Beyer, several critical questions about the full potential of salvage brachytherapy remain unanswered. Provided such treatment is done in the context of a carefully controlled study with exhaustive local staging, accurate postimplant dosimetry, and translational laboratory research, it remains a worthy enterprise with great promise. As a standard practice for patients with low-risk recurrence and local control as a goal, it remains a highly suspect practice. I would summarize the current literature on implant salvage therapy this way: We don't know what we are treating (inadequate staging), we don't know how well we are treating (inadequate dosimetry), and we don't know why we are treating (local control vs survival). Until we know more, guidelines are misguided.

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