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Diagnosis and management of local recurrence after low-dose-rate brachytherapy

Nelson N. Stone[1,2,*], Pamela Unger[3], E. David Crawford[4], Richard G. Stock[2]

[1]*Department of Urology, The Icahn School of Medicine at Mount Sinai, New York, NY*
[2]*Department of Radiation Oncology, The Icahn School of Medicine at Mount Sinai, New York, NY*
[3]*Department of Pathology, North Shore Health System at Lenox Hill Hospital, New York, NY*
[4]*Department of Surgery, Division on Urology, The Anschutz Cancer Center, University of Colorado Health Sciences Center, Aurora, CO*

ABSTRACT

OBJECTIVES: To describe the diagnosis of local failure after prostate brachytherapy (BT) and treatment options when recurrence is present.

METHODS AND MATERIALS: Review of literature for local recurrence after prostate BT and salvage therapy was performed. A total of 6 patients with prostate-specific antigen increase were identified as local failures by transperineal mapping biopsy (TPMB) and treated with targeted focused therapy using cryoablation.

RESULTS: Local recurrence after prostate BT occurs in 2–20% and is dose dependent. The biologic effective dose greater than 200 Gy^2 is associated with a less than 2% recurrence rate. Confirmatory biopsy should include both the prostate and seminal vesicles, as prostate cancer can be found in 20% of the latter. The pathologist should be experienced in evaluating post-irradiation tissue because of the difficulty in distinguishing benign irradiated prostate from residual or recurrent tumor. Whole gland salvage, whether by prostatectomy or cryoablation, is associated with high complication rates. Focal therapy has fewer complications but accurate targeting remains a concern. Newer diagnostic and targeting modalities such as multiparametric MRI and TPMB offer improved opportunity to increase lesion identification and ablation. A TPMB approach, which incorporates new biopsy needle design and interactive targeting software, may offer the best avenue to true focused therapy.

CONCLUSION: Local recurrences after prostate BT are uncommon because of high delivered radiation dose. When present, improved lesion identification and targeting may be associated with better cancer control and lower morbidity.

Keywords: Brachytherapy; Salvage therapy; Focal therapy; Prostate biopsy

Introduction

Permanent seed implant therapy for prostate cancer is a recognized option for the successful management of this disease. Technology has evolved over the years where today it is delivered with a better degree of accuracy (1). Like all radiation treatments for prostate cancer, higher dose is associated with improved biochemical and local control (2, 3). However, given the nature of brachytherapy (BT), where the delivered dose can be substantially less than the planned dose, recurrence rates are higher than they should be (4). Poorer quality implants result in not only lower doses to the entire gland but also cold spots within the gland. Either scenario can increase the risk of local recurrence.

Local recurrence should be confirmed by biopsy and needs to include assessment of the prostate, seminal vesicles (SVs), and possibly the pelvic lymph nodes (5). Evaluation for systemic disease should also be undertaken. Once local recurrence is confirmed and suspicion for systemic disease is excluded, consideration for salvage therapy can be undertaken. The entire gland can be treated by cryoablation, re-irradiation, radical prostatectomy, and potentially

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* Corresponding author. Departments of Urology and Radiation Oncology, The Icahn School of Medicine at Mount Sinai, 350 East 72nd Street, Suite 8A, New York, NY 10021. Tel.: 845-323-1727

E-mail address: drnelsonstone@gmail.com (N.N. Stone).

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high-intensity focused ultrasound. Each of these modalities is associated with a significant degree of morbidity. Interest has been increasing to only treat the recurrent foci to limit morbidity associated with whole gland ablation. Targeted focal therapy in the salvage setting requires accurate localization of the areas of recurrence as well as the ability to ablate these sites at the time of treatment.

This manuscript will review the current data on local recurrence after permanent prostate BT as well as options available for total and focal gland ablation. A search for local recurrence after prostate BT was conducted using PubMed using "local failure after prostate brachytherapy" and 139 citations were returned and reviewed. It will also discuss the upcoming technology to diagnose and treat recurrences incorporating multiparameter MRI (mpMRI) and transperineal mapping prostate biopsy (TMPB). Reporting of data was approved by the institutional review board.

Diagnosis of local recurrence

After BT, prostate-specific antigen (PSA) slowly falls eventually reaching a nadir close to or below 0.2 ng/mL. Although the Radiation Treatment Oncology Group consensus specifies the Phoenix definition (nadir plus 2 ng/mL) for PSA failure, most brachytherapists recognize that a persistently rising PSA after nadir is a worrisome sign (6). Interpretation of a rising PSA within 3 years of therapy can be confused with a PSA bounce (7, 8). The use of neoadjuvant therapy further complicates the interpretation of PSA bounce as recovery of testosterone also results in an increase (9). Both scenarios can lead to unnecessary treatment, especially because the pathologist can misread radiation effect on prostate cancer tissue as active disease (10, 11). Before considering salvage therapy, a thorough investigation for systemic disease, which may include bone scan, CT scan, and MRI should be considered.

Pathologist role

Once biopsies are taken, an assessment by a pathologist experienced in evaluating irradiated tissue is critical. Radiation changes on the prostate can elicit profound morphologic changes. The pathologist must be aware of the patient's history, otherwise a misdiagnosis may occur. Although the stroma will be effected to some degree by the radiation, the most dramatic changes occur in the glandular tissues, whether benign or malignant. In benign glands, lobular pattern atrophy can be seen because of the vascular endothelial damage from the radiation. The radiated benign glands will have similar morphologic changes in both the basal and secretory cells; however, secretory cells are more depleted after treatment. Both cell types exhibit nuclear enlargement, which may be quite dramatic with prominent nucleoli often present. The chromatin in the enlarged nuclei may have a smudged appearance. Rare mitotic figures may be seen. Secretory cells may have Paneth cell–like metaplasia with eosinophilic cytoplasmic neurosecretory granules. The nuclear enlargement and hyperchromasia are not uniformly distributed in the gland often with nuclei showing radiation effect next to nuclei with no effect.

Immunohistochemistry such as 34beta E12, k903, and p63 will highlight basal cells in these benign glands and should be used in assessing any problem cases. Because the benign irradiated glands have some enlarged nuclei and prominent nucleoli and may have mitotic figures, these histologic features can no longer be used to assess whether the gland is benign or malignant. The overall pattern of the gland's nuclear pleomorphism and the demonstration of the presence of basal cells by immunohistochemistry will support a benign diagnosis with treatment effect (12–15).

The postradiation changes in cancer can be divided into carcinoma without radiation effect vs. those with radiation effect. Some cases will exhibit both features. If there is no radiation effect on the cancer, it will look identical to those prostate carcinomas, which have not been exposed to radiation. These postradiation cancer cases without radiation should be given a Gleason grade and score. Cancers with radiation effect can be more diagnostically challenging for the pathologist. The residual tumor may be extremely focal, thereby making assessment of abnormal patterns in glands difficult. The malignant glands, when there is a sufficient number clustered together, will still harbor an infiltrative or nonlobular arrangement. The malignant cells lining these glands may be incomplete, resulting in incomplete visualization of the cytoplasm with nuclei rimming the entire gland circumference. The nuclei are enlarged compared with the non-irradiated carcinoma but frequently are smaller in size compared with the radiated benign glands. Nucleoli are prominent but may also be smaller in size than that seen in the benign glands. Unlike the benign nuclei, which will have variation in appearance within the same gland after radiation, the malignant nuclei are monotonous in histology. The malignant glands after radiation like the non-irradiated cases have no basal cells. The basal cell immunohistochemistry as mentioned previously will continue to be negative in the postradiation cancer cases. Basal cell immunohistochemistry should be performed on any case with radiation effect to confirm the diagnosis of carcinoma. The PSA immunohistochemistry may be negative as PSA can be depleted in the malignant glands after therapy. Any carcinoma showing radiation effect should not receive a Gleason score and should just be reported as prostate carcinoma with radiation effect. In cases that demonstrate carcinoma with and without radiation effect, the carcinoma without radiation effect should be given a Gleason score and an additional sentence should mention that there is carcinoma with radiation effect. The volume of cancer on a given core should be stated as either percent of core with tumor or as a linear measurement. The biologic activity of malignant glands with radiation effect cannot be determined and cases need