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The clinical significance of persistent cancer cells on prostate biopsy after high-dose-rate brachytherapy boost for intermediate-risk prostate cancer

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ABSTRACT

PURPOSE: To evaluate the association between post-treatment biopsy results and the probability of biochemical disease-free survival (bDFS).

METHODS AND MATERIALS: Two sequential prospective clinical trials were undertaken in men with intermediate-risk prostate cancer (T1–T2 with either Gleason score 7 and prostate-specific antigen [PSA] level lower than 20 ng/mL or Gleason score 6 and PSA level of 10–20 ng/mL). All patients had high-dose-rate brachytherapy (two fractions of 10 Gy separated by 1 week or a single 15-Gy fraction) followed by external beam radiotherapy. Both study groups were followed prospectively with regular PSA readings and prostate biopsy at 2 years. Biopsies were reported as: positive = malignant cells with no or only partial radiation effect, negative = no malignant cells seen, and indeterminate = malignant cells with marked radiation effect. Biochemical failure was defined using the nadir + 2 ng/mL definition and estimated using the Kaplan–Meier curves. Fisher exact test was performed to investigate any relationships between high-dose-rate treatment and biopsy results.

RESULTS: A total of 181 patients were included in this analysis. The median followup for all patients was 6.2 years (range, 0.3–10.5). Post-treatment biopsy was performed in 111 patients of which 82 (74%) were negative, 17 (15%) indeterminate, and 12 (11%) malignant. The 5-year bDFS was 97.5%, 93.8%, and 83.3% for those with benign, indeterminate, and malignant biopsies, respectively ($p = 0.4398$). Median PSA nadir was 0.08 ng/mL (range, 0.01–3.63), with no difference in PSA change over time by treatment ($p = 0.9953$) or biopsy result ($p = 0.4398$)

CONCLUSIONS: Routine biopsy at 2 years was not able to reliably predict which patients would ultimately fail as even those with a positive biopsy had a long-term bDFS higher than 80%.

Keywords: HDR brachytherapy; Prostate; Biochemical outcomes; Biopsy

Introduction

Prostate brachytherapy delivers a highly conformal radiation dose to the prostate with a sharp dose drop-off, thereby minimizing the dose to surrounding normal tissue. Brachytherapy treatments can be delivered by implanting permanent seeds, which decay in activity over time (low dose-rate brachytherapy) or by temporarily inserting a stepping radioactive source through afterloading catheters (high-dose-rate [HDR] brachytherapy). Long-term published data show that both types of brachytherapy treatments are associated with high biochemical control rates and low rates of long-term morbidities (1–3). Although brachytherapy monotherapy is commonly used for patients with low-risk disease, brachytherapy is commonly used as a boost in combination with external beam radiotherapy (EBRT) for patients with intermediate- and high-risk disease.

Prostate cancer control after radiotherapy treatment is assessed using serial serum prostate-specific antigen (PSA) measurements (4). A persistently rising post-treatment PSA is considered a treatment failure and generally precedes clinical recurrence, either local or systemic. Post-treatment

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biopsy provides another measure of treatment success and provides direct information on the local effect of treatment on the prostate but is uncomfortable for the patient, uses health care resources, and is associated with a risk of complications (5, 6). In addition, the significance of prostate biopsy results in the post-radiotherapy setting remains uncertain as the interpretation of these pathological data can vary and pathologic findings can vary with time after treatment (7). We postulated that pathological findings on biopsy 2 years after high-dose radiotherapy may provide an early indicator of subsequent treatment failure.

As the clinical significance of post-treatment biopsies remains unclear (5, 8, 9), particularly in the era of high dose radiotherapy, the purpose of this work was to investigate the clinical significance of persistent cancer cells on biopsy 2 years after treatment and to determine the association between post-treatment biopsy result and biochemical disease-free survival (bDFS) in prostate cancer patients treated with HDR brachytherapy boost.

Methods and materials

Patient population

As previously described (10), two sequential prospective clinical trials were undertaken in men with intermediate-risk prostate cancer (clinical stage T1–T2 with either Gleason score 7 and PSA level lower than 20 ng/mL or Gleason score 6 and PSA level of 10–20 ng/mL). No androgen deprivation therapy was allowed, and prostate volume was limited to 60 cc.

Radiotherapy treatments and followup

All patients had HDR brachytherapy, either two fractions of 10 Gy each separated by 1 week apart, or 15 Gy as a single fraction, followed by a short course of EBRT, either 45 Gy in 25 fractions or 37.5 Gy in 15 fractions, respectively. Transperineal catheters were inserted under transrectal ultrasound guidance, and planning was performed using CT-based inverse optimization. EBRT was delivered using three-dimensional conformal radiotherapy to the prostate and base of seminal vesicles. Both study groups were followed prospectively with regular PSA readings. A protocol mandated biopsy was performed 2 years post-treatment.

Biopsy interpretation

In our center, postradiation prostate biopsies are consistently reported using one of the following categories, namely negative for malignancy with radiation effects, adenocarcinoma showing marked radiation effects, adenocarcinoma showing partial (mild to moderate) radiation effects, and adenocarcinoma without radiation effect.

1. Negative for malignancy with radiation effects: Biopsies in this category are characterized by benign, often atrophic glands with enlarged hyperchromatic or smudgy nuclei that often appear more atypical than malignant glands (Fig. 1a).
2. Adenocarcinoma showing marked radiation effects: Biopsies in this category are characterized by small, sometimes poorly formed atypical glands or single atypical cells, often with foamy or vacuolated cytoplasm. Prominent nucleoli may or may not be present. Luminal features of malignancy such as crystalloids may be retained. The atypical glands or cells may be deceptively bland looking and difficult to distinguish from blood vessels or histiocytes, sometimes necessitating the use of immunohistochemical markers for diagnosis. Tumors in this category cannot be accurately graded because their architecture may artifactually resemble Gleason patterns 4 and/or 5 (Fig. 1b).
3. Adenocarcinoma showing partial (mild to moderate) radiation effects: Biopsies in this category are characterized by atypical glands having some of the usual features of prostatic adenocarcinoma but with an appearance intermediate between Categories 2 and 4. In our experience, they comprise the least common category and usually cannot be accurately graded (Fig. 1c).
4. Adenocarcinoma without radiation effect: Biopsies in this category show the characteristic histologic features of prostatic adenocarcinoma (including loss of the basal layer, prominent nucleoli, and an infiltrative pattern) and are routinely given a Gleason score (Fig. 1d).

In our study, biopsies were considered indeterminate if they showed residual tumor with marked radiation effects. Biopsies were considered positive if they showed no or only partial (mild to moderate) radiation effects. Some biopsies showed a mixture of different features (adenocarcinoma with and without radiation effects) within the same biopsy core or different features in different cores. These were also considered positive.

Statistical analysis

A general linear mixed model of PSA over time was used to evaluate PSA changes by treatment groups. Natural log-transformation was applied for normalizing the PSA distributions. Biochemical failure was defined using the nadir + 2 definition. The bDFS (in years), was calculated from radiation therapy start date until the failure date (for those patients with biochemical failure) or until the last followup date (for those patients without failure), and estimated using Kaplan–Meier curves with 95% confidence interval (CI). To compare biochemical failure-free survival curves among patients with different biopsies, log-rank test was conducted. Biopsies were grouped as follows: positive = malignant cells with no or only partial (mild) radiation effect, negative = no malignant cells seen, and