Autopsy Evaluation of a Prostate Cancer Case Treated with Brachytherapy

ANNA SHAPIRO¹, OLEG SHAPIRO², NICOLAS B. DELONGCHAMPS²,⁴, JEFFREY A. BOGART¹, GABRIEL P. HAAS² and GUSTAVO DE LA ROSA³

Departments of ¹Radiation Oncology, ²Urology, and ³Pathology, Upstate Medical University, Syracuse, NY, U.S.A.; ⁴Department of Urology, Cochin Hospital, René Descartes University, Paris, France

Abstract. Morphological analyses of prostate specimens after brachytherapy are rare and present a challenge to the pathologist due to an inherent difficulty in determining the difference between dying glands and surviving cancer cells. We have taken the opportunity to analyze an autopsy specimen in an attempt to set criteria by which one can analyze post-radiation therapy prostate biopsies. The patient had undergone brachytherapy and experienced a clinical complete response based on undetectable prostate-specific antigen and died of unrelated disease. Immunohistochemical studies were performed with the following antibodies: p63, P504S/AMACR and high molecular weight cytokeratin (HMWCK). Using a combination of molecular staining techniques, we were able to conclude that there were no viable tumor cells present in the specimen. The requirement to use various techniques to come to this conclusion demonstrates inherent difficulty in differentiating viable tumor cells from those that may appear viable but have been affected by ionizing radiation and will be unable to undergo cell division. It is crucial that this uncertainty is kept in mind in making further management decisions in patients who have undergone radiation therapy and follow-up biopsy of the prostate gland.

Radiation therapy is the treatment of choice for many patients with prostate carcinoma. Prostate brachytherapy represents one of the oldest techniques of using radiation therapy to treat prostate cancer. Over the past 20 years, there have been major improvements in the techniques used in prostate brachytherapy, including the introduction of new radioactive isotopes, new seed distribution techniques with the goal of minimizing side-effects, new afterloading techniques, and an improved understanding of the radiobiology associated with differing dose rates. Morphological analyses of prostate specimens after brachytherapy are rare as only a few patients with local failure undergo prostatectomy after brachytherapy. Needle biopsies of the prostate are carried out for patients with a rising prostate-specific antigen (PSA) and are not representative of those with good therapeutic results. We explore a unique opportunity to evaluate a cadaver prostate specimen following prostate seed implantation. The effect of brachytherapy on the histology of prostate was analyzed in a patient who experienced a clinically complete response based on undetectable PSA and died of unrelated disease (myocardial infarction).

Case Report

A 73-year-old Caucasian man presented with 4-year history of elevated PSA and a prior prostate biopsy revealing large amount of chronic inflammation. He was treated with a course of Levaquin with a repeat PSA of 14.7 ng/ml, representing a rise over previous results of 12.4 ng/ml 9 months prior. Digital rectal examination revealed an enlarged gland without nodularity. A transrectal ultrasound was performed at the time of the biopsy revealing the prostate to be 37 g, with a large hypoechoic region seen in the posterior peripheral zone measuring 2.8 cm in greatest dimension. There was another lesion seen in the mid-peripheral zone measuring 7 mm. Biopsy revealed adenocarcinoma, Gleason score 6 (3+3), involving the right base (2 of 2 cores representing 15-20% of the specimen) and left apex (1 of 2 cores and 10% of tissue involved by tumor) without evidence of perineural invasion. The patient did not complain of any urinary symptoms. Metastatic workup included a bone scan, which did not reveal any evidence of osseous metastases.

Treatment plan. The patient was evaluated in the Genitourinary Multidisciplinary Oncology Clinic and was found to be a poor candidate for radical prostatectomy due to significant coronary artery disease. After reviewing all
treatment options, brachytherapy was decided as a definitive treatment modality. The patient was treated with 103Pd prostate brachytherapy using 104 sources of 1.64 mCi each resulting in a total activity of 170.6 mCi. Eighty-three % of the prostate was treated to the prescription dose of 115 Gy. The D90 (dose delivered to 90% of the prostate) was 105 Gy. The isodosed distribution is demonstrated in Figure 1.

Follow-up. The patient tolerated treatment well and recovered from the procedure uneventfully. His first postoperative PSA two months following the procedure was 1.44 ng/ml, representing marked diminution from the pre-treatment PSA level. During the following year, the serum PSA rose to 3.35 ng/ml and then returned to 1.4 ng/ml 16 months after treatment. His last PSA, drawn at 36 months follow-up, was 1.0 ng/ml. The patient was initially managed with Flomax for irritative urinary symptoms of frequency and urgency, however, the medication was discontinued later. The patient suffered a severe myocardial infarction leading to his death. An autopsy was performed and the prostate was removed en bloc and examined histologically.

Pathologic findings. After retrieval of the prostate gland during the autopsy, the gland was immediately fixed in 10% formalin. All excess tissue around the capsule was removed from the gland before measurements were taken. The gland measured 5.0 cm in length, 4.0 cm in width and 3.5 cm in thickness. Its weight was 35 g and its volume, measured using a graduated 100 ml-cylinder with water, was 32 ml. The gland was then sectioned perpendicular to the posterior plane at 0.4 cm intervals (Figure 2), but sectioning was difficult because of the innumerable number of seeds present throughout the gland. The seeds were carefully removed and all defects inked with India ink to highlight their presence for future microscopic examination. While distorted by the defects created by the seeds, the cut surface of gland was smooth and uniform without nodules or any focal lesions (Figure 3). The 0.4 cm-thick sections were put in individual, numbered cloth bags for paraffin embedding and then sectioned to produce 5-μm whole-mount slides that were stained with hematoxylin and eosin.

The entire prostate gland was microscopically examined. At scanning power, all sections were characterized by markedly distorted glandular architecture, round to oval seed defects, extensive fibrosis and scant glandular elements (Figure 4A). The defects were not lined by epithelium and most were surrounded by a rim of hyalinized fibrous tissue with an outer layer of atrophic glands and hyalinized blood vessels (Figure 4B). This zonation pattern was seen throughout the gland. The glandular acini were distorted and markedly atrophic, but preserved some of their lobular architecture. They had a double cell layer with smaller, basal and flattened cells and a second layer of large acinar cells with moderate to severe atypia (Figure 5A and 5B). The acinar cells had large and hyperchromatic nuclei with irregular nuclear contours, occasional prominent nucleoli, and rare intranuclear inclusions. Most cells had relatively abundant eosinophilic cytoplasm with occasional vacuoles. Some of the glands exhibited squamous metaplasia (Figure 4C). The blood vessels had very prominent and swollen endothelial cells (Figure 4D). In some vessels, the endothelial cells had mild to moderate atypia and in others, there was extensive hyalinization of the media. While the preservation of a lobular pattern and the presence of a double cell layer were mostly in keeping with radiation therapy-related atypia, it was difficult to exclude the possibility of small foci of residual carcinoma.
Immunohistochemical studies were performed on a Biotek Solutions TechMate 1000 automated immunostainer (Tucson, AZ, USA) using the standard avidin-biotin peroxidase technique with the following antibodies: p63 (Neomarkers, Fremont, CA, USA), P504S /AMACR (Biocare Medical, Concord, CA, USA), high molecular weight cytokeratin (HMWCK) clone 34βE12 (Dako, Carpinteria, CA, USA). There was strong and diffuse staining with HMWCK of the basal cells in all glands (Figures 5C and 5D), but no staining with p63. No cytoplasmic staining was seen with P504S/AMACR. These findings did not support the presence of any residual carcinoma and were entirely consistent with radiation-induced changes.

**Discussion**

Common management for clinically localized prostate cancer include watchful waiting, radical prostatectomy, open or laparoscopic, with or without robotic assistance, and radiation therapy, either using external beam radiation therapy, brachytherapy or a combination of the two.

Many patients feel very strongly about having surgery, driven by the instant gratification, or the opportunity to physically eliminate the tumor. While radiation therapy has shown long-term outcomes similar to surgical prostatectomy (1, 2), we have limited tools that allow us to monitor tumor response. PSA is a valuable marker of tumor activity and our understanding and ability to use it continues to evolve as we investigate the value of PSA kinetics (3).

Evaluation of local tumor response and accurate diagnosis of persistent cancer are critical in assessing the efficacy of radiation therapy (RT) for prostate adenocarcinoma. Despite the fact that RT of the prostate is a commonly used procedure, there is little information regarding the degree and duration of the RT-induced changes in the prostate gland (4). Much of what we know today is derived from post-RT prostate biopsy samples (5, 6, 7-12), although the prognostic significance of these remains uncertain and their use to evaluate disease control is controversial. The sample size is small and it is therefore impossible to comprehensively describe the architectural and other changes as they relate to dose distribution within the gland. This limitation can be overcome by using post-radiation prostatectomy specimens to learn about the degree and duration of radiation-induced change. This, however, can be problematic since there are limited numbers of these procedures performed due to technical difficulty and adverse side-effects. All of these samples are taken from patients who have experienced radiation treatment failures by definition and therefore are not representative of usual radiation response rates. They may often demonstrate viable tumor cells along with radiation-induced stromal atypia.

There have been a number of attempts published in the literature to describe the morphological changes induced by RT on prostate carcinoma as well as on benign glandular tissue (4, 7, 12). Crook et al. (13) suggested a scoring system of radiation effect, a modification of Dhom and Degro (14). There are two types of morphological changes described. The first is represented by a heterogeneous tumoral focus, with significant differences between the minimal and marked RT effect score. The second is represented by a homogeneous focus, when the marked RT effect score is the same as the minimal effect score. The degree of the nuclear and cytoplasmic changes is graded and the grades for the two types of changes make up the final radiation effect score that ranges from 0-6.
In light of this inherent difficulty in determining the difference between dying glands and surviving cancer cells, we have taken this unique opportunity to analyze an autopsy specimen and attempt to set the standard to which one can compare the material from post-prostatectomy specimens and post RT biopsies. With the aid of immunohistochemical studies, using basal cell marker and tumor markers, we were able to determine the lack of viable tumor cells present in the specimen. The use of ancillary histological techniques highlights the inherent difficulty in differentiating viable tumor cells from those that may appear viable but are affected by ionizing radiation and unable to undergo cell division on the basis of routine histology alone. It is crucial that this uncertainty is kept in mind in making further management decisions in patients who have undergone radiation therapy and follow-up biopsy of the prostate gland. This case, while it may be a single case report, demonstrates the effectiveness of brachytherapy, that it is possible to eliminate all viable tumor and provides an opportunity to correlate treatment planning, implant dosimetry and final histological response. This case illustrates the histological response and effectiveness of brachytherapy in prostate cancer.

Acknowledgements

This study was supported by grants CA097751 from National Cancer Institute and AG021389 from National Institute on Aging, USA.

References
