Differences in the Time Course of Metabolic Response of Prostate Cancer to EBRT versus Brachytherapy

J. Kurhanewicz[1], M. G. Swanson[1], B. Pickett[2], M. Roach[2], D. B. Vigneron[1]
[1]Radiology, UCSF, San Francisco, CA, United States, [2]Radiation Oncology, UCSF, San Francisco, CA, United States

Introduction

The serum prostate-specific antigen (PSA) test is the most commonly used method of confirming resolution of prostate cancer after radiation therapy. However, the use of PSA testing is not ideal since PSA is not specific for the local recurrence of prostate cancer and it may take > 4 years for PSA to reach its nadir. Preliminary studies suggest that combined magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI) can provide a more direct measure of residual/recurrent prostate cancer after radiation therapy, and a time course of metabolic response that may yield important mechanistic and prognostic information. Early after radiation therapy, prostatic citrate and polyamine levels are reduced or lost, followed by a slower decrease of choline and creatine, eventually resulting in an absence of all metabolism (metabolic atrophy) which has been associated with effective therapy (1,2). It has also been demonstrated that residual prostate cancer after radiation therapy can be metabolically identified based on the presence of 3 or more voxels with elevated choline to creatine ratios (Cho/Cr > 1.5) with an overall accuracy of ≈ 80% (3). The goal of this study was to investigate differences in the time course of metabolic response of prostate cancer to external beam radiation therapy (EBRT) and Brachytherapy and correlate these differences with radiation dose and changes in serum prostate specific antigen levels (PSA).

Methods

Sixty-eight biopsy proven prostate cancer patients were studied prior to and serially after receiving EBRT (N=29) and ^{125}I Brachytherapy (N=39) as their sole therapy. There was no significant difference in the pre-therapy Gleason score, clinical stage, or serum PSA values between the two patient cohorts. 3-D MRSI data were acquired using a water and lipid suppressed, double-spin echo PRESS sequence utilizing high bandwidth spectral-spatial 180º pulses and very selective outer voxel suppression pulses. Axial T2 weighted images were used to graphically select an oblique PRESS volume encompassing the prostate, and this volume was phase encoded to produce three-dimensional arrays of 0.3cc proton spectra. Radiation dose to the prostate, time to PSA nadir, the presence of residual metabolic abnormalities (3 or more voxels having Cho/Cr ≥ 1.5) and time to complete metabolic atrophy (no metabolites having S/N ≥ 5 to 1) were measured and compared between the EBRT and Brachytherapy patient cohorts.

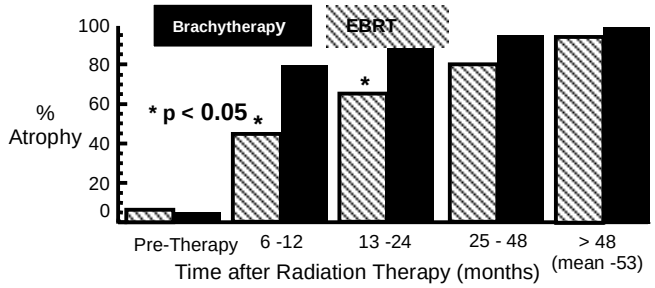

Figure 1. The % of the prostate demonstrating metabolic atrophy on MRSI prior to and serially following EBRT and

Results

The mean prescribed minimal radiation dose to the prostate for ^{125}I brachytherapy (144 Gy) was much higher than that for EBRT (74-81 Gy). Brachytherapy was also associated with an earlier more dramatic decrease in prostate metabolism than EBRT resulting in an significantly larger % of the prostate demonstrating metabolic atrophy at the 6-12 and 13-24 month time points (Figure 1). Moreover, the amount of residual metabolism was higher for EBRT at all time points, but the difference was small at the >48 month time point. There was also a significant ($p<0.05$) difference in the amount of residual metabolic abnormality observed after EBRT (14% of patients) as compared to Brachytherapy (only 4% of the patients). In general the decrease in PSA levels over time after Brachytherapy and EBRT (Pre-therapy - 6.6 ± 2 and 6.9 ± 2.4 ng/ml; 6-12 months -1.7 ± 3 and 2.8 ± 4 ng/ml; 25-48 months -1.0 ± 2.1 and 1.3 ng/ml; > 48 months – 0.6 ± 1 and 0.7 ± 1.5, respectively) correlated with increased metabolic atrophy (Figure 1). However, there was no significant difference in the PSA of patients with and without detectable metabolism. Additionally, in 22% of the post radiation studies (12% after Brachytherapy and 10% after EBRT), there was a significant transient increase in PSA (mean 0.3 to 3.8 ng/ml) prior to reaching a PSA nadir after radiation therapy, and this blip in PSA was associated with a decrease in metabolism rather than an increase in metabolism. The PSA nadir was also reached significantly ($p <0.05$) earlier for Brachytherapy (41.8 months) as compared to EBRT (49.9 months), and for patients attaining complete metabolic atrophy of the prostate, time to complete metabolic atrophy was significantly ($p<0.05$) earlier than the PSA nadir (30.2 months for PPI and 39.5 months for EBRT, respectively).

Discussion and Conclusions

Brachytherapy provided a much higher radiation dose to the prostate than EBRT resulting in an earlier and more dramatic reduction in both prostate metabolism and lower serum PSA levels. However, at later time points differences in residual metabolism and PSA after Brachytherapy and EBRT were not significantly different and 10 year clinical outcomes are necessary to determine if Brachytherapy provides more effective local control of disease. In general, serum PSA levels paralleled reductions in prostate metabolism; however PSA levels did not accurately reflect the amount of residual metabolism present in individual patients. This was demonstrated by the fact that the amount of residual metabolism within the prostate after either radiation therapy did not correlate with serum PSA. Transient rises in PSA after radiation therapy also cause patients and their physicians great concern but have not been linked with poor patient outcomes. In this study metabolism decreased during these transient rises in PSA and therefore MRSI may help in assessing whether rises in PSA are truly due to local cancer recurrence. This study also suggests that metabolic atrophy may compliment PSA nadir after as a measure of therapeutic effectiveness, but again 10 year clinical outcomes are necessary to confirm these results.

References
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