Risk factors for PSA bounce following radiotherapy: outcomes from a multi-modal therapy analysis

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Introduction: *To identify risk factors for PSA bounce (PSAb) and compare characteristics of prostate cancer patients treated with brachytherapy and external beam radiotherapy (EBRT).*

Materials and methods: *We identified 362 patients treated for low risk prostate adenocarcinoma (D'Amico criteria) with a follow up time of at least 36 months. Patients received either: 1) EBRT 76 Gy in 38 fractions (n = 58); 2) hypofractionated EBRT, 45 Gy in 9 once-weekly fractions (n = 74); 3) seed brachytherapy (n = 230). PSAb was defined as a rise ≥ 0.2 ng/mL with subsequent return to baseline within the first 3 years after treatment. Univariate and multivariate logistic regression models were estimated to assess the association between clinical factors and occurrence of PSAb.*

Results: *There was no significant difference between treatment groups (p = 0.349), with an overall PSAb rate of 28.5%. Upon univariate analysis, the following were predictive of a lower PSAb rate: older age (OR = 0.96), higher PSA at diagnosis (OR = 0.87), more positive biopsy cores (OR = 0.98), and a higher Cancer of the Prostate Risk Assessment (CAPRA) score (CAPRA of 3 versus 1: OR = 0.33). Multivariate analysis confirmed the significance of fewer positive biopsy cores (OR = 0.99) and a lower CAPRA score (CAPRA 3 versus 1: OR = 0.34). These factors also predicted a shorter time to first PSAb.*

Conclusions: *We found comparable rates of PSAb after different regimens of radiotherapy. We hypothesize that it results from late damage to healthy prostatic tissue. This idea is supported by the fact that we found that clinical factors indicative of a lower tumor burden were predictive of a PSAb.*

Key Words: brachytherapy, prostate cancer, CAPRA, PSA bounce, external beam radiotherapy

Introduction

PSA values following radiotherapy for localized prostate cancer are known to decrease slowly and to occasionally rise temporarily. This PSA bounce (PSAb) effect can induce stress and provoke unnecessary investigations. Despite its frequent occurrence and numerous investigations into its etiology, no clear pathophysiological explanation for PSAb exists. Similarly, there are no consistent guidelines on how to determine whether PSAb is of benign physiological nature or represents early biochemical failure.[1-3] The ability to identify men at higher risk for a PSAb following radiotherapy would allow physicians to preventively counsel patients, thus reducing stress and unnecessary supplemental studies in relation to this phenomenon.

Previous reports have been consistent in demonstrating that younger age predisposes patients to PSAb.[3-10] However, there is some contradiction and lack of reproducibility in the literature as to the predictive significance of other factors.

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While PSAb has been well described following brachytherapy, there is a paucity of data on its frequency following normo-fractionated external beam radiotherapy (EBRT).[1,6] Only recently has the PSAb been described in patients receiving hypofractionated EBRT.[11] The frequency of PSAb (defnied as a rise ≥ 0.2 ng/mL) in the literature varies between 36% and 50% after low dose-rate (LDR) brachytherapy.[4,5] It has been suggested that PSAb is more frequent following seed LDR brachytherapy than external beam radiotherapy (EBRT),[6] but most data pertaining to PSAb after EBRT has been reported using a definition of a rise of 0.4 ng/mL or higher.[1] To our knowledge, no study has compared the occurrence rates between various radiation treatment regimens in men with hormone-naïve, localized prostate cancer at a single institution.

As such, the current study compares the incidence of a PSAb among three different forms of radiotherapy and evaluates potential risk factors for a PSAb in patients treated with standard EBRT, a hypofractionated EBRT protocol, or standard seed brachytherapy.

Materials and methods

Patient selection

We identified 362 patients in our institutional database with low risk prostate adenocarcinoma with a follow up time of at least 36 months. We chose to restrict our analysis to the first 3 years because of the similar number of follow up visits between the different treatments and because most PSAb occur within this time.

According to D'Amico stratification, low risk disease was defined as PSA lower than 10 ng/mL, Gleason 6 or less, and clinical stage T1a-T2a. Patients were treated with one of the following three modalities: 1) standard fractionation EBRT, 76 Gy in 38 fractions of 2 Gy (n = 58); 2) hypofractionated EBRT, 45 Gy in 9 once-weekly fractions (n = 74), in an in-house phase II prospective trial; 3) seed brachytherapy, prescribed dose 144 Gy (n = 234) with ^{125}I seeds. Seed activity was chosen in accordance with prostate volume. Mean dose to 90% of the prostate volume (D90) was 158 Gy (SD 27.9).

As most low risk prostate cancer patients are routinely offered the choice between brachytherapy and EBRT, the treatment received was largely based on patient preference.

Patients who received neoadjuvant or adjuvant androgen deprivation therapy were excluded.

Post-treatment monitoring aimed for a PSA test every 3 to 4 months for the first 2 years, and biannually thereafter.

Data collection

PSA data was collected from patient files. Approval for this study was obtained from the ethics committee at the institutional review board.

Statistical analysis

The primary endpoint was the occurrence of a bounce, which was defined as a PSA rise of ≥ 0.2 ng/mL with subsequent return to baseline or lower, within the first 3 years after the end of treatment. Univariate and multivariate logistic regression models were used to assess the association between clinical factors and occurrence of PSAb, as well as time to first PSAb, with control for the number of PSA readings obtained within 3 years of treatment. A p value < 0.05 was considered to be statistically significant. The statistical program « R » Vienna, Austria was used for all data analysis.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. The mean age in our cohort was 65.5 years (SD 6.3). Patients who had brachytherapy were slightly younger (median age of 64.2) than men in undergoing standard EBRT (median age 66.7) or hypofractionated EBRT (median age 68.6), (p < 0.01).

Predictive factors for the occurrence of a bounce

A PSAb occurred in 28.5% of all patients, Table 2. A second PSAb occurred in 13 patients (3.6% of the entire cohort). Median PSAb amplitude was 0.60 ng/mL in the hypofractionation group, 0.38 ng/mL in the standard EBRT group, and 0.64 ng/mL in the brachytherapy group.

Univariate regression results, which are summarized in Table 3, indicated that the following factors were found to be predictive of a lower PSAb occurrence: older age (p = 0.019), higher PSA at diagnosis (p = 0.037), more positive biopsy cores (p = 0.011), and a higher Cancer of the Prostate Risk Assessment (CAPRA) score, which accounts for PSA level, Gleason score, clinical stage, percentage of positive biopsy cores, and age (CAPRA of 3 versus 1: p = 0.005). A CAPRA score of one is indicative of a lower tumor burden than a score of three. To clarify, values cited are for increments of one, meaning 1 year older, 1 ng/mL higher, or 1% more positive biopsies.

On multivariate analysis, only more positive biopsy cores (OR = 0.99, 95% CI 0.97-1.00, p = 0.039) was correlated to a lower rate PSAb. In a separate multivariate model grouping all factors indicative of tumor load together in the CAPRA score, a lower

TABLE 1. **Patient characteristics. Results in mean (standard deviation) if not stated otherwise**

	All patients (n = 362)	Hypofractionated EBRT (n = 74)	Standard EBRT (n = 58)	Brachytherapy (n = 230)	p value*
Age	65.5 (6.3)	68.6 (5.5)	66.7 (5.7)	64.2 (6.3)	< 0.001
PSA at diagnosis	5.7 (1.9)	6.0 (2.0)	5.9 (2.1)	5.5 (1.8)	0.139
T1	257 (71%)	55 (74.3%)	35 (60.3%)	167 (72.6%)	0.143
% positive cores	35.2 (20.2)	38.7 (21.7)	34.3 (21.6)	34.4 (19.3)	0.274
CAPRA %					0.064
1	136 (37.6%)	17 (23.0%)	22 (37.9%)	97 (42.2%)	
2	154 (42.5%)	40 (54.1%)	25 (43.1%)	89 (38.7%)	
3	62 (17.1%)	14 (18.9%)	9 (15.5%)	39 (17.0%)	
NA	10 (2.8%)	3 (4.0%)	2 (3.4%)	5 (2.2%)	

EBRT = external beam radiotherapy; CAPRA = Cancer of the Prostate Risk Assessment
American Joint Committee on Cancer (AJCC) staging 7th edition
*ANOVA, Kruskal-Wallis test or chi-square test

CAPRA score was associated with a higher risk of PSAb (CAPRA 3 versus 1: OR = 0.34, 95% CI 0.15-0.73, p = 0.007).

There was no difference in occurrence between treatment groups on multivariate analysis (hypofractionated versus standard EBRT: OR = 0.66, 95% CI 0.26-1.75, p = 0.403; brachytherapy versus standard EBRT: OR = 0.85, CI 95% 0.39-1.91, p = 0.680).

We then performed an additional analysis in order to identify factors associated with a shorter time to first PSAb. On univariate analysis, these were, once again, younger age (HR = 0.97, 95% CI 0.94-1.00, p = 0.023), PSA at diagnosis (HR = 0.90, 95% CI 0.81-0.99, p = 0.033), fewer positive biopsy cores (HR = 0.99, 95% CI 0.98-1.00, p = 0.014), and a lower CAPRA score (CAPRA 3 versus 1: HR = 0.42, 95% CI 0.22-0.81, p = 0.010). On multivariate analysis, with treatment groups in strata, the proportion of positive biopsy cores remained significant (HR = 0.99, 95% CI 0.98-1.00, p = 0.031), as did, in a separate model, the CAPRA score (CAPRA 3 versus 1: HR = 0.43, 95% CI 0.22-0.83, p = 0.011).

Because patients in the hypofractionated EBRT were part of a phase II trial, they had more frequent PSA measurements. Therefore, to validate our analysis, we selected only patients who had a PSA test at least twice a year every single year for the first 3 years. A total of 213 of our 362 patients met this requirement. This repeat multivariate analysis confirmed the importance of the CAPRA score (CAPRA 3 versus 1: OR = 0.26, 95% CI 0.09-0.67, p = 0.08) as predictive of PSAb, and additionally identified younger age (OR = 0.94, 95% CI 0.90-0.98, p = 0.009) as being associated with a higher PSAb risk. The percentage of positive biopsy cores no longer appeared significant (OR = 0.99 95% CI 0.97-1.00 p = 0.093). Furthermore, lower PSA at diagnosis was statistically significant in predicting a higher risk for PSAb (OR = 0.78, 95% CI 0.66-0.92, p = 0.003).

Biochemical failure and occurrence of bounce

There were three biochemical failures in the hypofractionation group (4.1%), three in the standard EBRT group (5.1%), and 12 in the larger brachytherapy

TABLE 2 . **Occurrence of PSA bounce (PSAb) within different treatment groups**

	Hypofractionated EBRT (n = 74)	Standard EBRT (n = 58)	Brachytherapy (n = 230)
Total # of PSAb	31.1%	20.7%	29.6%
1 PSAb	25.7%	15.5%	27%
2 separate PSAb	5.4%	5.2%	2.6%

EBRT = external beam radiotherapy

TABLE 3. **Univariate and multivariate regression analysis for factors predictive of the occurrence of a bounce (within 3 years of treatment)**

Variable	Univariate analysis Odds ratio (95% CI)	p value	Multivariate analysis Odds ratio (95% CI)	p value
Age	0.96 (0.92-0.99)	0.019	0.97 (0.93-1.01)	0.100
T2a (versus T1)	0.64 (0.36-1.11)	0.120	0.68 (0.38-1.22)	0.204
PSA at diagnosis	0.87 (0.76-0.99)	0.037	0.88 (0.77-1.01)	0.063
Positive cores	0.98 (0.97-1.00)	0.011	0.99 (0.97-1.00)	0.039
Brachytherapy*			0.85 (0.39-1.91)	0.680
Hypofractionated EBRT*			0.66 (0.26-1.75)	0.403
CAPRA 2**	0.66 (0.39-1.13)	0.130	0.70 (0.41-1.20)	0.193
CAPRA 3**	0.33 (0.15-0.70)	0.005	0.34 (0.15-0.73)	0.007

EBRT = external beam radiotherapy; CAPRA = Cancer of the Prostate Risk Assessment
*versus standard EBRT
**versus CAPRA 1

group (5.1%). Due to this small number of cases, we were unable to conduct statistical analyses of the occurrence of a biochemical failure in relation to that of a PSAb. However, no biochemical failure occurred in patients having previously experienced a PSAb.

Discussion

In comparing different treatment strategies in a relatively homogeneous population of patients with low risk cancer, we were aiming to identify predictive factors of a PSAb. We chose the cutoff value of 0.2 ng/mL, as it is most commonly used in the literature.[2,4-8] First, we found no statistically significant difference in the occurrence of PSAb between different regimens of treatment. The overall PSAb occurrence was 28.5%, which is on the lower end of commonly reported values[4,5] after brachytherapy. If we choose to think of a PSAb as a late response of healthy tissues to radiation injury, it should come as no surprise that no difference was found between our treatment groups. All patients included in this study were low risk, therefore one could assume that they had an overall comparable, small volume of prostate cancer of lower aggressiveness.

We found that characteristics reflecting a lower tumor burden were predictive of PSAb occurrence. Younger patients, as well as patients with fewer positive biopsy cores and lower PSA at diagnosis had a higher occurrence of PSAb. A lower CAPRA score was also predictive of a PSAb. These findings are consistent with the theory that the PSAb is caused by late radiation damage to healthy prostatic tissue.[9] If this is the case, one would assume that though a similar phenomenon may be occurring in the normal tissue of a patient with intermediate or high risk prostate cancer, the PSA rise attributable to a PSAb would be hidden by the concurrent decrease in PSA secretion by the tumor cells owing to treatment response. In other words, lower PSA at diagnosis 'allows' the observation of late normal tissue damage. On the other hand, T-stage (T2 versus T1) as an indicator of larger tumor volume, was not statistically significant.

Further, because the incidence of PSAb was similar for all three treatment groups, we believe that it is less likely that the traumatic nature of seed implantation is responsible for the PSAb. We were able to confirm, on univariate analysis, that younger age is predictive of PSAb occurrence and a shorter time to first PSAb. This is the most commonly reported risk factor associated with the occurrence of a bounce.[3-10] Other reported patient and disease characteristics are T-stage (though correlations have been made with both lower and higher stage),[6,7] larger prostate volume,[8] a large transition zone volume,[9] low BMI,[12] and low PSA velocity before implantation.[9] Treatment characteristics that have been linked to higher PSAb occurrence in patients treated with brachytherapy include iodine 125 versus palladium 103[9] and low dose rate versus high dose rate.[6] We did not evaluate the predictive value of prostate size, as this value was not comparable between treatment groups: in brachytherapy patients, it would be obtained from either a preoperative echography or a

postoperative control scan, which are not comparable to a pretreatment scan in EBRT patients due to the swelling factor or the imaging technique.

There are some drawbacks in our study. We considered the possibility that the number of patients in the standard fractionation EBRT group was insufficient, or that the pattern of missing PSA values may have falsely led to a non-significant result. However, as brachytherapy patients were more tightly followed, if any PSAb were missed, they were more likely to have occurred in the EBRT cohort, such that in reality the PSAb values may be more similar between treatment groups than reported in this study. Furthermore, as the brachytherapy cohort was on average younger, and this is commonly found to lead to more PSAb, this should have caused a bias that would amplify the true rate of PSAb in brachytherapy and cause a significant difference between treatment groups. Interestingly, the rate of PSAb after stereotactic body radiation therapy (SBRT) in prostate cancer for patients treated at the Winthrop-University Hospital in New York has recently been published.[11] The authors also used a definition of 0.2 ng/mL, which yielded a PSAb rate of 28%, which is similar to our own results.

A potential bias we accounted for is that of the variation in frequency of PSA sampling after treatment. However, as the median duration of a PSAb ranges in the literature between 6.8 and 16 months,[7,9] with most studies quoting a value of at least 8 months, we believe that few PSAb were missed in this study, as the majority of patients had at least two PSA readings every single year. Nonetheless, we repeated our statistical analyses with a reduced cohort by excluding patients who had fewer than 2 yearly PSA tests. Results were consistent; therefore we consider our initial findings to be valid.

A plausible explanation for the influence of young age on PSAb is that greater androgen production in these patients may lead to greater reactivity of the epithelial cells.[8] Alternatively, it has been suggested that not all prostates increase in size with age, and rather, some undergo atrophy, for example as a consequence of arteriosclerosis.[13,14] In this case, a smaller volume of healthy prostatic tissue would be present in older patients.

Another theory about the etiology of PSAb is that it is caused by an inflammatory reaction. This is supported by a study by Kirilova et al. They tested the correlation between metabolic activity on 3D MR-spectroscopic imaging and PSA levels after the occurrence of a bounce. Although no significant correlation was found, this study showed that there was evidence of diffuse metabolic activity unrelated to residual malignancy in patients presenting with PSAb, supporting the idea that the etiology of this phenomenon is inflammatory and benign.[15] We were not able to test this theory in the present study.

Because of lack of long term follow up, we could not sufficiently test the observation that PSAb is associated with longer biochemical relapse-free survival.[2,3,16] There was an insufficient number of biochemical failures in our patients with low risk disease to report on its correlation with PSAb. Of note, no biochemical failure occurred, within our follow up period after the initial 3 years, in any of the patients having had a PSAb.

Tumor cells can remain detectable by biopsy up to 30 months after radiotherapy,[17] which exceeds the median time to PSAb. Thus, not only may such a procedure incur the unnecessary risk of bleeding and infection, it may actually be misleading in its results. If PSAb is indeed the result of late damage to healthy prostatic tissue, it should require no invasive investigations. Closer PSA monitoring, if anything, should be sufficient in the management of this phenomenon. As more light is shed on the etiology of this phenomenon, and if findings reflect our own, perhaps clinicians will feel more confident in reassuring their patients regarding such early increases in PSA values. Although the interpretation of a PSA rise remains the product of experience and clinical judgment, we hope clinicians will exercise caution in prescribing invasive tests or initiating additional treatments.

Conclusion

We found comparable rates of PSAb after standard fractionation EBRT, highly hypofractionated EBRT, and LDR brachytherapy. We hypothesize that these transient elevations in PSA values result from late damage to healthy prostatic tissue. This theory is supported by the fact that clinical factors indicative of a lower tumor burden are predictive of a PSAb. □

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