Deferred permanent prostate seed brachytherapy does not affect PSA outcome: results from a large retrospective cohort

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Introduction: *To examine the outcome of deferred permanent seed brachytherapy (BT) for localized low or intermediate risk prostate cancer in order to identify predictors of delayed therapy (DT).*

Materials and methods: *We studied 714 patients treated with BT with or without external radiotherapy. DT was defined as no treatment for > 350 days after the first biopsy with cancer. Factors influencing DT were analyzed. PSA outcome was assessed only in patients with a follow up ≥ 24 months. Patients with DT were compared to patients treated < 350 days using non-parametric tests. Multivariate analysis was performed using linear-regression analysis.*

Results: *BT was deferred in 125 patients (17.5%) for a median of 607 days (IQR 445-926). Patients with DT were older (71 years versus 69 years, p = 0.04) and had significantly less aggressive disease (percentage of positive biopsies, T1 disease, Gleason 6) on univariate analysis. On multivariate analysis, age (p = 0.01) and Gleason score (p = 0.05) were predictive for DT. Median (range) PSA follow up for DT patients was 36 months (24-78). The rate of patients with DT attaining a PSA at last follow up of < 0.2 ng/mL, < 0.5 ng/mL and ≤ 1 ng/mL was 53%, 73 % and 95%, respectively; only one patient (1.6 %) had biochemical failure (p = 0.61 compared to immediate BT). Multivariate analysis showed that age was predictive (p = 0.02) for a nadir of < 0.5 ng/mL and < 0.2 ng/mL (p = 0.017) and T-stage for a PSA < 0.2 ng/mL (p = 0.04).*

Conclusions: *This is the largest analysis of the effects of deferred BT showing a promising rate of early PSA response.*

Key Words: prostate cancer, permanent seed brachytherapy, deferred treatment

Introduction

About 1 in 6 men (16.7%) are diagnosed with prostate cancer in their lifetime but only a few (2.9%) are expected to die of this disease.[1] Furthermore, with the introduction of prostate-specific antigen (PSA) screening, a substantial proportion (50%) of these newly diagnosed men have a favorable disease risk (Gleason score ≤ 6 and PSA < 10 ng/mL).[2] As a consequence of a higher diagnostic rate and a low mortality rate there is growing concern about overtreatment.[3]

The often indolent clinical course of prostate cancer suggests that appropriately selected patients can safely defer definitive treatment for many years.[4] Active surveillance (AS) can postpone or avoid treatment-related side effects for many patients. AS with selective delayed intervention or deferred treatment (DT) based on PSA kinetics and repeat biopsy have been shown to

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be appropriate with excellent long term results.[5] While this approach has been reported in prospective studies involving over 4000 patients,[5,6] little is known about the biochemical outcome in men choosing deferred radiation treatment, either external beam radiotherapy (EBRT) or prostate brachytherapy (BT). Five year PSA recurrence-free survival for patients receiving deferred radiation therapy is lower, although not significantly, than for those undergoing deferred surgery. So far few published reports have focused only on few patients undergoing deferred BT.[5]

We sought to determine the short term biochemical outcome in men who deferred BT for at least a year following diagnosis. Our second objective was to evaluate the factors influencing the decision to defer BT.

Materials and methods

We retrospectively reviewed the medical records of all patients who received BT from July 2005 to February 2013. High risk patients (≥ T3a and/or Gleason 8 and/or PSA > 20 ng/mL) were excluded from this study. We identified 714 patients who received BT as monotherapy or in combination with EBRT (4.6%). 2.2% of patients received had cytoreductive androgen deprivation. The prescribed dose was 144 Gy for those receiving exclusive BT and 110 Gy for patients treated with a combination of EBRT with a BT boost. The complete description and general guidelines of the BT procedure were previously published.[7] The time to treatment was calculated from the date of the first biopsy diagnostic of cancer. DT was defined as no curative treatment for 1 year (or at least 350 days) after the first biopsy with cancer in accordance with Shappley and colleagues.[4] Others have used similar time frames, ranging from 9 months[8] to 19.2 months.[9]

Cancer characteristics include the Gleason score, total number of biopsies obtained and the number of positive cores, PSA and clinical stage. Patient characteristics such as age, comorbidity, sexual function determined by the Mount Sinai Erectile Function Score (0 = no problems, 1 = minor problems, 2 = occasionally medication necessary, 3 = no erections even with medication) and urinary symptoms using International Prostate Symptom Score (IPSS) were recorded.

The reason stated for BT intervention was obtained from the medical records of all patients with deferred BT. The causes for undergoing a deferred BT intervention were categorized as either cancer progression, patient preference or other causes. Cancer progression was defined as either PSA progression and/or progression on repeated biopsy. The latter was defined as follows: development of a Gleason score of 7 for those with a previous Gleason score of 6 or less, increased number of positive cores for those with initially two positive cores or positive core with more than 50% cancer involvement, regardless of the number of initial cores on previous biopsy.[10,11]

Among the entire cohort, 125 patients (17.5%) deferred BT (group 1) and 589 patients (82.5%) received a non-deferred treatment (group 2).

Both groups were further classified depending on follow up: ≥ 24 months or < 24 months. PSA outcome was assessed only in patients with a PSA follow up of ≥ 24 months who did not receive androgen deprivation therapy. Because of the relatively short follow up, we chose to use surrogate markers for freedom from biochemical failure. We used a PSA < 0.2 ng/mL and < 0.5 ng/mL at last follow up because both values have been shown to be a strong indicator of long term disease-free survival.[12,13]

This study received approval from the institutional review board of our institution.

Statistical analysis

Patients with deferred BT were compared with those who received non-deferred treatment using either the Wilcoxon or Fisher's Exact Test for categorical variables and Mann-Whitney test for continuous variables. Linear logistic regression analysis was used to determine which factors influence the time to brachytherapy after the initial biopsy with cancer. All factors that had a $p < 0.1$ in the univariate analysis were included in that analysis.

The rate of patients attaining a PSA at last follow up of ≤ 0.2 ng/mL, ≤ 0.5 ng/mL and nadir + 2 ng/mL (Phoenix definition for biochemical failure) was compared between both groups only in patients with a follow up of at least 24 months. Results were compared with the Fisher's Exact Test. A binary logistic regression including all cancer-specific factors and age was done to identify predictors for PSA at last follow up of < 0.2 ng/mL and < 0.5 ng/mL. SPSS version 17 (IBM Corporation, Armonk, NY, USA) was used.

Results

Patient characteristics

Patients in the non-deferred group had their BT procedure performed a median of 144 days (interquartile range, IQR 111-187) after the first biopsy with cancer. For patients in the DT group the median time to BT was 607 days (IQR 445-926). Sixty one percent (61%) of patients had their BT within 2 years, 23% between 2 and 3 years, 6% between 3-4 years, 6% between 4-5 years and 4% > 5 years.

Patient characteristics are summarized in Table 1. Patients with DT were older and had less aggressive prostate cancer characteristics including a lower percentage of positive biopsy cores, lower clinical stage and lower Gleason score. They were also more likely to have diabetes, although this was not statistically significant (p = 0.08).

Analysis by linear logistic regression revealed that diabetes (p < 0.001; OR 0.18, 95% confidence interval 71.1, 245.0) and a lower Gleason score (p = 0.015; OR -0.12, -165.7, -17,7) were predictive of the time to BT, but not T stage (p = 0.24) or the percentage of positive biopsies (p = 0.89).

Cancer progression was the reason why two thirds of the patients who were on AS for longer than 1 year finally chose BT, Table 2. Other reasons listed under « other causes » were intercurrent illness (e.g. diverticulitis, other cancers), or pathologic revision revealing a more aggressive cancer).

Biochemical outcome

Patients with DT with a minimum PSA follow up of ≥ 24 months were treated at a median interval of 602 days (350-2300 days) after the initial diagnosis. Median follow up in these patients was significantly (p = 0.014) shorter at 36 months (range 24-78) versus 40 months

TABLE 1. **Baseline clinical and pathologic characteristics of patients who received deferred treatment and non-deferred treatment**

Characteristic median (range)	**All patients n = 714**	**Deferred treatment n = 125 (17.5%)**	**Non-deferred treatment n = 589 (82.5%)**	**p value***
Age		71 (53-85)	69 (49-85)	**0.04**
< 70 years	367	42.4%	57.6%	**0.03**
> 70 years	347	57.6%	42.4%	
Baseline PSA		5.9 (0.8-14.3)	5.4 (0.2-18.8)	0.31
< 10	656	90.4%	92.3%	0.47
10-20	57	9.6%	7.7%	
Clinical stage				
T1	520	83.2%	70.6%	**0.004**
T2	194	16.8%	29.4%	
% of positive biopsies		17 (7.1-100)	33 (7.2-100)	**< 0.001**
≤ 33 %	450	83.2%	58.7%	**< 0.001**
34%-50%	177	12.8%	27.3%	
> 50 %	87	4%	13.9%	
Gleason score				
≤ 6	547	91.2%	73.5%	**< 0.001**
7	168	8.8%	26.5%	
IPSS median (range)		3 (0-23)	3 (0-24)	0.45
< 7	564	80%	79%	0.90
> 7	148	20%	21%	
Sexual function§				
0	340	48.2%	52.9%	0.20
1	152	21.1%	23.7%	
2	72	16.7%	9.8%	
3	89	14.0%	13.5%	
HTN	289	41.6%	40.2%	0.84
Heart disease	36	4.8%	5.1%	1.0
Diabetes	95	18.4%	12.2%	0.08

PSA = prostate-specific antigen; IPSS = international prostate symptom score; HTN = hypertension or high blood pressure
*Chi-Square or Fisher's exact test; §Mount Sinai Erectile Function Score

TABLE 2. **Reasons for ending active surveillance in patients who deferred treatment**

Reason for deferred treatment	Follow up		p value*
	≥ 24 months n = 64	< 24 months n = 61	
Cancer progression (repeat biopsy or rising PSA)	76.6% (49)	70.5% (43)	0.7
Patient preference	17.2% (11)	19.7% (12)	
Other causes	6.2% (4)	9.8% (6)	

PSA = prostate-specific antigen
*Chi-square test

(range 24-44) for patients receiving the non-deferred treatment, Table 3.

The rate of DT patients attaining a PSA at last follow up of < 0.2 ng/mL, < 0.5 ng/mL and ≤ 1 ng/mL was 53.1%, 73.4% and 95.3%, respectively. Four patients had a PSA value that ranged from 1 ng/mL-2.19 ng/mL, without fulfilling the Phoenix criteria for biochemical failure. Only one patient (1.6 %) experienced biochemical failure, with subsequent bone metastases in the absence of evidence of local relapse. Patients who were younger than 70 years old were more likely to achieve both nadirs when analyzed by binary logistic regression analysis (p = 0.017 and 0.02 for a PSA < 0.2 ng/mL and < 0.5 ng/mL, respectively.). The only other factor that was predictive of outcome was T-stage for a PSA < 0.2 ng/mL (p = 0.04), Table 4.

TABLE 3. **Follow up and PSA at last follow up of patients with deferred (> 350 days) or non-deferred prostate brachytherapy in patients with a follow up of ≥ 24 months**

Characteristic median (range)	Deferred treatment n = 64	Non-deferred treatment n = 324	p value*
Follow up (months)	36 (24, 78)	40 (24-84)	0.014
Last PSA	0.19 (0-22)	0.17 (0-12.3)	0.610

PSA = prostate-specific antigen
*Mann-Whitney test
*Chi-square test

TABLE 4. **Results from binary logistic regression analysis evaluating predictors of PSA outcome in patients with a PSA follow-up of ≥ 24 months**

Categorical dependent variables	PSA outcome			
	PSA < 0.5 ng/mL		PSA < 0.2 ng/mL	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age < 70 years	1.76 (1.10, 2.81)	0.017	1.65 (1.09, 2.50)	0.017
Baseline PSA < 10 ng/mL	0.73 (0.32, 1.67)	0.45	0.72 (0.34, 1.54)	0.40
T stage	0.96 (0.57, 1.61)	0.88	0.62 (0.39, 0.98)	0.04
Percentage of positive biopsies	1.28 (0.56, 2.95)	0.82*	1.27 (0.59, 2.71)	0.55*
Gleason score (total)	1.06 (0.59, 1.90)	0.85	0.93 (0.55, 1.56)	0.77
Deferred treatment	1.07 (0.57, 2.00)	0.83	0.95 (0.54, 1.65)	0.85

PSA = prostate-specific antigen
*for > 50% positive biopsies

Discussion

In our study of 714 patients treated with BT, 17.5% (125 patients) deferred treatment for at least 1 year. We found that patients younger than 70 years of age and patients with more aggressive cancer (lower T-stage, Gleason score and percentage of positive biopsies) were more likely to choose immediate treatment. Our results echo the findings in studies recently published by Shappley et al[4] and El-Geneidy et al.[14] They reported that a younger age (< 69 years and < 75 years) was independently predictive of active treatment after initial surveillance. Others found that neither age at diagnosis nor Gleason score are predictive of a choice of active treatment.[15] Other studies found that the aggressiveness of the cancer was predictive of active treatment that included the following measures: percentage of positive biopsy cores (≥ 34%),[14] PSA doubling time (> 2 years, < 3 years or 3.7 years)[15] length of cancer in biopsy,[16] clinical stage,[4] baseline PSA[4] and free/ total PSA ratio.[16,17]

Although for most patients, disease progression was a reason for stopping AS, 17.2 % chose to undergo BT without prior evidence of cancer progression. This indicates that there is an important psychological burden associated with living with an untreated cancer. Therefore reassuring patients plays an important role in maintaining them on AS.[5,18]

When suggesting AS to a patient, the benefits have to be carefully weighed (e.g. no immediate side effects from treatment) against a worsening outcome at treatment progression.

Klotz et al[5] reported a PSA-free survival at 5 years of 62% in surgery treated patients and 43% in patients who underwent radiation treatment after being under AS. This difference was not significant (p = 0.12). Sixteen percent of these patients had their treatment within the first 2 years on AS. These surprisingly low cure rates were a reason for caution and prompted us to study PSA data in our patients. With a median follow up of 3 years for patients with deferred BT using surrogates (< 0.2 ng/mL and < 0.5 ng/mL) for disease-free survival, our results indicate that a majority of patients (95%) achieved a nadir ≤ 1 ng/mL despite including 11 patients (17%) with intermediate risk cancer. Moreover, the last median PSA value was very similar between both groups (0.18 ng/mL versus 0.17 ng/mL, p = 0.61).

To our knowledge, information on PSA outcome from deferred brachytherapy is sparse. Shappley et al[4] reported on a series of 3331 patients from the Health Professionals Follow Up Study (HPFS), a prospective cohort of men diagnosed with prostate cancer. Among all patients, only 342 (10.3%) chose deferred (> 1 year) treatment (surgery, radiotherapy +/- androgen deprivation, brachytherapy) while the rest opted for immediate treatment (< 1 year after diagnosis). Only 22 patients received deferred BT. No difference was seen between patients who received immediate and deferred treatment when the rates of metastases and death from prostate cancer (endpoints of the study) were compared. However, individual data from the BT patients was not available. Bul et al[19] reported preliminary results of a large worldwide prospective AS cohort, the Prostate Cancer Research International Active Surveillance (PRIAS) study. A total of 2494 men with favorable risk prostate cancer (clinical stage T1/ T2, PSA ≤ 10 ng/mL, PSA density < 0.2 ng/mL per milliliter, 1 or 2 positive biopsy cores, and Gleason score ≤ 6) were prospectively followed for a median of 1.6 years. During follow up, of the 527 patients (21.1%) underwent active treatment, most the patients (93.2%) were treated by surgery or radiation therapy. For 24 patients the type of treatment was not clearly stated and results for patients treated by radiotherapy have not yet been reported separately. Disease-specific survival was 100%.

Similarly, other studies have reported equally excellent outcomes of AS or DT with disease-free survival rates of over 99.7 % (median follow up between 1.8 to 6.8 years). However, no specific data on deferred brachytherapy is available,[10] or only a small number of patients are reported (2 patients)[17] or no patients were treated with deferred BT.[5,15] To our knowledge the current study is the largest to report on PSA outcome after deferred BT either as a single modality treatment or in combination with EBRT. Our preliminary results in 64 patients with DT show after a median follow up of 3 years that 73% of patients were already below a PSA-value (< 0.5 ng/mL) associated with excellent long term outcome.[13]

Our findings corroborate the positive results in the European Randomized Study of Screening for Prostate Cancer (ERSPC) after initial surveillance. Bul et al[20] evaluated 509 men with low and intermediate risk prostate cancer. Two hundred and twenty-one men (43.4% of the total study group) underwent deferred treatment after an initial period of surveillance. The 10 year disease-specific survival rates for low-risk and intermediate risk disease were 99.1% and 96.1%, respectively. The Göteburg group[6] studied 439 men with low, intermediate, and high risk prostate cancer (1.4%) under AS and 37% chose DT after initial AS. One hundred and six (65.4%) were treated with radical prostatectomy, 32 (19.8%) received EBRT, and 24 (14.8%) received HT. The 5, 10, and 14 year Kaplan-

Meier estimates of cumulative incidence of failure were 6.7%, 13.6%, and 30.2%, respectively.

There are several exclusively surgical series of deferred RP versus immediate RP. Holmström et al[9] compared 2344 men with localized low to intermediate risk prostate cancer who underwent primary RP (median of 3.5 months after diagnosis) versus 222 men who received deferred RP (median of 19.2 months after diagnosis). There was no significant difference in cancer aggressiveness in the analysis of the surgical specimen between the two groups. No difference in prostate cancer specific or total mortality between the groups was seen after a median follow up of 8.2 years. Several other studies reported similar results for delayed RP compared to immediate RP.[21-23]

We are aware that the current study has its limitations. First, this is a retrospective study such that both groups may be subject to a selection bias. We have previously studied the factors that may affect treatment choice in patients with low risk prostate cancer at our center.[24] We found that as many as 31.8% of our patients choose AS. Second, there was no uniform protocol for AS, which could also introduce a selection bias. Finally, data on PSA-doubling time was not available. It would be interesting to examine whether PSA doubling-time DT is predictive of time to treatment and outcome. Our cohort includes only patients who had BT, excluding those patients who had such aggressive cancer on repeat biopsy or PSA elevation which no longer qualify for BT. Therefore only patients who had progression to not more than lower-tier intermediate risk prostate cancer were included in this study. Longer follow up is required to determine the disease-specific and overall survival of patients with deferred BT. Limitations of using PSA surrogate endpoints should be acknowledged.

Conclusions

Deferred (> 350 days) BT shows promising short term PSA results for low risk and lower-tier intermediate risk patients. Our findings need confirmation in a prospective setting. A current trial that randomly assigns patients with low risk prostate cancer to AS, RP or radiation is expected to report preliminary results shortly.[25] □

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