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ORIGINAL ARTICLE

Impact of percent positive random biopsies on biochemical outcome in prostate cancer patients treated with external beam radiotherapy with or without androgen deprivation

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Summary

Purpose: *To identify the prognostic factors for biochemical outcome in patients with localized prostatic adenocarcinoma treated with external beam radiotherapy (EBRT) with or without androgen deprivation (AD) and to investigate the impact of percent positive prostate core biopsies (PCB%).*

Methods: *From 1998 through 2003, 333 patients with newly diagnosed localized prostate cancer were retrospectively analyzed. The patients were treated in two institutions with definitive EBRT to a median dose of 72 Gy and 80% of them received short- or long-term AD. Biochemical failure was defined using ASTRO criteria with 3 consecutive rises in prostate specific antigen (PSA).*

Results: *Median follow up was 36 months. Gleason score, initial PSA, risk grouping, PCB%, AD and total duration of AD were found to be significant predictors for biochemical outcome in univariate analysis. Independent predictors for PSA failure on multivariate analysis were PCB% and duration of AD. Among 3 risk groups, in the intermediate risk group the biochemical control was significantly better in patients with < 67% positive core biopsies. In the subgroup analysis of patients who received a prostatic dose ≤ 70.2 Gy, and patients with no hormonal or short-term hormonal manipulation the 5-year biochemical outcome was significantly reduced in patients with ≥ 67% positive core biopsies. These significant differences did not exist in patients receiving > 70.2 Gy and long-term hormonal therapy.*

Conclusion: *Our results suggest that high PCB% could be a predictor of biochemical relapse, especially in the intermediate risk group. The role of PCB% in prostate cancer should be investigated in further trials.*

Key words: core biopsies, external beam radiotherapy, percent positive cores, prostate cancer

Introduction

It has been well established that serum PSA level, clinical T stage, and Gleason score are independent predictors of biochemical outcome after either radical prostatectomy (RP) or EBRT [1,2]. Patients have been categorized into different risk groups based on these pretreatment factors for treatment recommendations [3,4]. To further define additional prognostic factors within risk groups, some studies evaluated patients undergoing RP [5] as well as EBRT [6-8]. These studies suggested that the PCB%, as an estimate of tumor volume, is an important predictor for treatment outcome. In most of these studies EBRT with doses around 70 Gy was used [6-8].

The aim of this retrospective study was to evaluate the impact of the percent prostate positive core biopsies on the biochemical (PSA) outcome and overall survival in patients undergoing EBRT with a median dose of 72 Gy with or without AD.

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Methods

Patient population

Three hundred and thirty-three patients with newly diagnosed T1-3N0M0 prostate cancer, who were treated with definitive EBRT in the Radiation Oncology Departments of Metropolitan Hospital and Marmara University Hospital between 1998 and 2003, comprised the study population. Patients without complete information regarding the established pretreatment prognostic factors like PSA, Gleason score, 1997 AJCC clinical T stage and the number of positive biopsies, as well as the number of biopsies obtained, were excluded. The pretreatment clinical characteristics of all studied patients are listed in Table 1.

Preoperative staging and treatment

The staging evaluation included digital rectal examination (DRE), serum PSA, transrectal ultrasound (TRUS)-guided needle biopsy of the prostate with Gleason scoring. Computed tomography (CT) scan of the pelvis and bone scan were done if the pretreatment PSA level was ≥ 10 ng/ml or the Gleason score ≥8. The clinical stage was defined from the DRE findings using the current 1997 AJCC staging system.

Random biopsies were obtained from a median of 8 cores (range 6-26). The PCB% was defined as the number of positive cores in biopsy material divided by the total number of the cores obtained. Biopsies from seminal vesicles, abnormal areas on DRE and hypoechoic regions on TRUS were excluded. The PCB% was calculated for all patients and was found < 67% in 245 (74%) patients and ≥ 67% in 88 (26%) patients.

Perineural invasion (PNI) was defined as the presence of prostate cancer cells within the spaces surrounding or along the prostatic nerves and was seen in 102 (31%) patients.

Three risk groups were defined based on PSA, T stage and Gleason score; these were low risk (T1c-2a and Gleason's ≤ 6 and PSA ≤ 10 ng/ml), high risk (T3 or Gleason's ≥ 8 or PSA ≥ 20 ng/ml) and intermediate risk (all other patients). Of the 333 patients, 70 (21%) were classified in the low risk group, 113 (34%) in the intermediate risk group, and 150 (45%) in the high risk group.

EBRT was delivered to 61 patients with CT-aided simulation but without custom blocking before 1999 in one of the institutions. All other patients were treated with 4-6 conformally shaped fields using either multileaf collimator or cerrobend blocks. The initial planning target volume (PTV1) included the prostate and seminal vesicles with a 1 cm margin to all directions except 0.6 cm to the rectum and patients were treated to 55.8-56 Gy with 1.8/2 Gy daily fractions. This was followed by a boost to the prostate PTV (PTV2= prostate plus 0.5 cm to all directions). Median minimum dose to PTV2 was 72 Gy (range 66-76). The ICRU dose was 5-7% higher than the prescribed dose.

Seventy (21%) patients received no AD, whereas 117 (35%) patients were put on short-term and 146 (44%) on long-term AD before, during and after radiation therapy. Although similar guidelines regarding AD for patients receiving EBRT were followed in both institutions (no AD for low risk, short term [≤ 6 months] for intermedi-

Table 1. Patient and treatment characteristics and biochemical control at 5 years

Characteristic	*n (%)*	*Biochemical control at 5 years (%)*
Median age, years (range)	71(44-85)	
T stage		
T1-2	246(74)	83
T3	87(26)	81
Gleason score		
2-6	158(47)	88
7	131(39)	79
8-10	44(14)	68
Initial PSA(ng/ml)		
≤10	165(50)	84
11-20	83(25)	83
>20	85(25)	79
Percent positive cores		
<67	245(74)	85
≥67	88(26)	76
Perineural invasion		
Absent	231(69)	84
Present	102(31)	80
Risk groups*		
Low	70(21)	85
Intermediate	113(34)	87
High	150(45)	79
Androgen deprivation		
Yes	263(79)	81
No	70(21)	90
Androgen deprivation duration		
No hormones	70(21)	90
Short-term (≤6 months)	117(35)	74
Long-term (>6 months)	146(44)	86
Median dose, Gy (range; minimum to PTV)	72(59.4-76)	
≤70.2	162(49)	82
>70.2	171(51)	86
RT technique		
Conventional	61(18)	84
3-D conformal	272(82)	83
Median follow-up, months (range)	36(12-91)	

*Risk groups: low (T1-2a, Gleason's ≤ 6 and PSA ≤ 10ng/ml); high (T3 or Gleason's 8-10 or PSA ≥ 20ng/ml); intermediate (all others). PTV: planning target volume

ate risk and long term [> 6 months] for high risk patients) an inhomogeneous group was created because most of the patients were put on AD before they were referred for radiation treatment. The median length of long-term hormonal treatment was 24 months (range 9-36).

Follow-up

Using the last day of radiation as time zero, the median follow-up for the entire study cohort of 333 patients was 36 months (range 12-91). Treatment outcomes were measured in terms of biochemical (PSA) control (biochemically no evidence of disease [bNED]), and prostate cancer-specific and overall survival. PSA failure was defined using the ASTRO consensus criteria with 3 consecutive rises above the nadir value [9]. Patients generally had a serum PSA measurement and DRE performed every 3-6 months for the first 2 years and then every 6-12 months. The median number of PSA measurements per patient obtained in the follow-up period was 8 (range 3-32).

Statistical methods

Potential risk factors like Gleason score, T stage, initial PSA level, PNI, use of AD, duration of AD, radiation dose, PCB% and risk groups were analyzed for their impact on the rates of biochemical control. The breakpoint for the PCB% variable was selected after analyzing the most significant difference between two cohorts below and above that value and also taking into consideration studies that had evaluated the clinical utility of this parameter [5,6,8]. Survival rates and curves were determined using the Kaplan-Meier method [10]. Univariate analysis for pooled and pair wise comparisons was performed using the log-rank test. Factors that showed significance on univariate analysis were tested for proportional hazards and then submitted to multivariate analysis by the Cox's regression method [11].

Table 2. Factors associated with biochemical control in univariate and multivariate analysis

Factor	*Univariate*	*Multivariate*
Age (≤ 70 vs. > 70 years)	0.18	ns
Gleason score (continuous)	0.0042	ns
Gleason score		
2-6 vs. 7 vs. 8-10	0.06	ns
2-6 vs. 8-10	0.02	
Risk group		
Low vs. intermediate vs. high	0.08	ns
Intermediate vs. high	0.0281	
Initial PSA (continuous)	0.0001	ns
Initial PSA (≤10 vs. 11-20 vs. >20 ng/ml)	0.3931	ns
AD (no vs. yes)	0.05	ns
Duration on AD (no vs. short vs. long-term)	0.0019	0.0016
PCB% (≥ 67 vs. < 67%)	0.0342	0.025
Prostate dose (≤ 70 vs. >70Gy)	0.33	ns
RT technique (conventional vs. 3-D)	0.80	ns
Perineural invasion (yes vs. no)	0.33	ns
T stage (local vs. locally advanced)	0.61	ns

ns: non significant, AD: androgen deprivation, PCB%: percent of positive core biopsies

Results

The 5-year overall survival rate for the entire group of 333 patients was 88%. Three patients died of prostate cancer and 23 died of other causes. The 5-year bNED and prostate cancer-specific survival rates were 83% and 98%, respectively. For the whole patient group initial PSA (p=0.0001), Gleason score (p=0.0042), risk group (p=0.0281), PCB% (p=0.0342), use of AD (p=0.05) and duration of AD (p=0.0019) were significant predictors of time to postradiation PSA failure on univariate analysis.

On multivariate analysis PCB% (p=0.025) and duration of AD (p=0.0016) correlated significantly with bNED. The odds ratio was 2.00 (95% CI: 1.11-3.6) for PCB% and 2.66 (95% CI: 1.42-4.97) for total time on AD. Table 2 shows the individual p-values for the univariate and multivariate analysis.

PCB% had a statistically significant impact on bNED. For patients with a PCB% <67%, the 5-year bNED rate was 85% compared to 76% for those with a PCB% ≥ 67% (p=0.0342). The effect of PCB% was also analyzed within each risk group. For the intermediate risk group, biochemical outcome correlated significantly with PCB%. The 5-year biochemical control rate was 90 vs. 74% in patients with < 67% and ≥ 67% positive cores, respectively (p=0.036). For the low risk and high risk groups no such association between PCB% and bNED was found (p=0.39 and 0.47, respectively).

One hundred and sixty-two (49%) patients were treated with doses ≤ 70.2 Gy in this study. In this subgroup of patients PCB% was a significant predictor of biochemical outcome. The 5-year bNED rate for patients with < 67% positive cores was 85% vs. 69% in those with ≥ 67% positive cores (p=0.03). This significant difference did not exist in patients who were treated with doses > 70.2 Gy (Figure 1).

Also in the patient subsets receiving no or short-term AD the biochemical outcome was significantly worse for those with higher PCB%. In patients with no hormonal manipulation the 5-year bNED rate of those

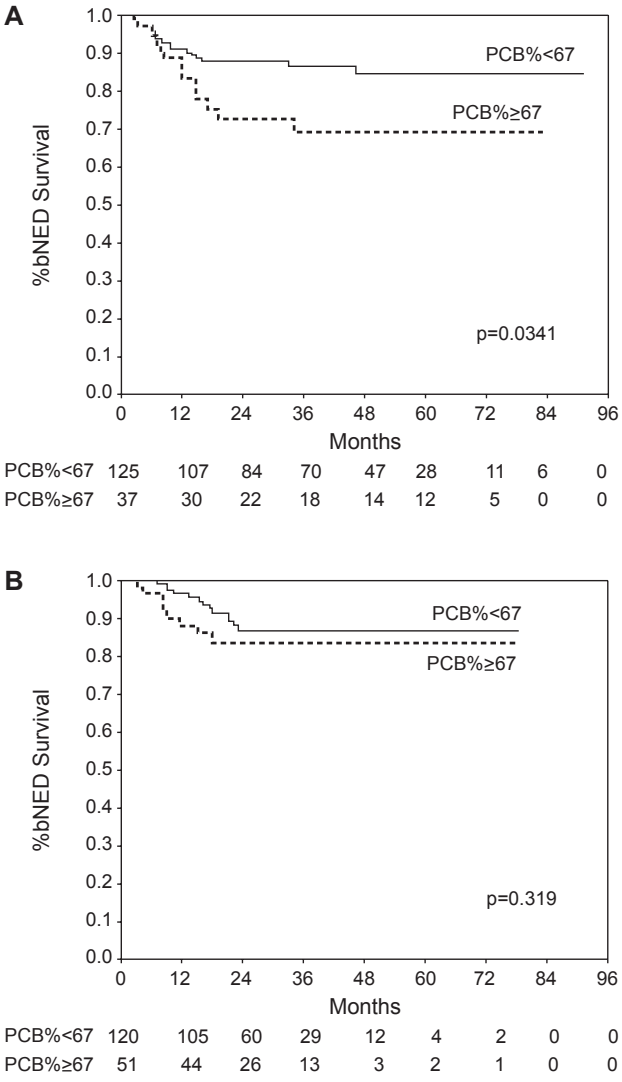

Figure 1. Biochemical NED survival after radiation therapy stratified by PCB% according to prostatic dose: **A:** ≤70.2 Gy; **B:** >70.2Gy. PCB%: percent positive cores.

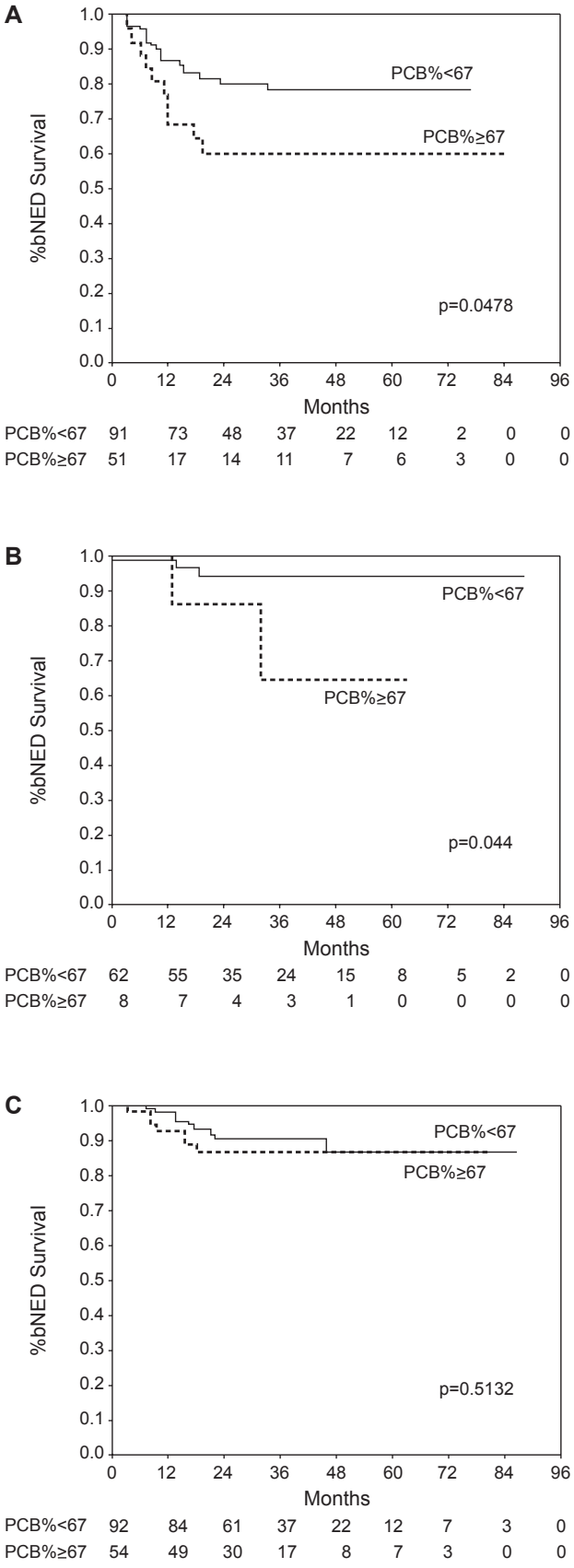

Figure 2. Biochemical NED survival after external beam radiotherapy stratified by PCB% adjusted for hormonal manipulation. **A:** no hormones; **B:** short-term hormones; **C:** long-term hormones. PCB%: percent positive cores.

with < 67% positive cores was 97% vs. 64% of patients with ≥ 67% positive cores (p=0.0457). The rates were 78 vs. 60% (p=0.0444) in patients receiving short-term AD. But in patients receiving AD for more than 6 months this significant difference disappeared. The 5-year bNED rate was 86% for both groups (Figure 2).

Discussion

Many studies have evaluated the prognostic factors for prostate cancer patients treated with EBRT [12-15]. The pretreatment PSA level, Gleason score and clinical T stage are commonly used for decision-making and treatment recommendations. Patients are further stratified into different risk groups using these 3 well-established prognostic factors. Our data concur

with the literature, as pretreatment PSA, Gleason score and risk groups were significantly associated with biochemical control in univariate analysis.

PCB% may reflect the volume of disease, thus providing further information over the disease prognosis. Several studies have shown the significant impact of PCB% on biochemical control after RP [5,16], EBRT [6,8], as well as AD therapy [17].

D'Amico et al. showed first on RP-managed [5] and then on EBRT-managed [6] patients that PCB% provided a clinically significant improvement in predicting the PSA outcome. For RP-managed patients in the intermediate risk group the bNED rate was 11 vs. 86% for PCB% > 50% and < 34%, respectively [5]. In the RT-managed intermediate risk cohort they reported a 5-year PSA control rate of 30% if the PCB% was > 50% compared with 85% if that percent was < 34%, thus further classifying the intermediate risk group into low and high risk cohorts [6]. In another study D'Amico et al. [18] also showed that PCB% was not only an independent predictor for bNED, but also for the prostate cancer-specific mortality. By 5 years after conformal radiotherapy, 5-9% vs. < 1% of the patients showed prostate cancer-specific mortality if they had ≥ 50% compared with < 50% PCB%, respectively. The authors concluded that dose escalation techniques, addition of hormonal therapy, or both should be considered in the management of patients with low or favorable intermediate risk disease and ≥ 50% positive biopsies.

Selek et al. [7] demonstrated that PCB% was a predictor of post EBRT PSA outcome in clinically localized prostate cancer, but could not show any significant difference between the traditional risk groups for the time to PSA failure. The 5-year bNED rate in their study was 79 vs. 69% (p=0.02) for patients with < 50% vs. ≥ 50% positive core biopsies, respectively.

Wong et al. [8] reported their experience with 331 clinically localized prostate cancer patients. Their definition of risk groups was different than in the above mentioned studies. Patients with T1-2, initial PSA ≤ 10 ng/ml, and Gleason's score ≤ 6 were included in the low risk category, the ones with only one factor increased in the intermediate risk, and those with two or more factors increased in the high risk category. They were able to show a statistically significant impact of PCB% on the bNED rate. For patients with PCB% ≤ 33%, 34-66%, and ≥ 67% the 5-year bNED rate was 75, 67, and 51%, respectively. Within the intermediate risk group, the PCB% was significantly associated with the bNED rate: 67, 52, and 30% for those with positive biopsies ≤ 33, 34-66, and ≥ 67%, respectively (p=0.0046).

All these 4 studies, addressing the clinical utility of PCB% in predicting the PSA outcome had one thing in common: the median EBRT dose delivered was ≤ 70.4Gy. In 3 studies the patients were treated exclusively with EBRT, no hormonal manipulation was used. In the Wong's study [8], 74 out of 331 patients were administered a short course of AD therapy combined with EBRT.

In our study, the prognostic significance of the PCB% was evaluated in a cohort of 333 patients treated mostly with 3D conformal techniques and was also found to be clinically relevant. Patients with a higher PCB% had a significantly worse PSA outcome. In multivariate analysis PCB% remained a statistically significant predictor of biochemical control. Although the difference between the two groups with PCB% <67% and ≥67% was just 9%, we think that these results could encourage investigators to further define the role of PCB% in prospective trials with longer follow-up. We were unable to show an impact on prostate cancer-specific survival, because of our rather short follow-up period (only 3 patients had died of prostate cancer).

Our results suggest that PCB% provides significant prognostic information for the biochemical disease control within the intermediate risk group. The 5-year biochemical control rate was 90 vs. 74% in patients with < 67% positive cores and ≥ 67% positive cores, respectively. No correlation could be demonstrated in the low and high risk groups. Further stratification of the intermediate risk group according to PCB% could be important in the evaluation and management of these patients. However, in a retrospective study the significance of a subgroup analysis is unclear, and these results should be interpreted with caution.

Our study differed from the above mentioned studies for two reasons. First, more than half of the patients were treated with doses ≥ 72Gy, and second, about 80% underwent hormonal manipulation in combination with EBRT. In the subset of patients treated with doses above 70.2Gy, we found that the significantly worse PSA outcome seen in patients with higher PCB% managed with ≤ 70.2 Gy, did not exist. Also in patients with long-term AD in combination with EBRT, the significance between the two groups with PCB% <67% and ≥ 67% diminished, and the bNED rate rose to 86% in both groups. But the effect of long-term hormonal manipulation may be overshadowed by our rather short median follow-up time of 3 years. After using AD for a median of 24 months, we would need another 2-3 years of follow-up to demonstrate a biochemical relapse. Therefore, the median follow-up of 31 months of our patient group with long-term AD would misdiagnose the real number of biochemical failures. We think that longer follow-up is needed to better define the role of adjuvant hormonal treatment in this subset of patients.

In the modern RT practice, where doses ≥ 74Gy are widely used for intermediate and high risk patients, PCB% may lose its prognostic significance. This finding has been also reported by Buyyounouski et al. [19]. In their study they have treated patients with localized disease to a median ICRU dose of 76 Gy with 3D conformal radiotherapy. They concluded that PCB% should not be used to make any decisions regarding the management of prostate cancer with high dose RT. The percentage of positive regions could be a more reliable estimate of tumor burden from the prostate biopsy.

Defining the biochemical control with 3 consecutive rises of PSA in a cohort where 80% of the patients underwent hormonal manipulation could be a potential limitation of this study. At the time of analysis, although it was well known that the 1996 consensus performed poorly in patients undergoing hormonal treatment, it was still not clear which definition to choose. The new Phoenix consensus definition, where a rise by 2 ng/ml or more above the nadir PSA is considered as biochemical failure after EBRT with or without hormonal therapy, seems more able to overcome this difficulty [20].

Conclusions

Our study demonstrated that PCB% has a statistically significant impact on the biochemical control in localized prostate cancer patients treated with EBRT with or without AD. High percent positive biopsies could be a predictor of biochemical relapse, especially in the intermediate risk group. However, in patients treated with doses above 72 Gy and who had long-term AD, PCB% seems to lose its prognostic significance. Although our data has some limitations due to its retrospective nature, these results could encourage investigators to further define the role of PCB% in prospective trials.

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