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Original Article

Correlation between postoperative prostate-specific antigen and biochemical recurrence in positive surgical margin patients: Single surgeon series

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ABSTRACT

Background: To evaluate the relationship between postoperative prostate-specific antigen (PSA) levels and biochemical recurrence (BCR) after radical prostatectomy, especially in patients with positive surgical margins (PSMs).

Materials and methods: A total of 144 patients who underwent radical prostatectomies performed by a single surgeon without any neoadjuvant or adjuvant treatment were analyzed. Differences in clinicopathological factors were compared by surgical margin status, and the relationship between postoperative PSA level and BCR in patients with PSMs was evaluated.

Results: Fifty of the 144 patients (34.7%) had PSMs. Of these, 74% experienced BCR. The negative surgical margins and PSMs groups differed significantly in terms of PSA level at diagnosis, clinical T stage, and risk group by the cancer of the prostate risk assessment score ($P = 0.002$, $P = 0.002$, and $P = 0.004$, respectively). Also, the nadir PSA level, tumor volume, and BCR rate differed between the two groups ($P = 0.007$, $P = 0.015$, and $P = 0.005$, respectively) On Kaplan–Meier analysis, BCR-free survival was better in the negative surgical margins than the PSMs group (64.1 vs. 55.4 months, log-rank test, $P = 0.011$). BCR-free survival did not differ significantly in PSMs patients according to whether PSA level was or was not detectable at 1 month postoperatively. However, BCR-free survival improved when the nadir PSA level was undetectable (compared to detectable) in PSMs patients (64.3 vs. 26.1 months, log-rank test, $P < 0.001$). In PSMs patients belonging to the high risk group by cancer of the prostate risk assessment score, BCR-free survival was significantly better when the PSA level attained the nadir within 3 months, compared to > 6 months, postoperatively (64.2 vs. 29.5 months, log-rank test, $P = 0.022$).

Conclusion: If PSA is detectable in PSMs patients until 1 month after operation, cautious observation may be possible. If the nadir is attained within 3 months postoperatively in high-risk patients with PSMs, better BCR-free survival may be expected.

1. Introduction

Radical prostatectomy is a valuable option for clinically localized prostate cancer.[1] However, about one-third of patients undergoing radical prostatectomy will experience biochemical recurrence (BCR), defined as an elevation in prostate-specific antigen (PSA) level.[2–5] Positive surgical margins (PSMs) are unfavorable pathological findings including seminal vesicle invasion and extraprostatic extension, and associated with BCR. PSMs suggest that some cancer cells remain in the surgical bed. However, PSMs are affected by remnant normal tissue, inadequate surgical skill, and iatrogenic incision.[6,7] Regardless of the cause, PSMs affect postoperative PSA levels; patients with PSMs may have detectable levels despite the apparent success of prostatectomy.[8] However, some patients with PSMs experience undetectable PSA levels during serial checking, without any adjuvant treatment. Thus, the interpretation of PSMs as primary treatment failure remains controversial.[8,9] When PSMs occur after prostatectomy, it is important to know which patients will benefit from additional

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treatment. Not all patients with PSMs or low but detectable PSA levels after prostatectomy benefit from adjuvant therapy.[9,10]

Many studies have explored the associations among PSMs, the PSA level, and BCR. We explored how the postoperative PSA level was related to BCR, especially limited to the patients with PSMs, after evaluating the clinical characteristics of them. Kaplan–Meier analysis was used to focus principally on the relationship between postoperative PSA status and BCR in patients with PSMs.

2. Materials and methods

A total of 144 patients who underwent radical prostatectomy from 2008 to 2014 were reviewed retrospectively. All patients were operated upon by a single surgeon; no patient received any adjuvant or neoadjuvant therapy. Medical records were retrieved after the work was approved by the Institutional Review Board of Inje University Busan Paik Hospital. Postoperative PSA levels were initially checked 1 month after surgery, followed by serial evaluation. The nadir PSA was defined as lowest PSA during the observation period and detectable PSA was defined as PSA > 0.01 ng/mL. BCR was defined as two consecutive PSA levels ≥ 0.2 ng/mL at any time postoperatively. All patients were divided into negative surgical margins (NSMs) and PSMs groups.

Preoperative and postoperative variables were compared between the groups. Age, PSA level at diagnosis, Gleason score (from biopsy specimens), and clinical T stage, were the preoperative variables included. Three risk groups (low, intermediate, and high) were calculated by cancer of the prostate risk assessment (CAPRA) scores and also included in preoperative variables.[11] Postoperative 1 month PSA, nadir PSA levels, the time from surgery to attainment of the PSA nadir, total tumor volume (reported by the pathologist), BCR rate, and the time from surgery to BCR were analyzed as postoperative variables. In the PSMs group, PSA recurrence was analyzed by the postoperative 1 month PSA level (detectable vs. undetectable), nadir PSA level (detectable vs. undetectable), and the time to the nadir PSA level (in 3-month intervals).

SPSS software, version 20, was used for all analyses, and the significance level was set to $P = 0.05$. Data are presented as means with standard deviations. Analysis of variance was used to compare numerical values including age, PSA level, prostate volume, and the times to the nadir PSA level and BCR rate. Categorical variables were compared with the aid of the Chi-square test. Kaplan–Meier survival curves of BCR were drawn, and the log rank test was used to compare the two groups.

3. Results

Table 1 shows the clinicopathological variables by surgical margin status. The PSA level at diagnosis differed significantly between the groups, being higher in the PSMs group ($P = 0.002$). The NSMs group contained significantly more patients of clinical stage ≤ T2 and at low risk by CAPRA score. Of the postoperative variables, the nadir PSA level was lower in the NSMs than the PSMs group (mean 0.014 ng/mL and 0.019 ng/mL, respectively; $P = 0.007$). Additionally, the tumor volume of the PSMs group was about twice that of the NSM group (mean 33.1 vs. 15.7%, $P = 0.015$).

BCR was more common in the PSMs than the NSMs group (74 vs 8.5%, $P = 0.005$). However, the postoperative 1-month PSA level did not differ significantly by surgical margin status, being in fact higher in the NSMs group. The time to BCR did not differ significantly between the two groups.

On Kaplan–Meier analysis, the estimated mean BCR-free survival periods were 55.4 ± 3.9 months and 64.1 ± 2.0 months in the PSMs and NSMs groups, respectively, with statistical significance (log rank test, $P = 0.011$; Fig. 1). Fig. 2 shows that BCR-free survival in the PSMs group did not differ significantly between those in whom PSA was and was not detectable 1 month postoperatively (55.1 ± 4.1 months vs. 52.7 ± 6.8 months, log rank test, $P = 0.852$). However, when the PSA nadir was undetectable in the PSMs group, BCR-free survival was superior to that of patients in whom the PSA nadir was detectable (64.3 ± 3.1 months vs. 26.1 ± 6.7 months, log rank test, $P = 0.001$) (Fig. 3).

Fig. 4 shows the correlations between BCR-free survival and the time to the PSA nadir in high risk patients with PSMs. A total of 24 patients of PSMs were classified high risk group by CAPRA score. Among them, 15 patients (62.5%) attained the PSA nadir within 3 months postoperatively. In addition, seven patients (29.2%) attained the PSA nadir from 3 months to 6 months after surgery. Two patients (8.3%) attained the PSA nadir after 6 months postoperatively. Survival differed significantly between those in whom the PSA nadir was attained within 3 months of surgery and those in whom the nadir was not attained within 6 months of surgery (64.2 ± 5.1 vs. 29.5 ± 8.5 months, log rank test, $P = 0.022$).

Table 1
Preoperative and postoperative variables according to surgical margin status

Variables	NSM group ($n = 94$)	PSM group ($n = 50$)	P
Preoperative variables			
Age (yr)	67.3 (± 6.7)	64.6 (±6.5)	0.654
PSA at diagnosis (ng/mL)	10.5 (± 6.7)	16.3 (± 11.4)	0.002
Prostate volume (g)	35.5 (± 18.6)	36.4 (± 16.1)	0.859
GS at diagnosis			0.225
≤ 6	40 (42.5)	14 (28)	
7	37 (39.4)	24 (48)	
≥ 8	17 (18.1)	12 (24)	
Clinical T stage			0.002
≤ T2	84 (89.4)	34 (68)	
> T2	10 (10.6)	16 (32)	
CAPRA score risk group			0.004
Low	39 (41.5)	9 (18)	
Intermediate	32 (34)	17 (34)	
High	23 (24.5)	24 (48)	
Postoperative variables			
Postop. PSA (ng/mL)	0.960 (±0.186)	0.140 (±0.209)	0.422
Nadir PSA (ng/mL)	0.014 (±0.016)	0.019 (±0.027)	0.007
Period until nadir PSA (mo)	4.3 (±2.9)	4.2 (±3.2)	0.842
Tumor volume (%)	15.7 (±16.7)	33.1 (±21.9)	0.015
No. of biochemical recurrence	8 (8.5)	37 (74)	0.005
Period until BCR (mo)	32.7 (±20.4)	35.2 (±22.6)	0.497

BCR, biochemical recurrence; CAPRA, cancer of the prostate risk assessment; GS, ; NSM, negative surgical margin; PSA, prostate-specific antigen; PSM, positive surgical margin.
a) Variables are presented as mean and standard deviation or number (%).

4. Discussion

PSMs are one cause of BCR after radical prostatectomy and elevations in PSA level may be seen even after complete removal of the prostate gland in patients with PSMs. PSMs may be caused not only by incomplete cancer excision, but also by inadvertent capsular incision during surgery, artifacts associated with tissue processing, and remnant normal prostatic tissue.[6,12] The incidence of PSMs is 10–60%.[13–15] Our incidence was 34.7% in a single-surgeon series, comparable to previous data.

A large retrospective analysis found that PSMs were significantly associated with a higher preoperative PSA level, a greater body mass index, more advanced pathological stage, a higher Gleason score, greater tumor volume, and a smaller prostate volume.[16] Another Asian report also found that a PSMs group had a higher preoperative PSA level, a lower prostate weight, a higher pathological T stage, and a higher Gleason score.[15] Likewise, other reports have consistently found that adverse clinicopathological features

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