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Correlation between Bladder Neck Preservation, Positive Surgical Margins, and Biochemical Recurrence in Laparoscopic and Open Radical Prostatectomy: A Prospective Cohort Study

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Abstract: Background: Bladder neck preservation (BNP) has been adopted in open (ORP), laparoscopic (LRP), and robot-assisted radical prostatectomy (RARP). However, there are concerns that this technique can compromise oncological outcome and increase positive surgical margins (PSM). The aim was to evaluate the outcome of BNP, focusing on surgical and pathological outcomes, as well as biochemical recurrence (BCR). Methods: We prospectively collected demographic and clinical data from 170 consecutive patients who underwent ORP and LRP between 2014 and 2020. ORP was performed in 63 patients, and the rest underwent LRP. BNP was performed in 85 patients. Results: PSM were found in 24.7% of patients. Of patients with BNP, 22.4% had PSM. There was no significant statistical difference between patients with or without BNP in the form of PSM. Base-positive margins were detected in 9.4% of patients with BNP and in 5.9% of patients without BNP with no statistical significance. Bioptic Gleason score, clinical stage, and preoperative PSA were statistically significantly correlated with PSM. BCR was more common in patients without BNP (23.5%) vs. non-BNP (21.2%). The only statistically significant predictor of BCR was PSM. Conclusion: This study suggests that BNP in RP is not associated with an increased level of PSM. Preoperative PSA, bioptic Gleason score, and clinical T stage of disease were identified as predictors of PSM occurrence.

Keywords: bladder neck preservation; prostate cancer; radical prostatectomy; surgical margin

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1. Introduction

Prostate cancer (PCa) presents the second most commonly diagnosed cancer and the sixth most common cause of cancer death in the male population worldwide [1]. Radical prostatectomy (RP) remains the most frequently performed treatment modality in patients with localized PCa. While the open surgical approach was the gold standard in the past, the advancements in minimally invasive techniques recently enabled their wide adoption [2]. Currently, the laparoscopic and robotic-assisted approaches are the established techniques in the treatment of clinically localized prostate cancer that respect the same oncological principles of open surgery and strive to preserve continence and erectile function to the greatest extent possible [3]. Thus far, no difference in oncological outcomes has been demonstrated between ORP, LRP, and RARP. A recent meta-analysis concluded that the positive surgical margins (PSM) rate was similar, regardless of the technique [4].

The internal lissosphincter is limited in preserving urine continence, while the external urethral sphincter at the level of the membranous urethra plays a substantial role [5]. Therefore, it has been proposed that preserving the bladder neck will enhance the rehabilitation

of continence after RP. Bladder neck preservation (BNP) procedures were first implemented in 1992 in order to preserve the internal urethral sphincter, thus enhancing early recovery and long-term urinary continence after RP [6]. Studies suggest that BNP is associated with a significantly higher urinary continence rate and improved quality of life, probably without any adverse effect on oncological outcome [7,8]. The BNP procedure has been widely applied in all types of radical prostatectomies in recent decades.

However, there is concern that this technique can compromise oncological outcome and increase the positive surgical margins rate at the base of the prostate (base-positive margins) [9,10]. Additionally, PSM are an independent predictor of biochemical recurrence (BCR) and local disease recurrence. The aim was to evaluate the oncological outcome of BNP, focusing on surgical, pathological outcomes, and BCR.

2. Materials and Methods

The study was carried out in the University Clinical Center of Serbia, at the Clinic of Urology, Belgrade, between December 2014 and January 2020. The study had a prospective cohort design. The clinical and pathological data were collected from 170 consecutive patients diagnosed with PCa who underwent ORP and LRP in our institution. All radical prostatectomies were performed by one surgeon experienced in both laparoscopic and open approaches.

Preoperative diagnostics included: prostate-specific antigen (PSA), digitorectal exam (DRE), computer tomography (CT) scan, bone scintigraphy, and, in some patients, magnetic resonance imaging (MRI). Pre-operative MRI was not performed routinely in this study. Of the 170 patients that participated in this investigation, 63 underwent ORP, while the remaining 107 underwent LRP. BNP was performed in 85 patients. BNP implies the preservation of the proximal aspect of the prostatic urethra as it joins the bladder neck. The selection criterion for performing BNP was the absence of a large prostatic median lobe. Patients with overgrowth of the median prostatic lobe into the bladder underwent bladder neck reconstruction, thus constituting the control (non-BNP) group.

Before starting the dissection of the bladder neck, it is necessary to have an adequate orientation of its projection. We used three methods to identify the bladder neck. The simplest involves identifying the bladder neck by following the lateral edges of the prostate toward the expected location of the bladder neck. The second consists of identifying the bladder neck by pulling the balloon of the urinary catheter towards the base of the bladder, thus illustrating its projection. The third and perhaps the safest is based on the projection of the V-shaped fibrous tissue that extends from the puboprostatic ligaments, with the tip of the V directly above the projection of the bladder neck. During the dissection of the bladder neck, a combination of blunt preparation with a dissector, control of hemostasis with bipolar current, and cold resection with scissors was used. The urinary catheter is of great help when dissecting the neck, as it enables the precise detection of the frontal and lateral sides of the bladder neck. After freeing the frontal and lateral sides of the urethra, it is cut with scissors, thereby accessing the interior of the posterior wall of the bladder neck. After the dissection of the bladder neck described above, the urinary catheter is removed from the bladder, and a Ch18 Bougie is inserted in its place. With manipulation (elevation of the prostate using the Bougie), the posterior wall of the bladder neck is easily incised. Then, by blunt dissection, the base of the prostate is freed from the bottom of the bladder towards the seminal vesicles and the vas deferens. This method of preparation preserves the circular fibers of the bladder neck.

After surgery, one expert uro-pathologist performed all macro–micro examinations on the prostate samples. The prostate specimen underwent standard formalin fixation following the Stanford protocol [11]. Information collected included: the pathologic stage of the tumor, Gleason score, the presence of PSMs, and lymph node invasion (pN). The specimens were preserved by soaking them for at least 24 h in buffered formalin before cutting. A more homogenous fixation was achieved by injecting formalin and sectioning a day later. The apex and base (bladder neck) were removed and divided into parasagittal or radial

portions in our unit. The remainder of the material was split into transverse, 3–4 mm pieces cut perpendicular to the urethra's long axis. After quadrant sectioning, the resulting slices were implanted and processed as complete mounts [12]. Surgical margins were regarded as positive when cancer cells made contact with the surface of the radical prostatectomy specimen. Additionally, we divided PSM at five localizations: the base of the prostate, left and right lobes, both lobes, and the apex.

Postoperative follow-up included a clinical exam and PSA measurement. The occurrence of two successive serum PSA rises above 0.2 ng/mL after radical prostatectomy indicated a BCR. During the first two years after RP, PSA measurements were performed in 3-month intervals. Afterward, they were obtained in 6-month intervals.

In our study, we compared the BNP and non-BNP groups of patients. The presence of PSM was evaluated in both groups. After a pathological verification of PSM and their localizations, we found patients with PSM at the base of the prostate. We analyzed preoperative clinicopathological parameters, PSM rates, localizations of PSM, BCR rates, and BCR-free survival between BNP and non-BNP cohorts.

2.1. Statistical Analysis

Demographic characteristics, clinical and pathological parameters were compared between BNP and non-BNP groups in order to evaluate the homogeneity of the groups. The numerical parameters among the groups were compared with the Student's *t*-test, while the nominal data were analyzed with the Pearson Chi-Square test and Fischer test. Kaplan–Meier analysis and log-rank test were implemented for the calculation of BCR-free survival. The Cox regression model determined potential predictors of positive surgical margins and biochemical recurrence. Statistical analysis was performed with Statistical Package for the Social Sciences 22.0 (SPSS Inc., Chicago, IL, USA). The statistical significance level was set at $p < 0.05$.

2.2. Ethical Approval

Ethical approval of this study was obtained from the Institutional Ethical Board of the Faculty of Medicine, University of Belgrade (approval number 1322/XI-6). Informed consent was acquired from all patients who participated in the study.

3. Results

Demographic, clinical, and pathological data of both groups are presented in Tables 1 and 2. BNP and non-BNP groups were comparable according to clinical and pathological characteristics. Out of 170 patients, PSM were found in 42 (24.7%) patients. Only 19 (22.4%) patients with BNP had PSM. No statistically significant difference was noted between patients with or without BNP in terms of PSM ($p = 0.477$).

Table 1. Patient's data—Demographic and clinical data.

	BNP	Non-BNP	*p*-Value
Age (years), mean (SD)	65.5 ± 5.04	65.7 ± 5.15	0.752
Clinical stage of disease:			
T1c	10 (11.8%)	5 (5.9%)	0.078
T2a	42 (49.4%)	37 (43.5%)	
T2b	23 (27.1%)	29 (34.1%)	
T2c	8 (9.4%)	10 (11.8%)	
T3a	2 (2.4%)	4 (4.7%)	

Table 1. *Cont.*

	BNP	Non-BNP	*p*-Value
Risk classification (%):			
Low risk	24 (28.2%)	26 (30.6%)	
Intermediate risk	50 (58.8%)	47 (55.3%)	0.878
High risk	11 (12.9%)	12 (14.1%)	
Operation technique:			
LRP	56 (65.9%)	51 (60%)	
ORP	29 (34.1%)	34 (40%)	0.427

Table 2. Patient' data—Pathology findings.

	BNP	Non-BNP	*p*-Value
Final Gleason score:			
6 (3 + 3)	8 (9.4%)	12 (14.1%)	
7 (3 + 4)	46 (54.1%)	36 (42.4%)	0.246
7 (4 + 3)	23 (27.1%)	32 (37.6%)	
8 (4 + 4)	7 (8.2%)	3 (3.5%)	
9 (4 + 5)	1 (1.2%)	2 (2.4%)	
Final PH staging:			
pT1	0 (0%)	1 (1.2%)	
pT2	60 (70.5%)	57 (67%)	0.845
pT3	24 (28.2%)	27 (31.8%)	
pT4	1 (1.2%)	0 (0%)	

We divided PSM at five localizations: base of the prostate, left and right lobes, both lobes, and apex. The most significant part of the prostate with PSM for our study was the base of the prostate. Base-positive margins were detected in eight patients (9.4%) with BNP and five (5.9%) without BNP. No statistically significant difference in the occurrence of PSM at the base or any other localization of the prostate in patients with or without BNP (Fischer's exact test $p = 0.256$).

Using univariate analyses, preoperative PSA ($p < 0.0001$), bioptic Gleason score ($p = 0.007$), and clinical stage ($p < 0.0001$) were statistically significant in correlation with PSM (Table 3). There was a significant difference in pT3 stage distribution between PSM and non-PSM groups ($p < 0.0001$). Multivariate logistic regression analysis indicated that, from all preoperative parameters, only preoperative PSA was a statistically significant predictor of PSM ($p = 0.025$, OR = 1.06, 95% CI 1.01–1.1).

The median follow-up was 48 months (IQR, 44.6–51.4). A total of 38 (22.4%) patients had a BCR. BCR was more common in patients without BNP (23.5%) compared to BNP patients (21.2%) ($p = 0.713$). Biochemical recurrence-free survival rate in patients with BNP was 49.2 months (95% CI 44.8–53.8), while in patients without BNP it was 46.7 months (95% CI 44.8–53.8) (Log Rank, $p = 0.643$) (Figure 1). In a multivariate model with BCR as a dependent variable, the only statistically significant predictor of BCR was PSM ($p < 0.001$).

Table 3. Clinico-pathological parameters and surgical margin status—Demographic and clinical data.

	PSM	Non-PSM	*p*-Value
Age (years), mean (SD)	65.8 ± 4.94	65.6 ± 5.13	0.819
Preoperative-PSA (ng/mL), median (IQR)	14.2 (4.59–53.5)	8.9 (2.47–35.0)	**<0.0001**
Bioptic Gleason score:			
6 (3 + 3)	9 (21.4%)	57 (44.5%)	
7 (3 + 4)	20 (47.6%)	47 (36.7%)	**0.007**
7 (4 + 3)	9 (21.4%)	18 (14.1%)	
8 (4 + 4)	4 (9.5%)	6 (4.7%)	
Clinical stage of disease:			
T1c	1 (2.4%)	14 (10.9%)	
T2a	12 (28.6%)	67 (52.3%)	**<0.0001**
T2b	20 (47.6%)	32 (25.0%)	
T2c	6 (14.3%)	12 (9.4%)	
T3a	3(7.1%)	3 (2.3%)	
Final pathological stage of disease:			
pT1	0 (0.0%)	3 (2.4%)	
pT2	12 (28.6%)	103 (80.5%)	**<0.0001**
pT3	29 (69.0%)	22(17.2%)	
pT4	1 (2.4%)	0 (0.0%)	
Operation technique:			
LRP	29 (69.0%)	78 (60.9%)	
ORP	13 (31.0%)	50 (39.1%)	0.345

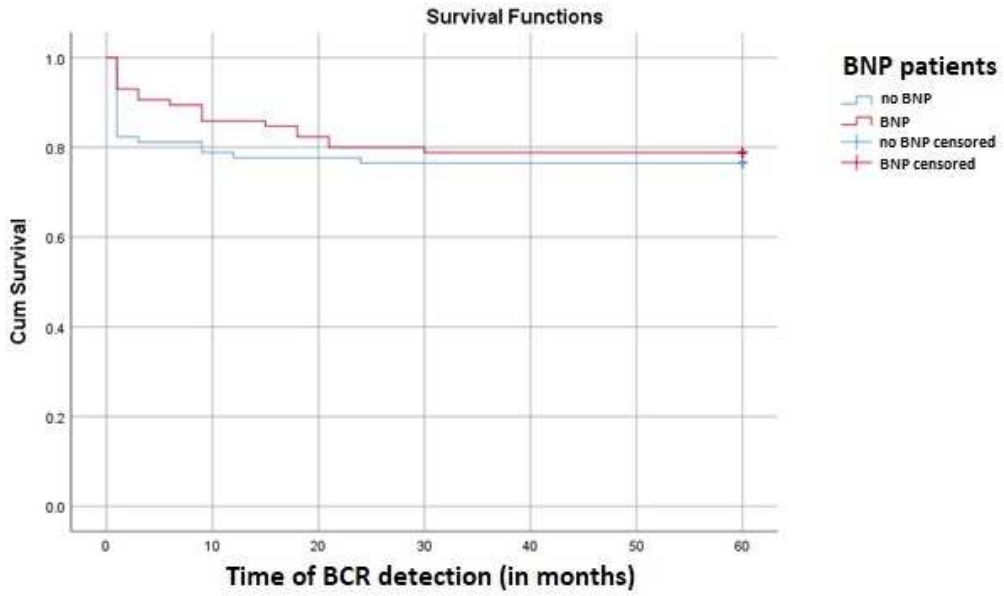

Figure 1. Kaplan–Meier survival curve showing the BCR-free rates according to BNP.

4. Discussion

Conserving urinary control without compromising oncological safety is one of the key problems of RP. According to different authors, the continence rate after RP varies between 85% and 100% [13]. In order to improve the post-prostatectomy recovery of continence, numerous surgical method improvements have been developed due to a deeper understanding of the anatomical structures of the pelvis. These include maintaining the length of the urethra, conserving the puboprostatic ligaments and the posterior rhabdosphincter, and maintaining the bladder neck [13,14].

Klein introduced BNP in 1992 [6]. This procedure was established as a result of a better understanding of the complexity of the urethral sphincter's anatomy. The inner lissosphincter, made of smooth muscle, and the outer rhabdosphincter, composed of skeletal muscle, constitute the urethral sphincter. Koraitim claims that the rhabdosphincter coats the urethra under stress and circumstances of heightened intra-abdominal pressure, while the lissosphincter is in charge of maintaining baseline and resting continence [15]. The aim of BNP is to maintain the lissosphincter mechanism intact by the dissection and preservation of the circular bladder neck fibers from the base of the prostate. Keeping these fibers makes it possible to directly anastomose the urethral stump and bladder neck circumference without the requirement for bladder neck reconstruction [6,16]. One meta-analysis and two systematic reviews confirmed that BNP is associated with statistically significant improvement in early and long-term continence rate, with lower rates of anastomotic stricture compared to the non-BNP patients [6,17,18].

The main focus of our study was not continence recovery but surgical and pathological outcomes of BNP in LRP and ORP. The potential risk of BNP is an investigated but very controversial theme. Sparing of the bladder neck during surgery can be associated with a higher risk of PSM as a consequence of the potentially incomplete tumor excision. Some authors state that BNP may increase the number of PSM, especially at the base of the prostate. Srougi et al. evaluated the rates of PSM following RRP in the group of patients who had undergone bladder neck resection and BNP in a randomized prospective study with a targeted recruitment of 120 participants. Of patients in the preservation group, 10% had PSM, which were exclusively seen at the bladder neck, whereas there were none in the resection group. Due to this finding, the study was discontinued after the enrollment of 70 patients [9]. Additionally, Katz hypothesized that avoiding BNP during LRP would reduce the PSM rate at the prostatic base [10]. A systematic review from 2017 found that the mean base PSM were 4.9% in men who had bladder neck sparing surgery and 1.85% in those who did not [5]. On the other hand, multiple authors maintain that BNP will not compromise oncological control of the disease. Smolski concluded in a systematic literature review that BNP was not linked to worse cancer control or a greater incidence of PSM [17]. Patients with or without BNP had comparable PSM results in one meta-analysis from 2016 [18]. Similar findings were observed in a prospectively planned trial involving 1057 males who underwent RARP [19]. The reported rate of PSM after RP exhibits considerable variability in the published literature (6–32%), which can be explained by the different frequency of extracapsular disease in the studies, the difference in surgical experience, and sizeable inter-observer variability in pathologic interpretation of PSM [17]. In our series, PSM were detected in 24.7% of prostatectomy specimens. This rate belongs to the PSM range of 16.6% to 39.4%, which has been reported in some similar studies [20,21]. Overall, the PSM rate in our study was relatively high, which is likely associated with a high frequency of extracapsular disease (52 of 170 patients, 30.6%). The PSM rate in our BNP group was 22.4%, and 27.1% in the non-BNP group. A statistically significant difference between those two groups, in regard to the occurrence of PSM, was not detected ($p = 0.477$).

The rate of PSM at the base of the prostate in the literature varies between 0% and 16.3% [22,23]. In a retrospective study involving 365 patients who underwent RRP with BNP, Shelfo et al. reported a rate of PSM at the prostate base of 7% [24]. On the other hand, in a prospective study with 555 patients treated similarly, Bianco reported a base PSM rate of 2% [25]. In a study from 2009 involving 619 patients treated with RARP, Freire et al. compared the rate of positive margins at the prostate base in the group of patients who underwent BNP and another group treated with the standard surgical technique. In the first group, the base PSM rate was 1.4%, while in the other, it was 2.2%. No statistically significant difference was noted ($p = 0.547$) [26]. Friedlander et al. reported similar results, with a base PSM rate of 1.1% in patients with BNP and 2.5% in patients without [25]. In our study, the overall rate of PSM at the prostate base was 7.6%. For patients who underwent BNP, the rate of PSM at the prostate base was 9.4%, compared to 5.9% of those who did not.

We demonstrated that performing BNP during RP is not significantly associated with the incidence of PSM at the base of the prostate or any other localization ($p = 0.256$).

A more accurate patient risk assessment and personalized treatment strategies can be achieved by identifying preoperative predictors of PSM following RP. Preoperative PSA and bioptic Gleason score have been identified as preoperative risk factors for PSM after RP in one meta-analysis from 2021 [27]. On the other hand, multiple studies identified PSA and clinical T stage as independent preoperative factors affecting PSM status [7,23]. In our univariate analysis, we confirmed these results while also recognizing the bioptic Gleason score as a predictor of PSM. However, multivariate analysis indicated that, from all preoperative parameters, only PSA was a statistically significant predictor of PSM (B = 0.057, $p = 0.025$, OR = 1.06, 95% CI 1.01–1.1). Understanding that tumors with higher preoperative PSA, bioptic Gleason score, and clinical T stage, are associated with significantly higher PSM rates can improve patient selection for BNP.

PSM after RP can be correlated with a higher risk of BCR [28–30]. BCR related to PSM may imply local as well as potential distant relapse of the disease. At a median follow-up period of 79 months, Alkhateeb et al. found that patients with PSM had a BCR-free survival rate of 79.9%. In contrast, non-PSM patients had a BCR-free survival rate of 93.8%, which was statistically significant [31]. Only a small number of studies with inconsistent definitions of BCR compared biochemical recurrence-free survival in the BNP versus the non-BNP group of patients. Friedlander et al. reported that rates of BCR-free survival for BNP and non-BNP groups were the same after considering pathological stage, grade, preoperative PSA, and status of margins. However, BCR in this study was defined as an elevation of PSA above 0.1 ng/mL [19]. A study conducted by Bianco et al. with a follow-up period of 7 years reported that disease-free survival (DFS) is not modified depending on whether the patients underwent RP and BNP, or RP alone. The same study using univariate and multivariate analyses of PSM at BNP showed no significant importance considering DFS. [18]. According to Gaker et al., almost all BNP patients (90%) had a PSA lower than 0.2. On the other hand, at 12.5 years of follow-up, 80% of the patients without BNP had a PSA of less than 0.2 mcg/L [23].

In our study, at a median follow-up of 48 months (IQR, 44.6–51.4), the overall BCR rate was 22,4%, which is in accordance with the current literature [19,28]. Comparing patients with BNP versus non-BNP, there was no statistically notable dissimilarity in BCR incidence (21.2% vs. 23.5%, $p = 0.713$) and BCR-free survival (49.2 vs. 46.7 months, $p = 0.643$). In the Cox regression analysis, the only statistically significant predictor of BCR was PSM ($p < 0.001$). PSM at the base of the prostate were not significantly more associated with BCR compared to other PSM localizations ($p = 1.00$). Our results indicate that BNP is not associated with worse cancer control.

A small number of patients was a major limitation of our study, which could affect the conclusion due to the restricted statistical potential and a relatively short follow-up period. Since the study design involved the selection of patients according to the method of preservation of the bladder neck in relation to the presence of intravesical growth of the medial lobe of the prostate, another limitation of this study is selection bias. Another limitation of our study is the fact that multiparametric MRI was not applied in all patients, as a result of the limited availability of this procedure. A randomized clinical trial among patients who do not have intravesical growth of the medial lobe of the prostate would be a better study design. The advantages of our study were prospective, single-surgeon study design, and single pathologist evaluation. On the other hand, the learning curve of the surgeon during the time of study has to be considered. Additionally, we reported BCR-free survival in the BNP and non-BNP groups.

5. Conclusions

According to the findings of our study, performing BNP in RP is not linked with an elevated risk of PSM and BCR. Preoperative PSA, bioptic Gleason score, and clinical T

stage of disease were identified as predictors of PSM occurrence. Further studies about this theme are required to examine the oncological outcomes of this method more thoroughly.

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Data Availability Statement: The data supporting reported results can be found upon request in the form of datasets available at the Clinic of Urology, University Clinical Centre of Serbia.

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