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What would happen if neurovascular bundles were left behind in radical retropubic prostatectomy?

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Aim: To evaluate whether nerve-sparing radical prostatectomy (NSRP) results in a residual tumor in the remaining neurovascular bundle (NVB).

Materials and methods: A total of 88 patients underwent bilateral NSRP. The ipsilateral NVB was excised uni-/bilaterally on the tumor side, separately. Factors affecting NVB involvement were evaluated.

Results: The mean patient age and preoperative serum prostate specific antigen (PSA) were 63.8 ± 6.2 years (49–76) and 12.9 ± 9.4 ng/mL (2.4–45.5), respectively. Digital rectal examination (DRE) suggested nodules in 34 patients (38.6%). Uni- and bilateral NVB resections were performed on 40 (45.5%) and 48 patients (54.5%), respectively, according to transrectal ultrasound-guided prostate biopsy (TRUS-Bx) pathology findings. NVB dissection was performed easily in all patients. The only factors correlated with tumor presence in the remaining NVB were a positive DRE finding (85.7% vs. 34.6%, P = 0.012), final pathology Gleason score (P = 0.016), capsular penetration/extracapsular extension (P = 0.001), and seminal vesicle invasion (P = 0.002). NVB involvement was detected in only 7 (8%) patients (6 had bilateral NVB resections), and the mean PSA was 19 ± 14.3 ng/mL in this group. The number of biopsy cores ranged between 6 and 27. In 15 patients, prostate cancer was diagnosed on repeat biopsies, and none had NVB invasion on pathology.

Conclusion: NVBs seem to have been excised unnecessarily on the tumor side (81 out of 88 patients). No preoperative parameter other than DRE status was correlated with NVB involvement. Further criteria should be evaluated in performing NSRP.

Key words: Prostate cancer, neurovascular bundle, radical prostatectomy

1. Introduction

In the western world, prostate cancer is the most commonly seen malignant disease and the second leading cause of cancer-related death in men. The prevalence of latent prostate cancer in the Turkish population has been found to be 19.7%. Surveillance, radical prostatectomy (RP), external beam radiotherapy, and brachytherapy are the most commonly used options in the management of localized prostate cancer (1,2)

Radical retropubic prostatectomy (RRP) is one of the main treatment modalities for organ confined prostate cancer (PCa). If neurovascular bundle(s) (NVB) is/are not preserved, RRP may lead to erectile dysfunction and urinary incontinence. Due to the widespread use of serum prostate-specific antigen (PSA) screening, the number of patients with early-stage PCa has increased while the mean patient age has decreased (3,4). As the patients become younger, the issue of preserving erectile function following RRP gains importance. Currently, no established criteria exist in the literature regarding the indications of NVB excision during the performance of RRP. Generally, the NVB on the ipsilateral side of the tumor is excised. NVBs are excised bilaterally if cancer is locally invasive (T3), if there is a palpable lesion at the prostatic apex, if Gleason grade 5 disease is present, if serum PSA > 20 ng/mL, and if the patient is known to have erectile dysfunction before the operation (4).

Park et al. showed that the rate of ECE was 32% and the positive surgical margin was 15% on the side of positive biopsy (5). On the other hand, preservation of the NVB is strongly recommended, especially in relatively young patients, if there is no risk for surgical disease control. For

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this reason, Cangiano et al. recommended intraoperative frozen section evaluation of the biopsy from the posterolateral side of the prostate (6).

The aim of our study was to evaluate whether nerve sparing (NS) surgery results in a residual tumor in the NVB that is left behind, and to correlate pathological characteristics of the tumor with NVB invasion if present.

2. Materials and methods

A total of 88 patients with localized (cT1c and cT2) PCa willing to be treated surgically between June 2004 and December 2008 were included in this prospective study.

Diagnosis of PCa was done via transrectal ultrasound-guided prostate biopsies (TRUS-Bx) for elevated levels of serum PSA (cut-off 2.5 ng/mL) or abnormal digital rectal examination (DRE) findings performed either at our institution or at external centers and referred to us.

Patients with a previous history of hormonal therapy or radiotherapy were excluded.

Preoperative evaluation included bone scan and computed tomography of the abdomen and pelvis in addition to serum PSA measurements. Clinical staging of the patients was done using the 2002 modification of TNM system.

Patient demographics are presented in Table 1. The mean patient age and preoperative serum PSA were 63.8 ± 6.2 (49–76) and 12.9 ± 9.4 ng/mL (2.4–45.5), respectively. The number of cores was available in 85 of the 88 patients, and ranged between 6 and 27. In 15 patients, PCa was diagnosed on repeat biopsies. The median GS was 6, and 54 patients (61.4%) were assigned a clinical stage of T1c disease.

Staging pelvic lympadenectomy and bilateral NS RRP were performed by one of the authors (M.D.B.) or under his supervision. Lymph nodes between the external iliac veins superiorly, around the obturator nerve and above the incised endopelvic fascia inferiorly, in the pelvic musculature laterally, and in the bladder wall medially were removed. Initially, RRP was performed using a bilateral NS technique on each patient. There was no difficulty in dissecting NVB from the prostate in any patient. After the surgical specimen was out, NVBs were removed separately on the tumor-bearing side according to TRUS-guided prostate biopsy findings. If the tumor was present unilaterally, the NVB was removed ipsilaterally, whereas in patients with bilateral tumors on biopsy, NVBs were removed on both sides separately.

All specimens removed surgically were reviewed by a single pathologist. In addition to assignment of a GS, factors evaluated in the surgically removed prostate included the largest diameter of the tumor, multifocality, the closest distance from the border of the tumor to the prostatic capsule, and/or the presence of capsular penetration (CP)/extracapsular extension (ECE). In the NVBs removed separately, the presence of tumor cells was investigated and recorded.

Patients were grouped according to the presence or absence of NVB invasion and whether the pathological features of the tumor in the surgical specimen were correlated with NVB invasion status. Among preoperative parameters, age, PSA levels, DRE findings, biopsy GS, and the presence of perineural invasion were correlated. Since the numbers of biopsy cores taken were not similar for all cases (6–27 cores), and the percentage and length of tumors in each core were not reported uniformly, these parameters could have not been correlated statistically with the presence of NVB invasion. Statistical analysis was done using SPSS 16.0. Differences were considered statistically significant if $P \leq 0.05$.

Postoperatively, 71 of the patients (80.3%) were reached and serum PSA levels measured in addition to physical examination in this group. The mean follow-up time was 34.1 ± 15.3 months (1–70 months). PSA recurrence was seen in 19.7% of the patients in their postoperative follow-up evaluations, and the mean time to recurrence was 13.1 ± 11.9 months (1–45 months). Bone scan, computerized tomography (CT) of the abdomen and pelvis, and TRUS/endorectal coil magnetic resonance imaging (MRI) were performed in patients with postoperative PSA recurrence, all of which were found to be negative for local recurrence or distant metastasis.

3. Results

Patient characteristics are represented in Table 1. Mean patient age and preoperative serum PSA levels were 63.8 ± 6.2 (49–76) years and 12.9 ± 9.4 ng/mL (2.4–45.5), respectively. DRE findings were suggestive of malignancy (nodules or enduration) in 34 patients (38.6%). Uni- and bilateral NVB resections were performed in 40 (45.5%) and 48 patients (54.5%), respectively, according to TRUS-Bx pathology findings. There was no difficulty in dissecting the NVB from the prostate at surgery. On final pathology, there was a single tumor focus in 58 patients (65.9%), whereas in 19 (21.6%) and 8 (9.1%) patients, 2 or more foci were noted, respectively. CP was present in 49 (55.7%) and ECE in 11 (12.5%) patients. In the remaining 28 patients (31.8%), the distance between the tumor and the prostatic capsule was <1 mm in 8 and >1 mm in 17 patients. No tumor was detected on final pathology in 3 patients (3.4%). PI was detected in 65 patients (73.9%). NVB involvement was detected in only 7 (8%) patients, 6 of whom had bilateral NVB resections. Table 2 represents the tumor characteristics of the patients with NVB invasion.

Comparisons of patients with and without NVB invasion are presented in Table 3. Among these parameters, DRE status ($P = 0.012$), capsular status (CS: ECE and/or CP) ($P = 0.001$), surgical margin (SM)

Table 1. Patient characteristics.

Age (mean, range)	63.8 ± 6.2 (49–76)
PSA (ng/mL)	12.9 ± 9.4 ng/mL (2.4–45.5)
Biopsy GS (n, %)	
≤6	60, 68.2%
7	18, 18.2%
8–10	12, 13.6%
DRE (n, %)	
Palpable tumor/enduration	34, 38.6%
Negative	54, 61.4%
NVB resection (n, %)	
Unilateral	40, 45.5%)
Bilateral	48, 55.5%
Specimen GS (n, %)	
≤6#	37, 42%
7	33, 37.5%
8–10	18, 20.5%
Capsular penetration (n, %)	49, 55.7%
Extracapsular extension (n, %)	11, 12.5%
NVB involvement (n, %)	
Positive	7, 8%
Negative	81, 92%
Available patients for follow-up (n, %)	71, 80.3%
PSA recurrence (n, %)	14, 19.7%
Follow-up (months) (mean, range)	34.1 ± 15.26 (1–70)
PSA recurrence time (months) (mean, range)	13.1 ± 11.9 (1–45)

#: including 3 patients in whom no tumor was detected on final pathology
PSA: prostate-specific antigen, GS: Gleason score, DRE: digital rectal examination, NVB: neurovascular bundle

positivity (P = 0.044), seminal vesicle invasion (SVI) (P = 0.002), and GS on final pathology (P = 0.016) were found to be significantly associated with NVB involvement. In 15 patients, PCa was diagnosed on repeat biopsies (secondary or tertiary), and none of them had NVB invasion on the final histopathological examination. In the postoperative follow-up, 71 patients (80.3%) were reached. Serum PSA levels were measured in addition to physical examination. The mean follow-up was 34.1 ± 15.3 months (1–70 months) with a mean time to PSA recurrence of 13.1 ± 11.9 months (1–45 months) (Table 1). Serum PSA recurrence was detected in 14 (19.7%) patients. NVB involvement was present histopathologically in only 2 patients among patients with postoperative PSA recurrence, and no difference was detected between the 2 groups in terms of PSA recurrence (P = 0.337) (Table 3).

Preoperative serum PSA level (P = 0.005) and final pathology GS (P = 0.004) were significantly correlated with postoperative serum PSA recurrence in our study (Table 4). Bone scan, abdomino-pelvic CT, TRUS, and/

Table 2. Tumor characteristics of patients with neurovascular bundle (NVB) invasion.

Pt #	Preoperative						Postoperative				
	DRE	PSA	Bx GS	GS	PI	Focus	CP	ECE	SVI	SM+	LN+
1		5.48	7	7	+	2	+				
2	+	22.9	5	8	+	1	+		+	+	
3	+	7.95	6	7	+	1		+			
4	+	20.3	7	8	+	1		+	+	+	
5	+	4.47	6	7	+	1		+	+	+	
6	+	28.3	9	10	+			+	+	+	
7	+	43.6	8	8	+	1		+	+		+

Pt #: patient number, DRE: digital rectal examination, PSA: serum prostate specific antigen, Bx GS: biopsy Gleason score, PI: perineural invasion, Focus: number of tumor focus in the specimen, CP: capsular penetration, ECE: extracapsular extension, SVI: seminal vesicle invasion, SM: surgical margin, LN: lymph node

Table 3. Comparison of patient characteristics according to NVB status.

	NVB + (n = 7)	NVB - (n = 81)	P
Age (mean ± SD)	64.0 ± 4.2	63.8 ± 6.4	0.969#
PSA (mean ± SD)	19.0 ± 14.3	12.4 ± 8.8	0.351#
DRE + (n, %)	6, 85.7%	28, 34.6%	0.012*
N of + Bx	5.2 ± 3.5	3.8 ± 2.3	0.254#
Bx GS (n, %)			
≤6	3, 42.9	57, 70.4%	
7	2, 28.6%	14, 17.3%	0.300‡
8–10	2, 28.6%	10, 12.3%	
PI (n, %)	7, 100%	58, 71.6%	0.183*
LN + (n, %)	1, 14.3%	4, 4.9%	0.346*
CS (n, %)			
ECE CP	5, 71.4% 2, 28.6%	6, 7.4% 47, 58%	0.001‡
SM + (n, %)	4,57.1%	16, 19.8%	0.044*
SVI (n, %)	5, 71.4%	11, 13.6%	0.002*
Sp GS (n,%)			
≤ 6[&]	0	37, 45.7%	
7	3, 42.9%	30, 37%	0.016‡
8–10	4, 57.1%	14, 17.3%	
PSA recurrence (n, %) μ	2, 33.3%	12, 18.5%	0.337*

Mann–Whitney test, *Fisher's exact test, ‡Pearson chi-square test
&: including 3 patients in whom no tumor was detected on final pathology
μ: serum PSA follow up is available in 6 and 65 patients in the NVB positive and negative group, respectively
NVB +: neurovascular bundle involved in prostate cancer, NVB -: neurovascular bundle not involved in prostate cancer,
PSA: prostate-specific antigen (ng/mL), DRE: digital rectal examination, N of + Bx: number of positive biopsy, Bx GS: biopsy Gleason score, PI: perineural invasion, LN +: lymph node positive, CS: capsular status, ECE: extra-capsular extension, CP: capsular penetration, SM +: surgical margin positive, SVI: seminal vesicle invasion, Sp GS: specimen Gleason score

Table 4. Patients' characteristics according to PSA recurrence.

	PSA R + (n = 14)	PSA R – (n = 67)	P
Age	63.3 ± 7.4	64.3 ± 6.1	0.728#
PSA	19.7 ± 11.8	11.1 ± 7.8	0.005#
DRE + (n, %)	7, 25.9%	20, 74.1%	0.233*
N of + Bx	5.1 ± 2.5	3.8 ± 2.5	0.081#
Bx GS (n,%)			
≤6	7, 50%	39, 68.4%	
7	4, 28.6%	11, 19.3%	0.424‡
8–10	3, 21.4%	7, 12.3%	
Sp GS (n,%)			
≤6	0	27, 45.4%	
7	9, 64.3%	21, 36.8%	0.004‡
8–10	5, 35.7%	9, 15.8%	

Mann–Whitney test
*Fisher's exact test
‡Pearson chi-square test
PSA: prostate-specific antigen (ng/mL), DRE: digital rectal examination, N of + Bx: number of positive biopsy, Bx GS: biopsy Gleason score, Sp GS: specimen Gleason score

or endorectal coil MR were performed in patients with postoperative elevated serum PSA levels, all of which were negative for local recurrence and distant metastasis.

4. Discussion

The trifecta after RRP is to cure cancer and preserve both urinary control and erectile function. With the NS RRP technique, erectile function and urinary continence can be preserved in the majority of patients, and morbidity rates are decreased significantly, especially in young men with organ-confined PCa. Because of its favorable results, this technique is gaining increasing popularity (4). However, positive SM status remains an important issue. Positive SM rates are reported to be 11%–47% and are likely to occur at any side of the prostate (7).

Positive SM rates depend on the tumor itself and the surgical technique used. Patients with serum PSA ≤ 10 ng/mL, biopsy GS ≤ 6, clinical stage of T1c, T2a disease (AJCC 1992), and a low number of positive TRUS-Bx biopsies are considered to have a decreased SM risk (8,9).

In order to decrease positive SM rates, different surgical modifications have been suggested. Alsikafi et al. performed a modified RRP, and they obtained an 11.1% positive SM rate, most commonly occurring at the prostatic apex and posterolaterally (8). Their surgical modifications included wide excision of the NVB posterolateral to the prostate when adjacent induration or tumor is present, division of the dorsal venous complex of the penis 10–15 mm distal to the prostatic apex, transection of the urethra 3 mm beyond the prostatic apex, and division of the anterior aspect of the urethra. Shah et al. recommended excision of an additional 2–3 mm of apical soft tissue margin in order to decrease the incidence of residual benign and malignant prostatic tissue in the apical soft tissue margin (10).

Smith et al. suggested wide excision of the NVBs and periprostatic soft tissue because they thought that wide excision does achieve negative SMs more often than if the NVBs are left intact (11).

While urologists try to decrease the positive SM rates following RRP, the demographics of patients diagnosed with PCa have changed. Currently, men are diagnosed more often with localized PCa at a younger age due to the widespread use of PSA-based screening programs, and are still sexually active and very much concerned about their erectile function (3,4). Therefore, preservation of sexual function without sacrificing cancer control has become more important, and this trend has forced urologists to perform NS RRP procedures more commonly than in the past.

Unfortunately, ECE most frequently occurs at the posterolateral side of the prostate, where the NVBs are attached (5,8,12). Therefore, special attention should

be paid not to harm the NVB but at the same time not to leave any residual tumor during the dissection of the NVB. There are no strict parameters available to predict NVB invasion currently. Although the patient selection criteria for performing NS RRP have not been well described, urologists make their own decisions in excising NVBs, using criteria such as DRE, GS, and the presence of perineural invasion in TRUS-Bx. Some surgeons make their decisions about whether to perform NVB excision according to DRE findings or intraoperative palpation of the prostate (5,9,12). Quinlan et al. excised NVBs in some cases that they suspected to harbor tumors intraoperatively and demonstrated that in 75% of these selected cases the tumor did not go deeper than 2 mm (13). They concluded that NVB excision may be unnecessary even if the urologic surgeon thinks that NVB invasion is present during the performance of RRP.

Some authors have found that wide excision of the NVB on the side of positive biopsy decreased the positive SM rate, and excision of the NVB on the positive biopsy side may be required for the optimizing of cancer control (5). D'Amico et al. concluded that patients with low-risk prostate needle biopsy specimens may benefit from NVB resection on the side of invasion (9). Cangiano et al. suggested the use of intraoperative frozen section monitoring in order to select the right patients for NS RRP (6). They evaluated the lateral margins during NS RRP and pointed out that their technique can help to distinguish local tumor extension from other benign processes such as stones, inflammation, and changes associated with transurethral resection. In order to find a predictor for NVB invasion, we compared NVB invasion with preoperative PSA, DRE, and biopsy findings in addition to pathologic features of PCa on final pathology. Our results confirmed once again that there is a great discrepancy between preoperative biopsy and final pathology GS, as well as clinical and pathological stagings. According to preoperative biopsy findings, 60 out of 88 patients had GS ≤ 6. However, final pathological analysis revealed that only 37 patients had PCa with GS ≤ 6. Additionally, all of our patients were assigned a preoperative clinical stage of <cT2c; 11, 20, and 16 patients had ECE, SM positivity, and SVI, separately or in combination. Palpation of nodules and/or enduration on DRE, and final pathologic findings of GS, CP, ECE, SM positivity rates, and SVI were found to be significantly different between patients with and without residual tumors in the NVB tissue removed separately. Postoperative PSA recurrence rates were 33.3% and 18.5% in patients with and without NVB invasion, respectively, but this difference was not found to be statistically significant between groups (P = 0.337).

In our study, none of the patients diagnosed with repeat prostate biopsies who underwent radical prostatectomy had NVB invasion on final pathological examination. Very recently, Chen et al. have demonstrated that the percentage of patients with organ-confined disease was significantly higher and the percentage of patients with extra-prostatic extension was lower in patients who underwent radical prostatectomy following repeat prostate biopsies, which supports our findings (14).

We think that neither preoperative PSA nor prostate biopsy findings predict NVB invasion and specifically indicate removal of the NVB ipsilateral to the tumor site in the majority of patients, except with regard to DRE findings, at least due to results of the present series.

Final pathological findings including GS, CP, ECE, SM positivity, and SVI were all correlated with NVB involvement. Of the patients diagnosed with repeat prostate biopsies, none of them had NVB invasion on final pathological examination. This finding might be used in making the decision for NVB preservation in patients who are diagnosed with PCa on repeated prostate biopsies.

We cannot comment on the effect of the number of positive biopsy cores or percentage of cores involved by the tumor due to nonuniformity of the pathological evaluation.

In deciding whether to preserve or not to preserve NVB, new markers or parameters must be developed. Until that time, urologists should discuss the issue with the patient and decide together whether to preserve the NVB preoperatively.

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