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Prostate Cancer

Nerve Distribution along the Prostatic Capsule

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Abstract

Objectives: Recent literature describes indications for a more-complex course of fibres of the neurovascular bundle (NVB), despite the widely held assumption that it is gathered at the rectolateral side of the prostate. The objective of this study therefore was to determine the typical pattern of nerve distribution along the prostatic capsule.

Materials and methods: Permanent sections of 31 patients, who underwent non-nerve-sparing radical prostectomy (RP) at our institution, were investigated.

A total of 186 slides taken from the apex, mid-part, and base of the prostate was analyzed by microscopy. Before microscopy, slides were divided into 12 sectors and numbered clockwise starting from ''1'' for left ventral sides to ''6'' for the rectal sides (accordingly, ''12''–''7'' for right half). Every single nerve and ganglion in the prostatic capsule and the periprostatic tissue was counted in each sector.

Results: The majority of nerves found in the sectors corresponded to the typical location of the NVB at the rectolateral sides of the prostate (4/5 or 8/9 o'clock sectors). In these two sectors, a median of 45.9–65.6% of counted nerves per half was found. However, a significant amount of nerves (21.5%–28.5%) was detected above the horizontal line.

Conclusions: We conclude that 1/5–1/4 of nerves can be found along the ventral circumference of the prostatic capsule. To preserve a maximum number of nerves, we therefore recommend a modification of the surgical technique by focusing on a high incision for nerve sparing on the ventral parts of the prostate.

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1. Introduction

A nerve-sparing (NS) variant of radical prostatectomy (RRP), as described by Walsh et al. [1] is based on the finding that the cavernosal nerves (CNs), responsible for erectile function, pass the lower pelvis on the outside of the prostatic capsule. It is commonly assumed that the vast majority of these

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neuronal fibres are gathered in the so-called neurovascular bundle (NVB), which is supposedly located at the rectolateral side of the prostate [2]. Therefore, the key step during the classic NS-RRP is the incision of the lateral pelvic fascia just above the NVB and the lateral displacement of it within the correct plane.

Some more-recent reports indicate that the NVB might be more spread around the capsule. As a result, some authors advocate a modification of the standard nerve-sparing technique [3–6].

However to our knowledge there is no detailed description of the exact nerve anatomy in the literature to date, particularly regarding the ventral aspect of the prostate. Therefore, it is the intention of this report to determine the typical pattern of nerve distribution along the complete prostatic capsule.

2. Materials and methods

We investigated the permanent sections of 31 patients, who underwent non-nerve-sparing RRP at our institution. Specimens were processed by the 3-mm step section technique according to the Stanford protocol. Whole-mount histologic sections were prepared whenever possible and stained with hematoxylin-eosin.

Six representative slides of each patient were analyzed by microscopy (Olympus BH-2; Japan; magnification steps: 20×, 40×, 100×, 200×). Each slide was taken from the apex, the mid-part and the base of the prostate for the left- and right-hand side, respectively.

Before microscopy, slides were prepared by centring them on a half circle divided into six sectors and marking the sector borders directly on the coverslip of the specimen (Edding 400 permanent marker; Germany). Numbering of the sectors started clockwise from "1" for ventral sides to "6" for the rectal sides for the left prostatic half and accordingly from "12" to "7" for the right half (Fig. 1).

The focus of interest lay on the outside of the prostatic capsule and the periprostatic soft tissue, where the sum of every single nerve and ganglion was determined per sector.

For statistical analyses, the data of 186 counted prostatic half sides of the left- and right-hand side were combined. The median of nerves per prostatic half for all three locations, apex, mid-part and base, was determined. In addition, the median number of nerves for each of the six sectors at each of the three locations was determined. The median percentage of nerves found in a certain sector was defined as the median number of nerves in this sector divided by the median for the prostatic half at the corresponding prostatic location (apex, mid-part, base).

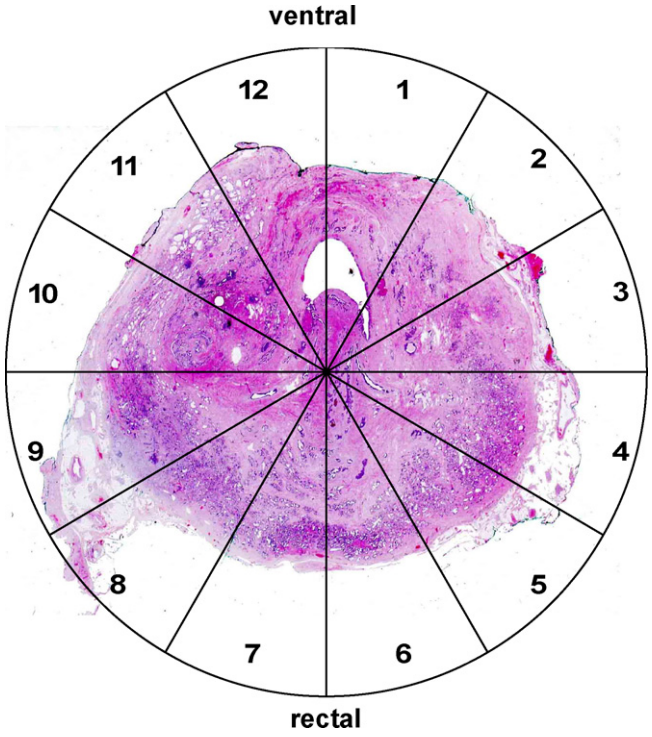


Fig. 1 – Whole-mount section of prostate with sector borders.

3. Results

The median number of spotted nerves per prostatic half was 53. The median and maximum numbers of nerves per each sector for both prostatic halves are summarised in Table 1. The median of nerves counted at the apex was significantly lower than the median identified at the mid-part and base sections. No significant difference was seen between the median nerve counting of the left and the right prostatic halves; therefore, the corresponding sectors of both halves were combined for further calculation (Fig. 2). As expected, the vast majority of nerves were found in the sectors corresponding to the rectolateral sides of the prostate in the 4 and 5 o'clock sectors and thereby at the typical location for the neurovascular bundle. In these two sectors, a median sum of 45.9%, 61.5%, and 65.6% of counted nerves were found in apex, mid-part, and base specimens, respectively. Only 3.3–5.4% of identified nerves were found in the area neighbouring the rectal Denonvilliers fascia (sector 6).

However, a significant amount of nerves was found above the horizontal line marked by the 3 o'clock sectors. The sum of the median percentage of nerves detected in sectors 1–3 were 21.5%, 21.3%, and 28.5% for apex, mid-part, and base, respectively.

4. Discussion

Radical prostatectomy marks the standard therapy of localized prostate carcinoma for patients with a life expectancy greater than 10 yr, who accept treatment-related complications [7].

Table 1 – Median (med.) and maximum (max.) numbers of counted nerves per sector for left and right side separately

		Sector	1	2	3	4	5	6	med. Σ
left half	Apex	median n	2,5	2	4	8,5	7	2,5	44,5
		max. n	13	13	31	44	42	12	
	Mid-part	median n	4	3	6,5	22	16	2	59
		max. n	10	15	31	40	63	16	
	Base	median n	3,5	5	9	20	16	3	53
		max. n	21	18	38	80	96	13	
		Sector	12	11	10	9	8	7	med. Σ
right half	Apex	median n	4	2	3	9	11	2	35
		max. n	13	18	23	66	39	39	
	Mid-part	median n	4	3	6	24	13	2	64
		max. n	20	15	32	55	62	8	
	Base	median n	3	6,5	6,5	23	14	2	62,5
		max. n	10	37	50	52	32	24	

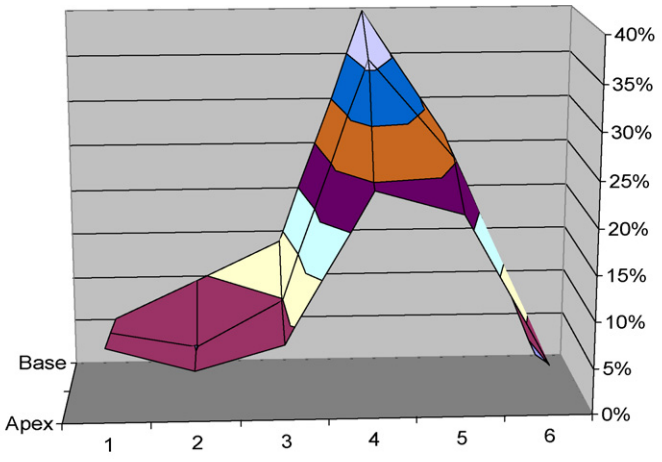
Sector 1-12: min n=0

min: minimum.

Since Walsh et al. [1] described the nerve-sparing technique of radical prostectomy, evoking a more-distinguished comprehension of the complex anatomy of the genital nerve courses in surgical urologists, a growing interest in understanding and thereby better preserving the lower pelvis innervations has been established.

However, with increasing research on the topic, it is becoming more obvious that the erectile function is not simply induced by a single bilateral nerve string at the outside of the prostatic capsule. Moreover, clinical experience, like the rather unsatisfactory results of nerve graft interposition [8,9] or the highly variable results in postoperative erectile function after NS-RRP [10,11], underlines the complexity of the neural anatomy.

Generally, parasympathetic fibres from S2–S4 activate the vasodilatation of the corpora cavernosa via the pelvic splanchnic nerves, whereas sympathetic fibres derived from Th12 to L2 within the



Sector	1	2	3	4	5	6	med. ∑
Apex	8,1%	5,4%	8,1%	24,3%	21,6%	5,4%	37
Mid part	6,6%	4,9%	9,8%	36,1%	25,4%	3,3%	61
Base	5,2%	9,5%	13,8%	39,7%	25,9%	5,2%	58

Fig. 2 – Percentage of median (med.) number of nerves per sector divided by median sum per half of each location (left and right combined).

hypogastric nerve trigger the secretion and rhythmical contraction of the ductus deferentes, the seminal vesicles, and the prostate [12]. It is widely accepted that the CNs, which generate the erection in the cavernosal corpora, derive from the pelvic plexus, in which both above-mentioned vegetative strands submerge. Furthermore, the CNs are supposed to run on the rectolateral aspect in a fascial triangle together with accompanying branches from the inferior vesical vein and artery, and thereby contribute to the NVB [1,3].

However, divergences in literature already start with respect to the formation of the various components within the NVB: Takenaka et al. [13] postulated that the fibres of the pelvic splanchnic nerves join the hypogastric fibres within the NVB in a considerably more spray-like manner and at a far more distant region than originally described. In their study they performed fresh cadaver dissections of seven male pelvises and found that the pelvic splanchnic nerves reach the prostate more than 20 mm distant to the vesicoprostatic junction. Their somewhat surprising conclusion was that CNs cannot be included in a surgical reconstructed NVB, and appear to be spread and located beyond the NVB. Moreover, these authors assumed that the maintained erectile function after NS-RRP therefore is exclusively caused by a highly variable portion of both sympathetic and parasympathetic fibres belonging to the hypogastric nerves alone, as already described in female anatomy [14].

To provide a detailed anatomic map for nerve-sparing radical prostatectomy from the laparoscopic perspective, Tewari et al. [15] performed simulated laparoscopic and robotic RPs in 12 male cadavers followed by open anatomic dissections. Among other findings, the authors described additional, smaller nerve fibres ramifying in the prostatic and Denonvillier's fascia outside the main bundles of the NVB.

In a careful study, Costello et al. [3] performed detailed anatomic dissections of 12 male cadavers. They found that the branches of the pelvic plexus form three projections, of which the most inferior, running between the rectum and the postolateral prostatic capsule, supplies the NVB. Variable numbers of macroscopic distinct nerves within the NVB, ranging from 6 to 16, were seen in their study. Furthermore, the authors were able to discriminate three functional but also anatomically defined compartments within the NVB. These compartments are supposed to innervate the levator ani muscle, the rectum, or, in case of the most anterior compartment, the corpora cavernosa and the prostate. They also noted that the neuronal components of the NVB are extensively spread by up to 3 cm (anterior–posterior), particularly at the prostatic apex and base. On the basis of these findings, they see an explanation as to why a single sural nerve graft would not always guarantee an adequate interposition to prevent an erectile dysfunction after non-NS-RRP.

In another recent study, Lunacek et al. [4] also described the topographic relationship of the CN to the prostate and its neighbouring structures. Besides eight adult male specimens, they investigated 29 male foetal specimens in different prenatal stages to follow the anatomic development during the growth of the prostate after the 10th week of gestation. The authors found that, with the proceeding of the prostatic expansion during its development, the formerly lateral and dorsal position of the CN increasingly dispersed anteriorly along the convex surface of the capsule. Moreover, this volume-induced spreading of the nerve fibres could also be followed during the development of benign prostatic hyperplasia in the investigated adult specimens. The authors therefore suggested a modified technique of nerve sparing, which they called ''curtain dissection,'' starting at a more-anterior point for the NVB preparation.

The data gathered by Lunacek et al. is notably coherent with the results described in this report.

To quantify the nerve fibres in the ventral aspects of the prostatic capsule that we frequently found in post-RRP specimens, we divided the transversal prostatic capsule circumference into 12 sectors. In each of the six sectors per prostatic half, the nerve and ganglional fibres were counted to derive a sector-specific ''nerve-density'' of the capsule. Surprisingly, with 21–28% of all counted nerves, a relatively high amount of nerve fibres was consistently found on the anterior half of the prostatic capsule.

Because of the method of investigation applied in this study, we can only speculate about the function of these nerve fibres. We assume that a fraction of the latter seems to contribute to the ''additional'' functions described by Costello [3]. This hypothesis is supported by the finding that the median total nerve sum goes down by nearly 40% on the route to the prostatic apex. According to Costello's study, these fibres supposedly innervate the prostate as parts of the anterior compartment. However, even at the apex close to the distal passage of the NVB alongside the membranous urethra, the percentage of nerves found on the anterior prostatic half remained relatively high at 21.5%.

We earlier described a clear connection between postoperative erectile function and the number of nerve fibres preserved [16]. Since we can neither prove nor rule out that the anterior fraction of nerves on the prostatic capsule described here do not contribute to the innervation of the cavernosal corpora, we, similar to Lunacek et al. [4], previously [17] recommended an adjustment in surgical technique. The central modification is to start the incision of the parapelvic fascia high up (e.g., above the 2 and 10 o'clock positions) to preserve a maximum number of nerves during the following preparation.

Certainly one limitation of this study is that we cannot provide follow-up data regarding improvement of potency rates attributable to this modification. However, in our latest analyzed bilateral NS-RRP series, 12-month follow-up potency rates range up to 70.3% without and 96.4% with the use of phosphodiesterase-5 inhibitors [18].

It certainly would be of clinical importance if the additional sparing of the ventral portion of nerves also resulted in functional improvements. In a recent publication Montorsi et al. [6] also stated that incision of the levator fascia should start high up to preserve the largest possible fraction of cavernous nerve fibres. The authors described excellent results regarding the postoperative erectile function and recovery of continence attributable to this modification. The establishment of the high incision affected the margin rate in neither their study nor ours; we identified a positive margin rate of around 16% in pT2 tumors before the modification and 5.4–10.4% afterwards (depending on surgeon and time period).

5. Conclusions

We conclude that, with between a fifth to a fourth of all counted nerves neighbouring the prostatic capsule, a significant number can be found along the ventral parts (i.e., ''outside'' the classic NVB). This conclusion taken together with the review of current literature, indicates that the wide-held understanding of a condensed NVB strictly located at the posterior-lateral aspect of the prostatic capsule is doubtful. Fibres of the CN might extend far more to the anterior aspect than is yet reflected by common surgical technique. However, since no functional investigation could be performed, we are not able to prove yet if these nerves really contribute to the erectile function. Nevertheless, we recommend the described modification in surgical technique of nerve sparing on the basis of the previously described positive relationship between the number of preserved nerves and the postoperative potency rates.

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Editorial Comment

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The authors are commended for a well designed study evaluating peri-prostatic neural anatomy. This subject has come into sharp focus recently with several investigators presenting both histological and physiological evidence questioning the hitherto accepted teaching of two distinct cavernosal nerves running posterolaterally between the prostate and rectum [1–3]. The technique of prostatic fascia sparing robotic radical prostatectomy has been described and there is strong suggestion that this results in better preservation of erectile function [4–6]. The authors' study provides confirmatory evidence to the concept of a network of periprostatic nerves and to variations in prostatic neuroanatomy.

What is the distribution of the periprostatic nerves?

The authors' study has shown that although over 50% of periprostatic nerves are concentrated between 4 o'clock and 7 o'clock (the site of the putative neurovascular bundle), a quarter of all periprostatic nerves are situated anterolaterally and laterally. These findings are complementary to other published studies. Kiyoshima et al. first showed that the classical NVB was seen in only 48% of 79 prostates; in 52% they could not identify a distinct NVB and the cavernosal nerves were seenas a network laterally and anteriorly in the prostatic fascia. They also found a distinct plane of adipose tissue separating the prostatic capsule and periprostatic fascia in 50%; a fact that may be used to develop a safe plane of dissection during radical prostatectomy. Lunacek et al. [7] in fetal studies showed that the NVB which were situated posterolaterally in fetuses less than 9 weeks gestation (sex undifferentiated stage) were pushed anterolaterally as the prostate developed in utero, possibly explaining the findings of Kiyoshima et al.

What is the function of the periprostatic nerves?

The mere presence of nerves in the periprostatic fascia does not mean that they are concerned with erections or that they ultimately innervate the corporal tissue. These nerves may possibly innervate the prostate or the urethral sphincter. The best evidence to prove their role in erections would be to trace these nerves distally to the corpora cavernosa using vital dyes and demonstrate evidence of increased cavernosal pressure on stimulation. Unfortunately such a study is impossible for technical reasons. The authors' study answered this question indirectly by evaluating sections from the base, mid-zone and apex. They found that up to 28% of nerves counted in the prostatic fascia at the base of the prostate were present at the apical section (indicating that these nerves did not innervate the prostate). Sato et al. showed that in rats cavernosal pressures increased on preoptic nerve stimulation despite transecting the cavernosal nerves (when the prostatic fascia was kept intact), again providing indirect evidence of cavernosal nerves in the prostatic fascia. However, this subject will continue to be controversial unless direct evidence of cause and effect is provided.

Are results better when these accessory cavernosal nerves are preserved?

Several centers have described modifications to the technique of radical prostatectomy incorporating preservation of the prostatic fascia [4–8], essentially dividing the prostatic fascia more anteriorly than the classical nerve sparing technique of Walsh. However, there is only one study that reports on functional outcomes with this technique. Dr Hulland reports higher potency results with his technique. We await a detailed report from his center.

For sure, there are nerves on the sides and the front of the prostate, but do they innervate the cavernous tissue? Or just the prostate? The jury is out on this issue. In the absence of evidence to the contrary, and with the suggestion that preservation of these nerves results in improved maintenance of erectile function, the onus is on the nay sayers to prove that an anterior release of the prostatic fascia is not beneficial to patients, As other groups such as these authors publish their results, the answer will become evident.

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