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Review – Prostate cancer

Penile morphometric changes after radical prostatectomy: Evidence-based

J.I. Martínez-Salamanca[a,*], *C. Martínez-Ballesteros*[a], *L. Portillo*[a], *I. Moncada*[b], *and J. Carballido*[a]

[a]*Area of Sexual Medicine, Urology Service, Hospital Universitario Puerta de Hierro-Majadahonda, Universidad Autónoma de Madrid, Madrid, Spain*
[b]*Urology Service, Hospital Sanitas-La Zarzuela, Madrid, Spain*

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A B S T R A C T

Introduction: Radical prostatectomy in all its approaches is the treatment of choice for localized prostate cancer and especially in young, sexually active patients with a desire to keep their sex life. In addition to the well-known and defined postoperative erectile dysfunction, erectile silent period causes, in many patients (9-71%), structural changes, in the penile structure, sometimes irreversible. These tissue changes, resulting in a loss of length and girth, concern patients.

Objective: To systematically review to date published data in the literature regarding penile changes after radical prostatectomy.

Material and methods: We performed a systematic search in: PubMed, EMBASE, Cochrane, SCOPUS, Science Citation Index period January 1990 to September 2009 for the terms "prostatectomy", "organ size", "fibrosis", "sexual activity", "erectile dysfunction", "penile size", "radical prostatectomy", "prostatic neoplasms", "body weights" and "penis measures".

Seven series of patients were selected for analysis.

Results: We described the different measurement methods and their potential biases and differences. Also, we reviewed main physiopathogenic theories to explain this phenomenon. Finally, we detail the results of different series of patients reported.

Conclusions: It seems to be a proven fact that the penis undergoes major changes in its length and girth after radical prostatectomy. Several authors have communicated the data of their series and the different treatment options (5PDE inhibitors, vacuum devices, penile extenders, etc.). Strategies addressed to preserve and protect cavernous tissue and tunica albuginea after the procedure, as well as to increase oxygenation and allow erection to be recovered in the shortest posible time positive will impact on the quality of life of our patients.

*Corresponding author.
E-mail: msalamanca99@hotmail.com (J.I. Martínez-Salamanca).

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Cambios morfométricos peneanos tras prostatectomía radical: revisión de la evidencia

Palabras clave:
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Penile girth
Penile changes
Erectile dysfunction
Quality of life

RESUMEN

Introducción: La prostatectomía radical en cualquiera de sus abordajes representa el tratamiento de elección del cáncer localizado de la próstata y especialmente en pacientes jóvenes sexualmente activos con deseo de mantener su vida sexual. Además de la bien conocida y definida disfunción eréctil postoperatoria, el período de silencio eréctil causa en muchos pacientes (9-71%) cambios estructurales, a veces irreversibles, en la estructura peneana. Estos cambios tisulares derivan en una pérdida de longitud y grosor del pene, que preocupa a los pacientes.

Objetivo: Revisar de manera sistemática los datos publicados en la literatura médica hasta el momento en relación con los cambios peneanos tras prostatectomía radical.

Material y métodos: Realizamos una búsqueda sistemática en PubMed, EMBASE, Cochrane, SCOPUS y Science Citation Index durante el período de enero de 1990 a septiembre de 2009 para los términos «prostatectomy», «organ size», «fibrosis», «sexual activity», «erectile dysfunction», «penile size», «radical prostatectomy», «prostatic neoplasms», «body weights» y «penis measures».

Se seleccionaron 7 series de pacientes para su análisis.

Resultados: Se exponen los diferentes métodos de medición peneana y sus potenciales sesgos y diferencias. Asimismo, repasamos las principales teorías fisiopatogénicas para explicar este fenómeno. Finalmente, se detallan los resultados de diferentes series de pacientes comunicadas.

Conclusiones: Parece un hecho demostrado que el pene sufre cambios importantes en su longitud y grosor tras prostatectomía radical. Diferentes autores han comunicado los datos de sus series así como las diferentes opciones de tratamiento (inhibidores de la 5-PDE, dispositivos de vacío [DV], extensores del pene, etc.). Las estrategias encaminadas a preservar y a proteger el tejido cavernoso y la túnica albugínea tras el procedimiento así como las que aumenten la oxigenación y permitan recuperar la erección en el menor tiempo posible impactarán positivamente en la calidad de nuestros pacientes.

Introduction

Radical prostatectomy (RP) is the first therapeutic option for patients with clinically localized prostate cancer.[1] Despite continuous improvements in the surgical technique, erectile dysfunction (ED) is a problem that ought to be treated, as it affects the quality of life of a large percentage of patients (20-97%) after surgery.[2,3] Consideration must also be given to the fact that men who experience postoperative ED may also exhibit a loss of length and girth of the penis.[4] Curiously, this issue has received only marginal attention in publications. Several studies have assessed the consequences of RP on sexual and urinary function, but only a few have studied the loss of penile length after surgery.[4-7] These studies showed penile shortening in 9 to 71% of patients included in their analyses. This is an important finding because the loss of penile volume can have a major negative impact on patients' quality of life, even among those who recover their baseline erectile function with or without phosphodiesterase type 5 (PDE5) inhibitors after surgery.[5,8]

The pathogenesis of this phenomenon is still debatable. The hypothesis of an overall shortening of the urethra resulting from the removal of the prostate (and thus of the prostatic segment of the urethra) is not consistent with the anatomy of the pelvis. The membranous urethra is fixed at the urogenital diaphragm, and thus not easily retractable from the pelvic floor. Most authors suggest that the mechanisms of fibrotic changes that develop in the cavernous tissue during the postoperative period of erectile silence may reduce the distensibility and volume of the corpora cavernosa.[9-11] Mulhall recently proposed a hypothesis to explain the changes in penile length. The author divides the changes—and thus the pathophysiologic mechanism—in two periods. One early and reversible period that is the result of a theoretical sympathetic overstimulation, and a later period of permanent structural damage resulting from the denervation caused by apoptosis, hypoxia, and subsequent collagenization-[12] Measuring the length of the penis immediately after surgery is necessary to elucidate these fascinating hypotheses. Additionally, if this pathogenic model is valid, penile changes should be minimized once the erectile function is recovered.

In this review, we have attempted to include all studies offering evidence that helps to understand this emerging phenomenon.

Table 1 – Patient series: Preoperative penile measurements

	Patients, n	Mean age	Pre-RP							
			Flaccidity		Suprapubic fat	Stretching	Erection		Functional
		Years	Length	Girth		Length cm	Length	Girth	Length
Dalkin et al[27]	39	–	–	–	–	12.7 (10.0-15.4)	–	–	–
Wessels et al[13]	80	54 (14)	–	–	–	12.45 (2.71)	–	–	15.75 (2.62)
Briganti et al[8]	33	56	13.2	11.1	–	–	16.8	15.6	–
Savoie et al[7]	63	59	9.3 (2)	9.4 (1.4)	2.5 (0.9)	13.5 (2.6)	–	–	–
Gontero et al[14]	126	65	8.59 (2.2)	9.59 (1.23)	–	11.02 (2.48)	–	–	–
Goodwin et al[39]	81	59	9.35 (1.6)	9.5 (0.98)	–	12 (1.8)	–	–	–

RP: radical prostatectomy.

Material and methods

We performed a systematic search in PubMed, EMBASE, Cochrane, SCOPUS, and Science Citation Index for the period between January 1990 and September 2009 for the terms "prostatectomy", "organ size", "fibrosis", "sexual activity", "erectile dysfunction", "penile size", "radical prostatectomy", "prostatic neoplasms", "body weights", and "penis measures". All articles were analyzed according to the evidence levels of the Centre for Evidence-Based Medicine, Oxford. All the studies analyzed are level 3b (individual case and control studies), and four are low quality series of cases, cohort studies, and case and control studies.

Measuring the penis: methodology and controversies

In a very interesting review, McCullough[10,11] writes that after innumerable measurements of penile length after RP, two facts are ascertained. It is important to make several measurements at different times. The exact nature of the measurement ought to be clearly identified. Some studies used the stretched penile length (SPL) and others used the erection length (EL) after injection of vasoactive agents. Wessels et al[13] have clearly shown that SPL correlates with EL. The measuring technique is also important. Authors should state whether they used a measuring tape or a ruler, and whether the suprapubic fat pad is included (tables 1 and 2).

Although it might seem that the degree of stretching of the penis may affect the results, the inter-observer measurement variations assessed at New York University were merely less than 20 mm. McCullough claims to have discovered that measurements that include the length of the glans penis tend to be more variable, in contrast to measurements up to the balanopreputial sulcus. The glans seems to be more malleable and therefore more subject to distortion than the shaft of the penis. In a longitudinal study on penile length after RP, a rigid ruler was used to measure the penis from the symphysis pubis (including the fat pad) to the balanopreputial sulcus; lengths similar to those reported in previously published studies were obtained.[11]

The length of the glans penis is supposedly comparable to that of the fat pad. The circumference of the penis is more difficult to measure when the penis is flaccid than when it is stretched due to the redundant skin of the flaccid penis. It is much easier to measure reliably the circumference of the erect penis because the redundant skin is stretched as a result of the erection.

For this team of researchers, ambient temperature is not a confounding factor because they judge that in most offices the temperature is the same in winter and in summer.[11] SPL/EL were measured by both the physician and female nurses. The inter-observer variation was less than 20 mm. Therefore, the gender of the observer does not seem to pose significant differences.

In contrast, Gontero et al state that any variation in the environment, the temperature of the room, and even the gender of the evaluator can affect the final measurement.[14]

Table 2 – Patient series: Postoperative penile measurements

	Patients, n	Mean age	Pre-RP							
			Flaccidity		Suprapubic fat	Stretching	Erection		Functional
		Years	Length	Girth		Length cm	Length	Girth	Length
Dalkin et al[27]	39	-	-	-	-	12.3 (9.9-15.4)	-	-	
Wessels et al[13]	80	54 (14)	8.85 (2.38)	9.71 (1.17)	2.85 (1.59)	12.89 (2.91)	12.30 (1.31)		
Briganti et al[8]	33	56	13	11	-	-	16.5	15.3	-
Savoie et al[7]	63	59	8.1 (1.8)	9.8 (1.2)	2.0 (0.8)	12.4 (2.2)	-	-	-
Gontero et al[14]	126	65	7.54	9.62	-	9.49	-	-	-
Goodwin et al[39]	81	59	7.7 (1.8)	9.7 (0.91)	-	9.9 (2.1)	-	-	-
Fraiman et al[4]	-	60	12.1	8.7	-	15.2	-	11.6	-

RP: radical prostatectomy.

Several methodological issues need to be considered when measuring the effects of RP on penile morphology. The number of patients should be appropriate for the power sought for the study, and most studies to date include a limited number of patients. Which two points used to determine penile length is also critical.

The classic points used are the tip of the glans to the pubic symphysis; however, other researchers exclude the measurement to the bone in order to exclude the thickness of the prepubic fat pad. This fat pad might have changed in size during the 12 months after surgery, but it is unlikely to have changed much in the days between the surgery and the catheter removal.

Variations in the technique for measuring penile length between preoperative and postoperative measurements can also affect the results. Additionally, the person recording penile dimension measurements is key, and should be the same both times, before and after surgery. Also, the timing of the measurements postoperatively may affect results. Finally, it is important to collect the comorbidity profiles of the patients. In Gontero's study, 80% of patients had preoperative ED, and thus it could be inferred that they were not healthy; however, a low International Index of Erectile Function score does not necessarily indicate an organic etiology. This issue is especially important when we try to extrapolate these data to our individual clinical practices.[15]

Pathogenesis: fundamentals and theories

Data derived from animal models of cavernous nerve injury show histologic and morphologic changes in the tunica albuginea that may represent the substrate for the overall final penile lesion. These changes can be mitigated by the postoperative administration of PDE5 inhibitors. There is growing evidence that the morphologic changes that occur during the period of neuropraxia after neurovascular-sparing RP cause structural damage of the organ. The histologic changes seem to reflect major penile morphometric changes, but no study has examined prospective and simultaneously the histologic changes of the corpus cavernosum and the morphometric changes of the penis. Morphometric changes seem to be more pronounced in men experiencing more severe postoperative ED.[11]

While there is evidence that penile rehabilitation may result in functional improvement in the long term, there is none that post-prostatectomy penile rehabilitation can prevent the morphologic changes in the corpora cavernosa or the loss of penile length and girth. More prospective randomized studies are required to determine which is the best surgical technique (open, laparoscopic, or robotic) and penile rehabilitation strategy to maximize functional recovery and to minimize the damage in the cavernous tissue after surgery.

Form the histologic point of view, apoptosis has been demonstrated after penile denervation in rats,[16] and the resulting fibrosis in the cavernous tissue that may contribute to the final shortening of the penis has been recently assessed and described.[9]

Mulhall et al studied this mechanism and attribute the changes to four basic principles:
1. Penile structural anatomy.
2. Cavernosal nerve injury and associated alterations.
3. Hypoxia of the cavernous tissue and its aftermath.
4. Sympathetic hyper-activation.[12]

The corpora cavernosa are composed of two distinct tissues: the trabecular smooth muscle and the tunica albuginea. Penile smooth muscle is subject to contractile and relaxation forces. Relaxation is accomplished through the release of nitric oxide (NO) and the generation of second-messengers such as cGMP and cAMP.[17] Contractility of the smooth muscle is generally tonic and under the control of erectolytic neurotransmitters such as adrenaline. Factors that result in reduced NO secretion (as occurs in patients with lower motor neuron lesions, e.g. those with diabetes and after RP) lead to relaxation or to decreased distensibility of smooth muscle and may cause loss of length. It is recognized that even in the hands of an experienced surgeon using neurovascular-sparing surgery, some damage (neuropraxia) is likely to occur to the cavernous nerve. Furthermore, some have suggested that the tunica albuginea may also undergo structural changes after RP, but other than a few data on Peyronie's disease after RP, currently there are no data to support tunical structural alterations[9].

Neural injury has been shown to lead to end-organ or tissue structural alterations. In 1995, Carrier et al[18] showed that in a rat model of bilateral cavernous nerve transection there was a significant reduction in NO synthesis as early as 3 weeks after injury, and that these reductions were sustained at 6 months.

Klein et al[16] showed that after cavernous nerve injury, the smooth muscle undergoes apoptotic changes; these findings were confirmed by User et al,[19] who showed that the weight of the penis and the DNA content were significantly reduced, especially when the nerve transection was bilateral. Apoptosis was more evident beneath the tunica albuginea of the smooth muscle.[19]

Leungwattanaki et al[20] also showed that cavernous neurotomy leads to the up-regulation of fibrogenic cytokines and the subsequent collagenization of the trabecular smooth muscle.

Similarly, it has been suggested that the chronic absence of erectile activity (postoperative erectile silence) leads to hypoxia in the cavernous tissue.[21] In the flaccid state, the corpora cavernosa have a venous pO_2 that favors the secretion of fibrogenic cytokines such as TGF-β. During erection, the smooth muscle is oxygenated, resulting in the secretion of endogenous prostaglandins 1, which in turn inhibit the production of fibrogenic cytokines.[21]

Thus, the health of the erectile tissue is based, to some extent, on the balance between erection and flaccidity. In patients lacking erectile activity, as often occurs in the early stages after RP, the scale tips in favor of hypoxia and collagen production; if this is not prevented, it can cause permanent injury in the cavernous tissue.

Sattar et al[22] showed that there may be a correlation between the contents in smooth muscle and the level of intracavernous pO_2. Moreland et al[21,23,24] published articles reporting that in cell culture models, cavernous smooth muscle cells exposed to hypoxia produce preferentially TGF-β, and this affects the release of endogenous prostaglandins 1 once the cells return to conditions of normoxia.

Finally, the concept of sympathetic hyperinnervation refers to the ability of autonomic sympathetic fibers (which inhibit erection-size reduction in flaccidity) to regenerate more quickly after injury than parasympathetic fibers (which favor erection-size increase in flaccidity). This implies an increase in the sympathetic tone, which results in a smaller penile size.[25]

To summarize these concepts in a working hypothesis: Changes in penile length can be classified as early and late. Regarding immediate changes, the nerves in the corpus cavernosum are subject to a Wallerian degeneration as a response to the neural injury caused by RP. In the early stage, when the sympathetic nerve function is increased, the penis is a hypertonic organ with sympathetic hyperactivation; taking into consideration that the penis smooth muscle is very contractile as a response to adrenergic tone, the result is a penis often described by patients as buried. Mulhall[12] asserts that his experience is that this hypertonic state is more marked during the first 3-6 months after surgery.

The late structural changes are the result of actual irreversible structural alterations in the smooth muscle of the corpus cavernosum. These structural changes most likely are the result of a combination of factors:

- Denervation of the apoptosis associated with neural injury.
- Hypoxia-induced cavernous collagenization in patients with a delayed return to the erectile function.

Case series and treatments

Gontero et al[14] monitored the changes in the penis after RP by measuring it at several intervals from the time of catheter withdrawal to one year after surgery. They also assessed whether neurovascular-sparing surgery and sexual function recovery have an effect on final penile size. The authors showed that neurovascular preservation and recovery of erectile function were independent predictive factors for a loss in length 12 months after surgery. This was the first team to show in a multivariate analysis that the postoperative erectile function is a predictor of loss of length[14] (tables 1 and 2).

Mulhall[15] writes that the published studies suggest that permanent structural alterations in the first 4 months after surgery are uncommon,[26] but Gontero found that the maximum degree of shortening occurs at the time of removing the catheter. This author has not satisfactorily explained the mechanism for such a dramatic loss of length in such a short period; it may be associated with the percentage of nerve sparing in his series.[14]

On the other hand, these authors assert that the degree of neurovascular preservation predicts venous leak as well as

the time to onset of this leak.[15] Another possible explanation for the phenomenon observed by Gontero is the decrease of pressure applied on the penis when the catheter is removed. This hypothesis is supported by the absence of change in the values of penile girth at that moment.

Dalkin et al[27] conducted a study to test whether early intervention after RP with a vacuum erectile device (VED) prevents changes such as shortening in the penile erectile tissue. This study presents a total of 42 patients with adequate preoperative sexual function who underwent nerve-sparing RP; the penis was measured by a single researcher before surgery and 3 months after surgery. A VED was used daily and continuously for 90 days as of one day after catheter removal. A penile shortening of 1.0 cm or more was considered significant. Thirty nine of the 42 men completed the study. Among the men (36) who used the VED at least 50% of the possible days, only one (3%) had a 1.0 cm shortening. Two (67%) of the men who used the device fewer days had a 1.0 cm shortening. When compared to prior studies in which men experience a significant postoperative penile shortening, it seems that early intervention with daily use of VED leads to a significantly lower risk of penile shortening ($p<0.0001$)[27] (tables 1 and 2).

Zippe et al[28] showed that patients used the VED successfully after RP, confirming the device's safety and tolerability. Numerous studies have been published that show that patients have good quality erections with the use of a VED in 84-95% of cases.[29-34] Most patients report an improved sex life,[31] given by better and more frequent intercourse and orgasm. This results in better marital relations and patient self-esteem.[30-32,35]

Colombo et al[36] published a series with 52 patients using a VED with no constriction ring daily, regardless of intercourse, with an improvement of spontaneous erections in 60% of the men studied.

Raina et al[37] showed that the use of a VED after RP (nerve-sparing or not nerve-sparing) improved the score in the International Index of Erectile Function, a preservation of the penis length, and a quick return to spontaneous erections.[38]

Conclusions

The changes that occur in the penis after prostatectomy seem to be the result of a multifactorial process in stages that is directly linked to nerve injury and the absence of erections (hypoxia). Furthermore, it constitutes one additional objective in the complex process of sexual rehabilitation, and is a permanent complaint among the vast majority of patients.

Strategies aimed at preserving and protecting the cavernous tissue and the tunica albuginea after the procedure and to increase oxygenation and allow erection to be recovered in the shortest possible time have a positive impact on the quality of life of our patients.

Conflict of interest

The authors state that they have no conflicts of interest.

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