Functional Outcome of Radical Retropubic Prostatectomy: Sexual function and urinary continence

Yvette Desirée Dubbelman

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Lay-out: Han van Oers and Indy van den Haak
Cover: The cover is designed by Han van Oers. My daughter Indy coloured the sketch with pentels. Aladdin and Yasemin are having a big problem: Aladdin is incontinent en impotent. Yasemin throws her heart and her love for Aladdin away.

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Functional Outcome of Radical Retropubic Prostatectomy: Sexual function and urinary continence

Functionele resultaten van de radicale retropubische prostatectomie: Seksuele functie en continentie voor urine

Proefschrift

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Contents


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Part I

General Introduction

General Introduction and scope of the thesis

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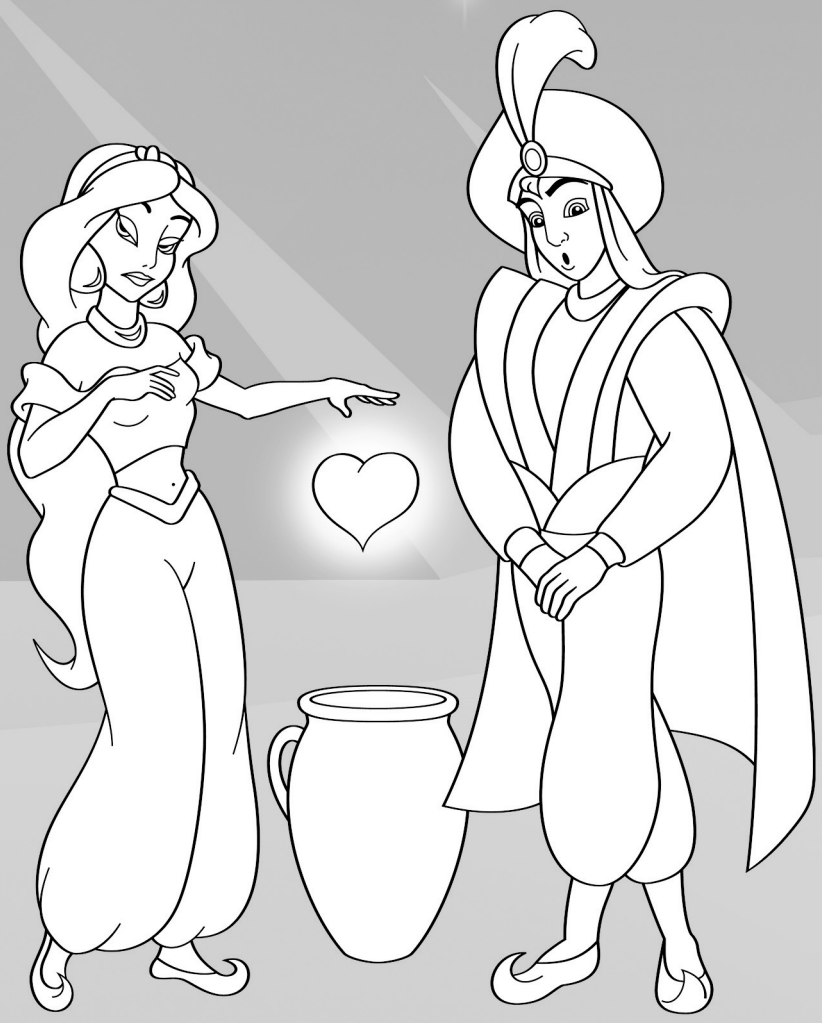

Introduction

Prostate cancer is the most common non-dermatological cancer in men in the Western world. [1] During the last 2 decades, the widespread use of early detection programs based-on prostate-specific antigen (PSA) screening has resulted in an increase of diagnosed prostate cancer. Screening of prostate cancer has resulted in a change of patient characteristics presenting with localized prostate cancer. Nowedays, men diagnosed with this disease are at a younger age, have less comorbidities and a longer life expectancy. [2] For patients with organ confined disease several treatment alternatives are available: active surveillance, brachytherapie, external beam radiation and radical prostatectomy. Radical prostatectomy is considered the standard for long-term cure in patients with a life expectancy of more than 10 years. Along with extended life expectancy, there is a need for better functional outcomes, including sexual function and urinary continence.

Open radical prostatectomy (RP) was first described in 1904 bij HH Young. [3] During this operation the prostate, seminal vesicles and ejaculatory ducts were removed by perineal incision. A new anastomosis was made between the urethra and the bladder. This operation was associated with significant peri- and postoperative mobidity, including excessive blood loss, urinary incontinence and sexual dysfunction. In the late 1970s and early 1980s several detailed anatomical studies provided important insights into the periprostatic anatomy, especially that of the dorsal venous complex, neurovascular bundles and striated urethral sphincter. [4-5] These observations allowed the development of an anatomical approach to RP, with significant reduction in postoperative morbidity.

1. Impotence

- First reported erectile dysfunction rates after radical retropubic prostatectomy (RRP) in a general urological practice in the 1980s and 1990 ranged between 11-40%. [6,7] After the introduction of the nerve-sparing technique potency rates improved to 31-86%. [8,9] Nerve-sparing radical prostatectomy became the operation of choice in potent and sexual active men. However, despite the preservation of the neurovascular bundles a significant number of patients still suffer from loss of sexual function. The aetiology of changes in sexual function

after radical prostatectomy is suggested to be multifactorial. The relative impact of psychosexual, vascular and neurogenic factors remains unclear. Beside erectile function, little information is available on other sexual functions like orgasmic function, sexual activity and desire. Alterations in sexual function are associated with significant reductions in emotional and physical satisfaction, which in turn may lead to sexual-avoidance behaviour and secondarily to discord in relationships. An intact sexual desire, erection and orgasm are common also in ageing men and are considered important to preserve. [10,11]

This thesis focuses on the aetiology and prognostic factors of sexual dysfunction after RRP. It aims to:

- evaluate hemodynamics of penile vascularisation before and after RRP in order to look for causes in the onset of erectile dysfunction.
- analyse sexual function before and after RRP, not only focusing on erectile dysfunction, but also on other important domains of sexual function (sexual interest, sexual activity, orgasm and spontaneous erections).

2. Incontinence

Urinary incontinence is one of the most bothersome complication of a radical prostatectomy and has a negative impact on quality of life. Reported incontinence rates six months after surgery vary between 10-87%. [12-14] Improved understanding of the anatomy of the prostatic apex and the pelvic floor, as well as attention to details of surgical techniques, like nerve sparing techniques, have all contributed to higher postoperative continence rates. Despite these improvements incontinence is still a problem in 6-15 % of men. [15-17]

The exact aetiology remains still unclear. Potential explanations for urinary incontinence after radical retropubic prostatectomy are detrusor dysfunction (impaired contractility, overactivity or decreased compliance), sphincter incompetence (due to the disruption of the sphincteric innervation, hypoperfusion or direct damage to the sphincteric muscles) and treated bladder outlet obstruction. [18,19] Urethral sphincter incompetence is generally considered to be the most important contributing factor to post-radical prostatectomy incontinence. An accepted therapy for post radical prostatectomy incontinence is physical therapy with pelvic floor muscle exercises. [20,21] However, studies of the effect of pelvic floor muscle exercises [PFME] on the

recovery of continence after radical prostatectomy have led to conflicting conclusions. [22]
The second part of this thesis focus on the aetiology and prognostic factors of incontinence after RRP.

It aims to:

- determine the reason for postoperative incontinence after radical retropubic prostectomy, and to find predisposing preoperative risk factors.
- analyse the impact of radical retropubic prostatectomy (RRP) on detrusor function, bladder outflow resistance and urethral sphincter function and its relation to post-radical prostatectomy continence status.
- confirm the beneficial effect of physiotherapist guided pelvic floor muscle exercises (PFME) versus PFME by an information folder only on the recovery of continence after RRP.
- analyse the effect of intensive PFME on lower urinary tract function.

A good understanding of the functional anatomy of the urinary sphincter complex is crucial to achieve continence. Pre- and postoperative assessment of sphincter function might help predict the outcome and help to choose the best treatment for incontinence in these men.
The last part of this thesis aims to:

- review the different assessment techniques to objectify urethral sphincter function before and after radical prostatectomy and to assess the value of specific measurement techniques as a preoperative diagnostic tool in counseling men with localized prostate cancer.

At the end of this thesis, I hope to be able to give an answer to the following question: Who is the most ideal candidate for undergoing a radical prostatectomy?

References

[1] Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010; 60:277-300.
[2] Noldus J, Graefen M, Haese A et al. Stage migration in clinically localized prostate cancer. Eur Urol 2000;38:74-78
[3] Young HH. The early diagnosis and radical cure of carcinoma of the prostate. J of Urol 2002;168:914-921 (reprinted version from the original version from Bull Johns Hopkins University;1905:315-321)
[4] Reiner WB, Walsh PC. An anatomical approach to the surgical management of the dorsal vein and Santorini's plexus during radical retropubic surgery. J Urol 1979;121:198-200
[5] Walsh, P.C. and Donker, P.J. Impotence following radical prostatectomy: insight into aetiology and prevention. J. Urol 1982;128,492-497.
[6] Fowler FJ, Barry MJ, Lu-Yao G, Roman A, Wasson J and Wennberg JE. Patient-reported complications and follow-up treatment after radical prostatectomy. Urology 1993;42: 622-629.
[7] Stanford JL, Feng Z, Hamilton AS et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer. JAMA 2000;283:354-360.
[8] Geary ES, Dendinger TE, Freiha FS and Stamey TA. Nerve sparing radical prostatectomy: a different view. J Urol 1995;154: 145-149.
[9] Walsh PC, Marschke P, Ricker D and Burnett AL. Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. Urology 2002;55:58-61.
[10] Helgason AR, Adolfsson J, Dickman P et al. Sexual desire, erection, orgasm and ejaculatory functions and their importance to elderly Swedish men; a population-based study. Age and aging 1996;25:285-291.
[11] Nicolosi A, Laumann EO, Glasser DB et al. Sexual behavior and sexual dysfunctions after age 40: the global study of sexual attitudes and behaviors. Urology 2004;64:991-997.
[12] Minervini R, Felipetto R, Morelli G et al. Urodynamic evaluation of urinary incontinence following radical prostatectomy: our experience. Acta Urol Belg 1996;64:5-8.
[13] Lepor H, Kaci L.The impact of open radical retropubic prostatectomy on continence and lower urinary tract symptoms: a prospective assessment using validated self-administered outcome instruments. J Urol 2004;171;1216-1219.
[14] Rudy DC, Woodside JR, Crawford ED. Urodynamic evaluation of incontinence in patients undergoing modified Campbell radical retropubic prostatectomy: a prospective study. J Urol 1984;132(4):708-12.
[15] Donnellan SM, Duncan HJ, MacGregor RJ, et al. Prospective assessment of incontinence after radical retropubic prostatectomy: objective and subjective analysis. Urology 1997;49:225-230.
[16] Fontaine E, Izadifar V, Barthelemy Y, Desgrippes A, Beurton D. Urinary continence following radical prostatectomy assessed by a self-administrated questionnaire. Eur Urol. 2000 feb;37(2):223-7.
[17] Catalona WJ, and Basler JW. Return of erections and urinary continence following nerve sparing radical retropubic prostatectomy. J Urol 1993;150:905-7
[18] Kleinhans B, Gerharz E, Melekos M, Weingartner K, Kalble T and Riedmiller H. Changes of urodynamic findings after radical retropubic prostatectomy. Eur Urol 1999; 35: 217-22
[19] John H, Sullivan MP, Bangerter U, Hauri D and Yalla SV. Effect of radical prostatectomy on sensory threshold and pressure transmission. J Urol 2000; 163(6): 1761-6
[20] Ribeiro LHS, Prota C, Gomes CM, de Bessa J, Boldarine MP, Dall'Oglio MF, Bruschini H and Srougi M. Long-term effect of early postoperative pelvic floor biofeedback on continence in men undergoing radical prostatectomy: a prospective, randomized, controlled trial. J Urol 2010;184:1034-1039
[21] Van Kampen M, De Weerdt W, Van Poppel H, et al. Effect of pelvic-floor re-education on duration and degree of incontinence after radical prostatectomy: a randomised controlled trial. Lancet 2000;355:98-102.
[22] Wille S, Sobottka A,Heidenreich A, et al. Pelvic floor exercises, electrical stimulation and biofeedback after radical prostatectomy: results of a prospective randomised trial. J Urol 2003;170:490-493.

Male urethral anatomy and sexual response cycle

Yvette Dubbelman

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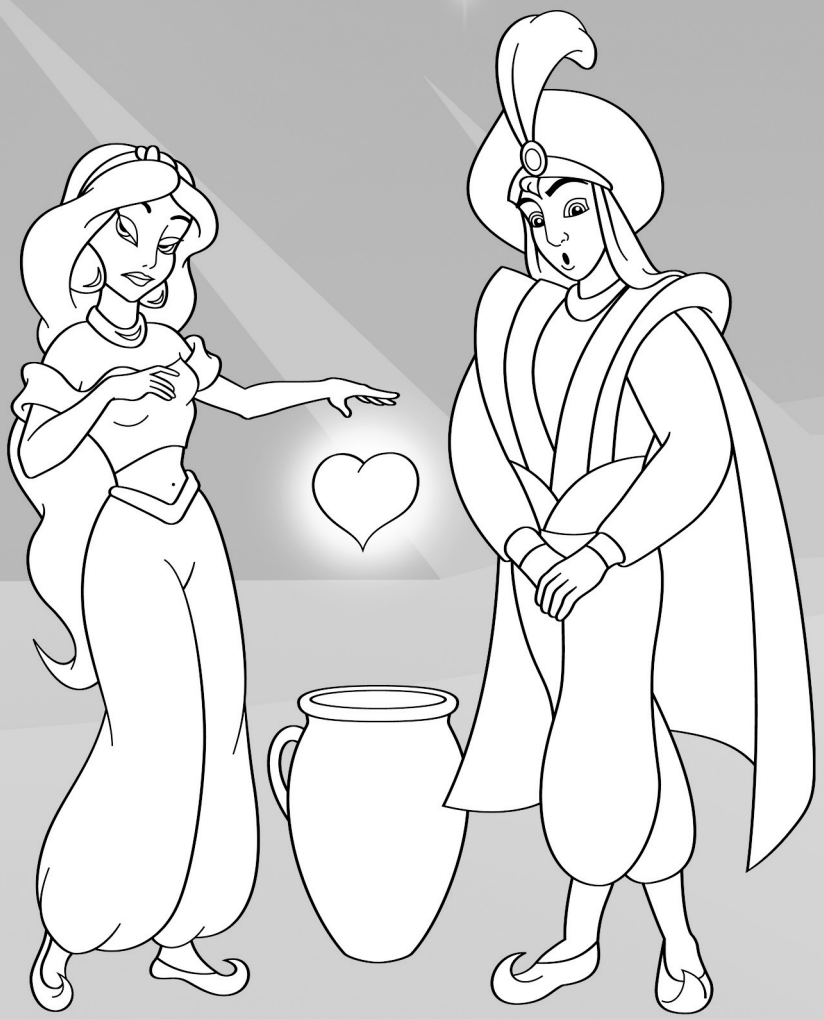


Male urethral anatomy

The average length of the male urethra is 20-22 cm. It is divided into an anterior (15 cm) and a posterior part (5 cm). The anterior urethra contains the bulbous urethra (7 cm), the penile urethra (6 cm) and the navicular urethra (2 cm). The urethra is surrounded by the corpus spongiosum within the penis. The penile urethra makes up more than half of the total anatomic urethral length. The posterior urethra contains the membranous urethra (1-2 cm) and the prostatic urethra (3-4 cm). The membranous urethra (which extends from the prostatic apex to the bulbar urethra) traverses the urogenital diaphragm, and contains the external urethral sphincter.

The prostatic urethra lies between the membranous urethra and the bladder neck. Smooth muscle fibers extend into the bladder neck and preprostatic urethra to form the internal sphincter, which preserves continence and prevents retrograde ejaculation.

The Urethral sphincter is the muscular mechanism that controls the retention and release of urine from the bladder. There are, in fact, two urethral sphincters, which may be considered to function independently:

(1) **Internal sphincter** (also named proximal sphincter / lissosphincter): smooth musculature of the bladder base, vesicourethral junction (bladder neck) and posterior urethra act as the internal urethral sphincter and prevents urine from leaving the bladder to enter the urethra. The function of this sphincter is coupled with detrusor activity, and involuntary bladder contractions will lead to bladder neck opening. This sphincter cannot be willfully controlled but is under automatic (involuntary) control by the brain.

(2) **External sphincter** (distal sphincter): the mechanism is comprised of intrinsic (passive continence) and extrinsic components.

The intrinsic part of the external urethal sphincter itself consists of two different muscle types. The inner muscle layer surrounds the urethra completely and consists of smooth muscle fibers and elastic tissue. The smooth muscle layer can be subdivided into an outer more circumferential oriented layer and an inner longitudinal oriented layer. It is capable to sustain tonic contraction which is responsible for the continence. The outer muscle layer consists of striated muscle fibers, has a vertical cylindrical to conical form and has been described as horseshoe shaped (rhabdosphincter).

The rhabdosphincter is the only striated muscle that acts unvoluntarily. [1] The fibers have been found to be predominantly of the slow-twitch type what suggests a passive function in urinary control. [2]

The extrinsic part of the external urethral sphincter includes periurethral striated muscles situated in the urogenital hiatus (transversus perineal muscles), muscles of the pelvic floor and the urogenital diaphragm (also called perineal membrane). It provides a second means of stopping the escape of urine from the body. This sphincter is under voluntary control.

The anatomical and functional continuity of the lissosphincter or the proximal sphincter mechanism is permanently disrupted during radical prostatectomy. Intrinsic sphincter deficiency (ISD) of the urethra is a condition characterized by poor sphincter function that can be present after radical prostatectomy. ISD typically causes stress incontinence, with urinary leakage during coughing, laughing, sneezing, or other activities that increase intra-abdominal pressure. However, it may also cause urinary leakage without an increase in intra-abdominal pressure.

Meticulous apical dissection, striated sphincter preservation techniques, mucosal eversion, anastomotic methods and cavernosal nerve preservation appear to protect the distal sphincter mechanism and may improve continence. [3-6] Bladder neck sparing technique appears to promote early urinary continence but the continence rate after 1 year remains unchanged.

Neuro-vascular anatomy of the lower urinary tract

Neuronal innervation of the lower urinary tract is considered part of the autonomic (motor i.e. efferent pathway) and somatic (sensory i.e. afferent pathway) nervous systems (Figure 1). The sphincteric mechanism of the bladder neck is innervated by the sympathetic system. The innervation of the distal sphincter is more complex, both the somatic system (pudendal nerve), sympathetic and parasympathetic system are involved. Voluntary control of micturition is controlled by the central nervous system.

- **The autonomic system** (parasympathetic and sympathetic components) receives visceral sensation and regulates smooth muscle actively during conscious and involuntary lower urinary tract functions. *Sympathetic contributions* from T10-L2 (hypogastic nerve) and *parasympathetic contributions* from S2-4 (pelvic nerve or

nervi erigentes) compose the neuronal control system and is called the pelvic plexus. The pelvic plexus innervated the bladder neck, the seminal vesicals, the vasa deferentia, the prostate, the urethral sphincter and the erectile bodies. [7,8] Caudal fibers of this plexus form the cavernous nerves (i.e. nervi erigentes). These nerves travel to the prostate and the membranous urethra and supply the autonomic innervation of the intrinsic smooth muscle of the membranous urethra. [9]

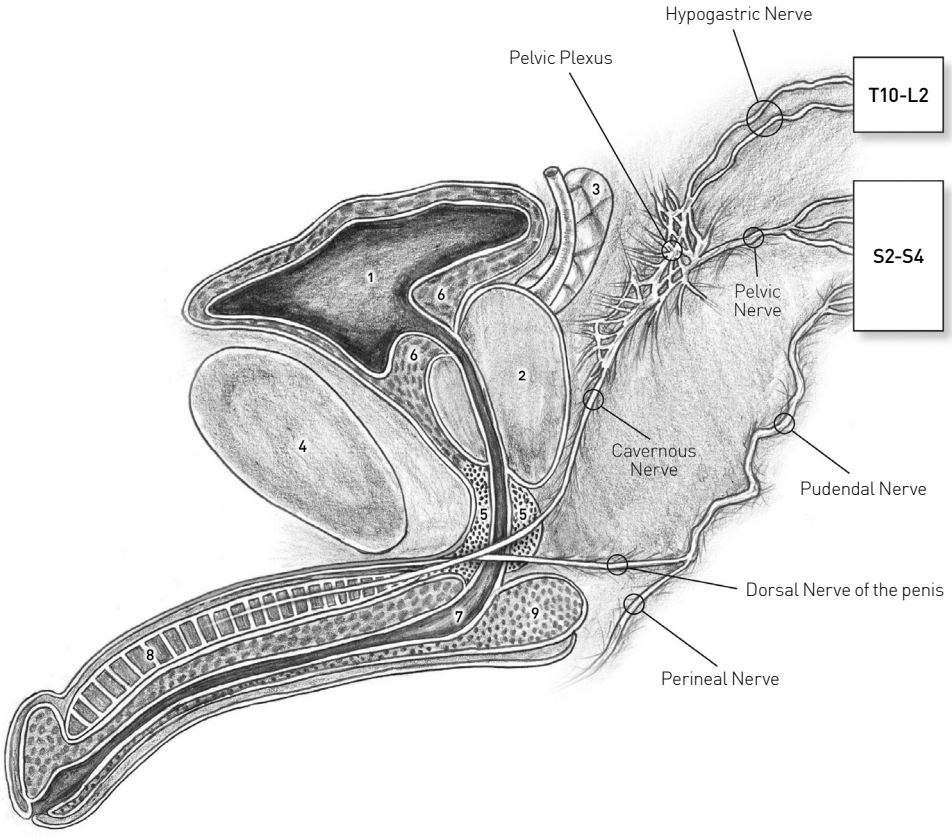
- **The somatic system** receive contributions from S2-S4 and consists of the pudendal nerves [10] and innervate the pelvis, the urethral sphincter, the perineum and the striated muscles of the pelvic floor (levator ani). [11-13] The pudendal nerve terminates as the perineal nerve and as the dorsal nerve of the penis (responsible for penile sensation).

It is clear that the innervation of the urethral sphincter is complex. The exact contribution of the different nerves is still controversial. Studies showed that section of one of these nerves does mostly not affect sphincter function significantly. [9,10] Schwalenberg et al [14] reviewed and evaluated published research results on neuroanatomy of the male pelvis. The concluded that despite the enormous increase in investigations on neuroanatomical structures of the male pelvis: the autonomic innervation of the smooth muscle component of the urethra remains to be elucidated and the composition and morphology of the urethral sphincter is still ambiguous.

Neurovascular bundle

Distal branches of the lower part of the pelvic (inferior hypogastric) plexus combined with adjacent vessels form the neurovascular bundle. The neurovascular bundle (containing the cavernous nerves and accessory pudendal vessels) is classically found along the posterolateral portion of the prostate. [8] However, Alsaid et al [15] showed in human male foetus that a significant amount of fibers travelled along the anterolateral surface (and also in the anterior and posterior position) of the prostate to reach the prostatic apex and the external urethral sphincter. At the external urethral sphincter the neurovascular bundles have two divisions: cavernous nerves (continuation of the anterior and anterolateral fibers) and corpus spongiosum nerves (continuation of the posterolateral fibers).

Figure 1. Simplified representation of penile innervation.



1. Urinary bladder
2. Prostate
3. Seminal vesicle
4. Symphysis pubis
5. Striated urethral sphincter (area of the distal sphincter)
6. Area of the proximal sphincter
7. Urethra
8. Corpus cavernosum
9. Corpus spongiosum

Vascularisation

The blood supply to the prostate and the membranous urethra is via branches from the internal iliac artery (formerly known as the hypogastric artery). The blood supply to the bulbo-penile urethra is dependent of the internal pudendal artery. The pudendal artery continues as the perineal artery to form the common penile artery. This artery divides into the terminal branches; the bulbar artery, the urethral artery, the cavernosal artery (also named the deep artery), the perineal artery, the inferior rectal artery and the dorsal artery of the penis. The venous drainage contains the deep dorsal vein, the periprostatic venous plexus and the internal pudendal veins.

Male sexual response cycle

The penis contains two corpora cavernosa (cylindrical, sponge like erectile tissue) and the corpus spongiosum. The male sexual response cycle consists of desire, excitement, plateau, orgasm, and resolution. Erection is a reflex response initiated by visual, olfactory, or imaginative stimuli impinging upon supraspinal centers or by genital stimulation that in turn activates spinal reflex mechanisms. The initial event, penile erection, is produced by arteriolar dilatation and increased blood flow to the erectile tissue of the penis. The pelvic plexus is beside urinary control also responsible for the mechanism of erection and ejaculation. Sacral parasympathetic and thoracolumbar sympathetic nerves provide the efferent vasodilator imput to the penis. Parasympathetic nerves also stimulate secretion from the seminal vesicles and prostate and Cowper's glands during the plateau phase. [16] Parasympathetic fibers (including nervi erigentes) that primarily derive from the pelvic and sacral splanchnic nerves and originate from the ventral rami of S2-4 are mainly responsible for vasodilatation and the increase in arterial blood flow in the corpora cavernosa during erection. [2] The cavernous nerves (autonomic) regulates penile blood flow during erection and detumescence and the dorsal nerve (somatic) is primarily responsible for penile sensation.

Nerve impulses cause the release of neurotransmitters from the cavernous nerve terminals and of relaxing factors from the endothelial cells in the penis. Nitric oxide is probably the neurotransmitter mediating penile erection. [17,18]

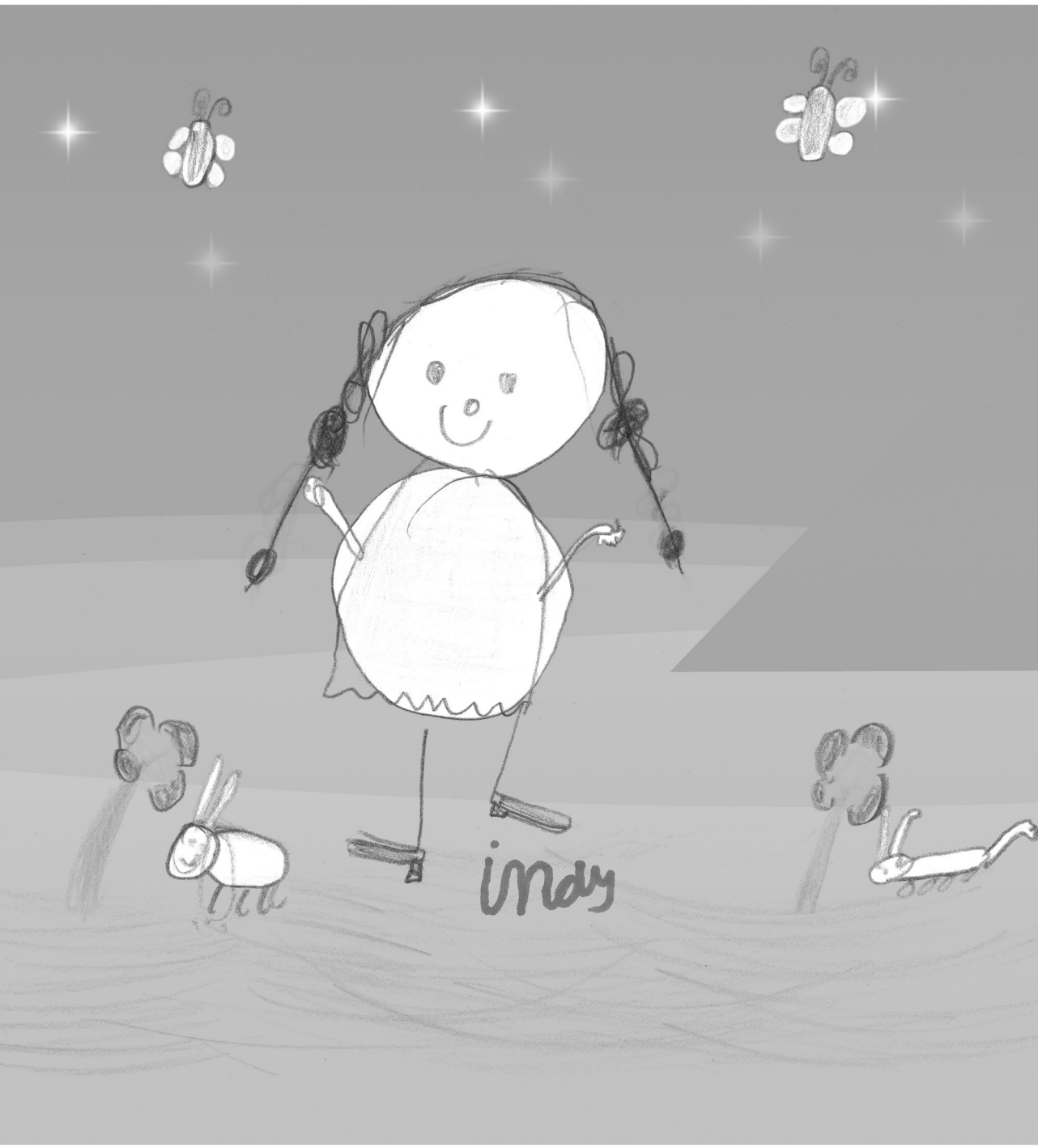
The orgasmic phase is characterized by seminal emission and ejaculation and the accompanying sensations. Emission of semen into the urethra depends on sympathetic nerves that elicit contractions of smooth muscles in the vas deferens, seminal

vesicles, and prostate. Rhythmic contractions of striated muscle (bulbocavernosus and ischiocavernosus) generated by efferent pathways in the pudendal nerve (somatic component) eject semen from the urethra. [16] Sympathetic fibers that derive from the hypogastric nerve originating mainly from ganglia of T10-L2 are responsible for ejaculation. [2]

Leading up to the point of orgasm, the internal sphincter, the surrounding bladder neck, and the external sphincter are closed in unison, generating a high pressure zone within the prostatic urethra. At the time of emission (semen deposition into the prostatic urethra) the external sphincter opens abruptly and the high intra prostatic pressure combined with periurethral musculature contraction (ischiocavernosus and bulbospongiosus muscles) leads to antegrade ejaculation in propulsive fashion. Simultaneous with ejaculation, the bladder contracts reflexively. [19]

References

[1] Dorschner W, Stolzenburg JU. A new theory of micturition and urinary continence based on histolmorphological studies. Urol Int 1994;52:185-188
[2] Walz J, Burnett AL, Costello AJ, Eastham JA, Graefen M, Guillonneau B. A critical analysis of the current knowlegde of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. Eur Urol 2010;57:179-192.
[3] Steiner MS, Morton A, and Walsh PC. Impact of anatomical radical prostatectomy on urinary incontinence. J Urol 1991;145:512-515.
[4] Catalona WJ, and Basler JW. Return of erections and urinary continence following nerve sparing radical retropubic prostatectomy. J Urol 1993;150:905-7
[5] O'Donnell PD and Finan BF. Continence following nerve-sparing radical prostatectomy. J Urol 1989;142:1227-8.
[6] Eastham JA, Kattan MW, Rogers E. Risk factors for urinary incontinence after radical prostatectomy. J Urol 1996;156:1707-13.
[7] Alsaid B, Bessede T, Diallo D, Moszkowicz D, Karam I, Benoit G, Droupy S. Division of autonomic nerves within the neurovascular bundles distally into corpora cavernosa and corpus spongiosum components: immunohistochemical confirmation with three- dimensional reconstruction. Eur Urol 2011;59:902-9.
[8] Schlegel PN and Walsh PC. Neuroanatomical approach to radical cystoprostatectomy with preservation of sexual function. J Urol 1987;138:1402-6
[9] Steiner MS, Morton RA, Walsh PC: Impact of anatomical radical prostatectomy on urinary continence. J Urol 1991:145:512-514.
[10] Tanagho EA, Schmidt RA, Gomes De Araujo C: Urinary striated sphincter: What is its nerve supply? Urology 1982;20:415-417
[11] Lawson JON: Pelvic anatomy: Pelvic floor muscles. Ann R Coll Surg Engl 1974;54:244-252
[12] Zvara P, Carrier S, Kour N-W, Tanagho EA: The detailed neuroanatomy of the human striated urethral sphincter. Br J Urol 1994; 74:182-187
[13] Hollabaugh RS Jr, Dmochowski RR, Steiner MS. Neuroanatomy of the male rhabdosphincter. Urology 1997;49:426-34
[14] Schwalenberg T, Neuhaus J, Liatsikos E, Winkler M, Loffler S and Stolzenburg JU. Neuroanatomy of the male pelvis in respect to radical prostatectomy including three-dimensional visualization. BJU Int 2009;105:21-27
[15] Alsaid B, Karam I, Bessede T, Abdisamad I, Uhl JF, Delmas V, Benoit G, Droupy S. Tridimensional computer-assisted anatomic dissection of posterolateral prostatic neurovascular bundles. Eur Urol 2010;58:281-7
[16] deGroat, W.C. and Booth, A.M. Physiology of male sexual function. Ann Intern Med 1980, Feb;92(2Pt2):329-31.
[17] Lue TF. Erectile dysfunction. N Engl J Med, 2000 Jun 15;342(24) 1802-1813
[18] Ignarro LJ, Bush PA, Buga GM, Wood KS, Fukuto JM, Rajfer J. Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. Biochem Biophys Res Commun 1990;170:843-50
[19] Choi, J.M., Nelson, C.J., Stasi, J. and Mulhall, J.P. Orgasm associated incontinence (climacturia) following radical pelvic surgery: rates of occurrence and predictors. J Urol, 2007, Jun;177(6):2223-6.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Part II

Erectile function after radical retropubic prostatectomy

Chapter 3 Sexual function before and after radical retropubic prostatectomy: a systematic review of prognostic indicators for a successful outcome.
European Urology 2006; 50(4): 711-8

Chapter 4 Penile vascular evaluation and sexual function before and after radical retropubic prostatectomy: 5 year follow-up.
International Journal of Andrology, 2008; 31(5): 483-9

Chapter 5 Orgasmic dysfunction after open radical prostatectomy: clinical correlates and prognostic factors.
Journal of Sexual Medicine, 2010; 7(3): 1216-23

Sexual function before and after radical retropubic prostatectomy: a systematic review of prognostic indicators for a successful outcome.

Yvette Dubbelman
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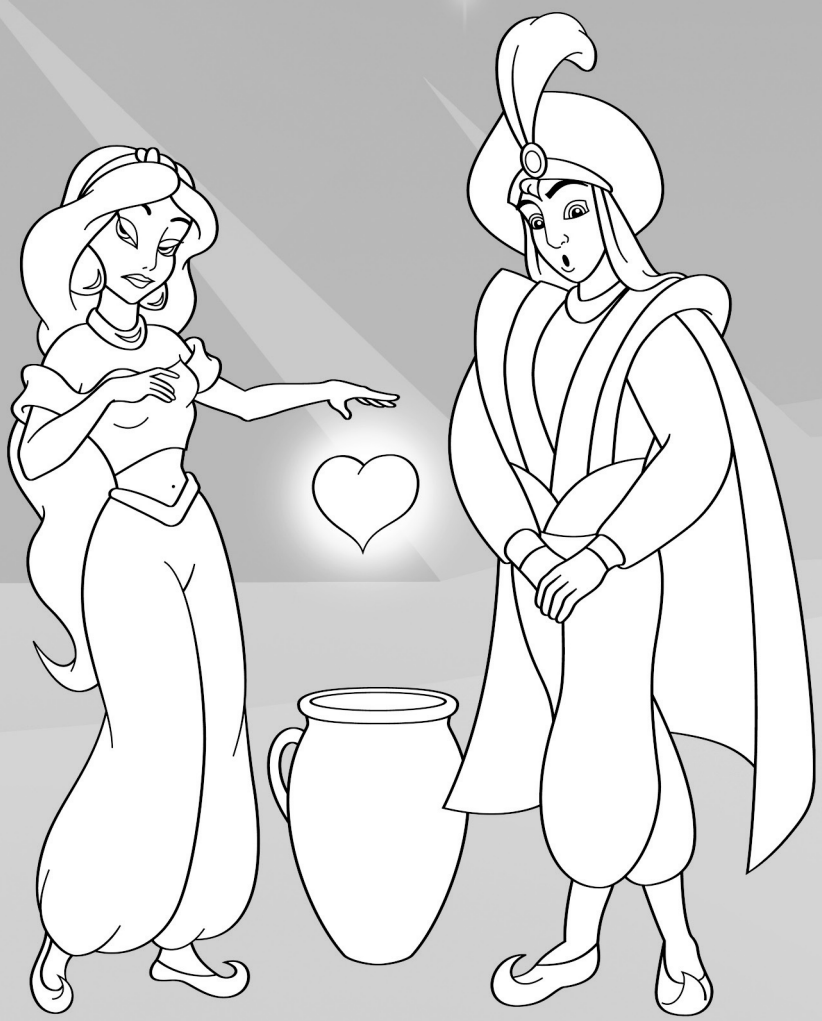

European Urology 2006; 50(4): 711-8

Abstract

Objectives

Erectile dysfunction is common after surgery for prostate cancer. Potency rates after radical retropubic prostatectomy (RRP) vary widely among different studies. Since the introduction of the nerve-sparing technique potency rates have increased. Erectile function recovery rates for selected groups of patients are high. However, studies from community practices have shown less favourable outcomes after RP.

Methods

We have performed a systematic review of the literature concerning sexual function after RRP and focused on prognostic indicators for a successful sexual outcome.

Results

Most important prognostic factors for the return of potency after RRP are preservation of the neurovascular bundles, age of the patient and sexual function before the operation. Neurogenic and vasculogenic factors seem to play an important role in the aetiology of the erectile dysfunction after surgery. The role of preserving the accessory pudendal artery is not certain, although some investigators found significant hemodynamic changes after sacrificing the accessory pudendal artery. Colour Doppler ultrasound studies in combination with intracavernous injection of vasoactive drugs or after PDE-5 inhibitors administration has shown to be a reliable test for vascular factors.

Conclusions

After bilateral nerve-sparing RRP sexual potency is preserved in 31% - 86% of sexually active men with organ-confined disease. The aetiology of impotence following RRP is multifactorial, but neurogenic factors seem to play a major role. Vascular factors may be of importance in selective cases. Colour Doppler ultrasound appears to be the most reliable, non-invasive diagnostic test for erectile dysfunction after RRP in patients who do not respond to pharmacotherapy.

Introduction

Radical prostatectomy (RP) is the standard treatment for patients with an organ confined prostate cancer and a life expectancy of more than ten years who accept treatment-related complications. (1) This operation is associated with a loss of sexual potency in the majority of cases, due to injury to the autonomic cavernous nerves. Since the introduction of the anatomical approach of the neurovascular bundles as described by Walsh and Donker (2), nerve-sparing radical prostatectomy has become the operation of choice in potent and sexual active men with organ-confined disease. Numerous reports of recovery of sexual potency after a nerve-sparing radical retropubic prostatectomy (NSRRP) have been published since, showing high rates of potency after the operation in selected groups of patients. (3.4) Most of these studies, however, were performed by experienced surgeons and have involved mainly sexually active and relatively young patients with early-stage cancer. In contrast, studies from community practices have shown a much lower rate of potency after radical prostatectomy (5-7), thus questioning the effectiveness of the nerve sparing procedure in general urological practice. We have performed a systematic review of the literature on aetiology and prognostic indicators of sexual function after radical prostatectomy.

Methods

A Medline literature search, from articles published between 1980-2005, was performed using the following key words: sexual function, potency, impotence, erectile dysfunction (ED), prostatic carcinoma, adenocarcinoma of the prostate, (nerve sparing) radical prostatectomy, hemodynamic profiles and colour Doppler ultrasound. Eighty-eight articles could be selected from Medline for this review.
We selected articles about erectile dysfunction rates after operation that contained at least the following information: age, sexual activity and potency before and after operation, nerve-sparing radical prostatectomy (bilateral and unilateral), follow-up time, definition of sexual potency, number of patients by study group (patients for whom postoperative potency rates were reported), bother of erectile dysfunction and risk factors. For this review 14 articles were found that had a minimal follow-up of 12

months, a minimal number of patients of 50, potency defined as the ability to achieve unassisted intercourse with vaginal penetration, pre- and post operatively potency rates and studies using prospective interviews or patient questionnaire based outcome analysis, since studies using retrospective chart analysis usually show higher success rates as compared to questionnaire based outcome analysis. (8)
Also articles about hemodynamic changes after radical prostatectomy and colour Doppler ultrasound investigations were selected with the following information: age, vascular evaluation, aetiology of erectile dysfunction and colour Doppler ultrasonography.

Results

3.1. Overall potency rates

The mean age of patients undergoing a radical prostatectomy is 59-68 years. (6,9,10) Before the operation sexual potency is reported in 43-84% (7,11-13) Not all studies used validated questionnaires to asses sexual function: Salonia et al reported on discrepant results between different verbally obtained information from the patient and information from questionnaires. Of three hundred men who reported full potency during the patient-physician interview only 43% had a normal erectile function according to the IIEF questionnaires score.
Total group potency rates are usually very disappointing. Fowler et al (5) reported on a sample of Medicare patients who underwent radical prostatectomy in different institutions in the United States: from their survey it was concluded that in only 11% of patients erections were sufficient for intercourse. It is unknown how many of these 855 patients had a nerve sparing radical prostatectomy. Schover et al (6) performed a postal survey on 1236 men after RRP and concluded that only 13% of men had reliable firm erections and another 8% of men were having erections with medical aids. Geary et al (14) evaluated 459 men who were operated between 1983 and 1991 and found potency in 51 cases (11%). Catalona and Basler (15) reported on 784 patients operated between 1983 and 1992 and found potency in 173 cases (22%) of the total group. More recently Korfage et al (16) reported on overall potency rates of 12% at 12 and 52 months after operation. Large studies of Karakiewicz et al (17), Potosky et al (18) and Stanford et al (19) containing 2415, 901 and 1291 patients respectively, reported overall potency rates of 25 %, 17,9% and 40,1%, respectively. In 2005, Penson

et al (7) published a study of 1288 men after RRP and found a potency rate of 17% one year after operation. Only 192 (14,5%) of them had a nerve sparing operation. There was a slight improvement in erectile funcion over time. At 60 months only 28% had erections firm enough for intercourse. Of these men 43% tried Sildenafil, 25% a vacuum erection device and 17% intracavernous injections.
We conclude that a mean potency rate of 19% (range: 11-40%) probably reflects the results of sexual function after RRP in a general urological practice irrespective of operation technique.

3.2. Potency rates and nerve-sparing approach

Since the introduction of the nerve-sparing technique potency rates after radical prostatectomy have substantially increased. Despite the improved surgical technique not all men will be potent after nerve-sparing prostatectomy. Other factors may contribute to the recovery of potency. Most important risk factors for remaining sexually potent after operation are: age, number of spared neurovascular bundles and potency status pre-operatively. (4,7,9-11,14,17,20,21) Some studies found incontinence, strictures, education level, pathological stage and cancer volume significant risk factors, while others could not confirm these observations. (10,14,15,17,19)
In most series a correlation is found between the number of spared neurovascular bundles and the recovery of potency. Kundu et al (9) reported on 1843 patients operated between 1983 and 2003 and found potency in 78% of the men who have had a bilateral nerve sparing procedure and 53% potency after a unilateral nerve sparing RP. Noldus et al (20) reported less favourable outcomes: they performed a study on 289 patients operated between 1992 and 1999 and found potency rates of 51.7 % and 16.1% after bilateral and unilateral nerve-sparing procedures, respectively. Walsh et al (21) reported an improvement of potency after bilateral nerve-sparing prostatectomy of 86% 18 months post-operatively, although 33% of the patients additionally used Sildenafil. Table 1 summarizes the prevalence of potency after nerve-sparing radical prostatectomy based on the criteria mentioned previously.

Due to different factors, like age of the patient and surgeons experience, there is a wide range of potency rates after nerve-sparing RRP in literature. After bilateral nerve-sparing radical prostatectomy potency is found in 31% - 86% of the cases (9-11,14,21-24), after unilateral nerve-sparing radical prostatectomy recovery of

Table 1. A summary of studies on nerve-sparing radical retropubic prostatectomy and the consequences for sexual function after the operation.

Study references	No. of subjects	Age (range)	Neurovasc. Bundles spared (No.)	% potency before	% potency after operation	% potency by age (years)
Penson 2005[7]	1213	39-79	Unilateral, Bilateral, non nerve-sparing	81	23; 40 and 23 overall 17[£] and 28[•]	61 (39-54); 49 (55-59); 44 (60-64); 18 (≥65)
Kundu 2004[9]	1834	61 (36-80)	Unilateral (64), Bilateral (1770)	84	53 and 76, overall 75	92 (40-49); 85 (50-59); 70 (60-69); 51 (≥70)
Tsujimura 2004[22]	67	67.7	Unilateral (18), Bilateral (9), non nerve-sparing (49)	100	44,7; 55.6 and 14.2	-
Schover 2002[6]	569	68.1[‡]	Unilateral (90), Bilateral (240), non nerve-sparing (239)	64[‡]	13; 18 and 5	-
Noldus 2002[20]	289	62.5 (42-74)	Unilateral (229), Bilateral (60)	100	16.1 and 51.7	19 v 45 (<60); 13 vs 38 (≥60)
Walsh 2000[3]	64	57[#] (36-67)	Bilateral (89%)	100	86	100 (30-39); 88 (40-49); 90 (50-59); 75 (60-67)
Stanford 2000[19]	1291	62.9 (39-79)	Unilateral, Bilateral, non nerve-sparing	72,7	41.4; 44 and 34.4[†] overall: 40.1	-
Rabbani 2000[24]	314	60.5[#] (37-81)	Unilateral (26), Unilateral/bilateral damage (107), Bilateral (181)	100	21; 41 and 55	61 (≤ 60); 42 (60.1-65) and 31 (>60)
Catalona 1999[4]	858	63 (38-79)	Unilateral (60), Bilateral (798)	100	47 and 68	48 vs 71 (<70); 40 vs 48 (≥70)
McCammon 1999[23]	203	62.8 (44-74)	Unilateral (95), Bilateral (31), non nerve-sparing (72)	-	30.5; 35.1 and 16.6 overall: 33.3	-
Davidson 1996[11]	83	63 (45-76)	Unilateral (17), Bilateral (42), non nerve-sparing (24)	100	24; 43 and 17 overall: 31	-
Geary 1995[14]	459	64.1	Unilateral (203), Bilateral (69), non nerve-sparing (187)	100[*]	13.3; 31.9 and 1.1	-
Catalona 1993[15]	295	64.2	Unilateral (59), Bilateral (236)	100	41 and 63	25 vs 75 (<60); 48 vs 60 (60-70); 38 vs 50 (>70)
Leandri 1992[27]	106	68 (46-84)	Nerve-sparing	100	71	76 (<60); 72 (60-70); 50 (>70)
Quinlan 1991[10]	503	59 (34-72)	Unilateral (109), Unilateral + ½ (96), Bilateral (291), non nerve-sparing (7)	100	56; 63, 76 and 0 overall: 68	Unilat vs Bilat: 91 vs 90 (<50); 58 vs 82 (50-59); 47 vs 69 (60-69); 0 vs 22 (≥70)

[*] only nervesparing patients ; [#] median age ; [†] only pt potent before; [‡] total group (n=1236), not specified for treatment modalities; [£] overall potency rate after 1 year; [•] overall potency rate after 5 years.

erection occured in 13% - 56%. (9-11,14,21-24)
Since advanced tumour stage usually coincides with wide excision of one or both neurovascular bundles, potency rates in these cases are limited. In practice in many patients, a nerve-sparing procedure is not achieved and potency is usually lost. In non-nerve sparing radical prostatectomy potency was reported in 0% - 17%. (10,11,14,22,23) The wide range of outcomes is probably affected by the method used to collect the data. The high potency rates were mostly based on interviews or non-validated questionnaires, while the lowest outcomes were based on validated questionnaires (IIEF).
Some concern was raised over the incidence of positive surgical margins with respect to nerve-sparing procedures. The number of positive surgical margins due to a nerve-sparing radical prostatectomy has been estimated as 2-3%. (10,14) Furthermore, the incidence of positive surgical margins in patients undergoing a nerve-sparing radical retropubic prostatectomy was found to be not significantly different from that of patients undergoing standard radical prostatectomy. Positive surgical margins are probably determined by tumour extent rather than by the operative technique. (10)
Recent data about laparoscopic radical prostatectomy showed similar outcomes for sexual potency following bilateral nerve-sparing radical prostatectomy as compared to open procedures. (25,26)

3.3. The influence of age

The outcome of potency after the operation is mainly determined by age and the number of neurovascular bundles saved during surgery. Recovery of sexual potency has become a realistic option for relatively young patients suffering from an organ-confined prostatic carcinoma who used to have a normal sexual function before the operation (14,15) Table 1 also summarises the post-operative potency rates sub-divided for age. In patients <50 years of age there seemed to be no difference between potency rates after unilateral or bilateral nerve-sparing techniques. Potency rates vary between 61 and 100%, post-operatively. (7,9,10,21) For men between 50 and 70 years of age the overall potency rate declined to 70-85%. (9,27) After unilateral and bilateral nerve-sparing procedures potency is found in 47-58% and 44-90%, respectively. (7,10,15,21) Men older than 70 years have low potency rates ranging from 0 and 51%, despite nerve-sparing procedures. (4,9,10)

3.4. Orgasm and sexual bother after RRP

Radical prostatectomy may also affect orgasm, both in total absence and reduced intensity or even pain. Steineck et al (28) reported orgasm to be absent in 34% of men after operation, reduced intensity in 30% and painful orgasm in 9% of men. Noldus et al (20) reported on the capability of orgasm after the operation: 80% of men had an unchanged orgasm, 9% reported an improved orgasm, and 11% a decreased experience of orgasmic function whether they were potent or not. None of the studies mentioned if there was a correlation between orgasmic function and number of neurovascular bundles spared.

Results of bother of severe sexual dysfunction after radical prostatectomy vary widely between 2 and 72% in literature. (7,18,19,21,29-31) Many men seem to suffer from the persistent sexual dysfunction. However, despite a decline in their sexual performance most men seem to be satisfied with the chosen treatment.

3.5. Aetiological factors

3.5.1.Neurogenic factors

We have reviewed articles on aetiology of erectile dysfunction after radical prostatectomy. (10, 12, 15, 24, 32-38) Neurogenic factors appeared to be the most common explanation for this feature. Arguments in favour of a neurogenic cause were: clear relation with the number of spared neurovascular bundles and absence of a history of a general vascular disea¬se. Also, a strong correlation between the number of preserved neurovascular bundles and age and the recovery of sexual potency was found. Younger patients in general might need fewer preserved bundles to remain potent compared to older patients. (10, 15)

If the neurogenic factor is really the most important factor for de development of ED after radical prostatectomy, surgical technique and patient selection is very important. Montorsi et al concluded in a recent systematic review that in the hands of experienced surgeons, properly selected patients undergoing a nerve sparing prostatectomy should achieve unassisted or medically assisted erections postoperatively. (39)

3.5.2. Vascular factors

Vascular factors may also play a substantial role in aging men, as the operation potentially compromises penile arterial blood flow. Also, ageing men are at risk

for cardio-vascular disease. Colour Doppler ultrasonography for the evaluation of erectile dysfunction was introduced by Lue et al. (40) as a non-invasive measurement for penile hemodynamics. A vascular component is suggested in studies using erectile function tests before and after nerve sparing radical prostatectomy. In general, primary arteriogenic dysfunction is considered with the peak systolic velocity (PSV) < 25 cm/s, veno-occlusive dysfunction may be present if the end diastolic velocity (EDV) > 5 cm/s and a resistance index (RI) < 0.9. Mulhall et al (32) reported on a vascular evaluation in 96 patients after NSRRP who had an excellent pre-operative erectile function. The vascular evaluation involved cavernosometry or penile duplex ultrasonography. They found a normal vascular status, arterial insufficiency and venous leakage in 35, 59 and 26% of the men, respectively. Return of erectile function with vaginal intercourse was possible in 47% of men with a normal evaluation in 31% with arteriogenic insufficiency and in only 9% of men from the venous leakage group 12 months post-operatively. They also found that the longer the duration of erectile dysfunction after radical prostatectomy, the greater the risk of venous leakage. It is postulated that a prolonged period of penile ischaemia and the absence of nocturnal erections after radical prostatectomy due to excision of the neuro-vascular bundles will result in corpus cavernosum insufficiency with venous leakage. Zelefsky et al (33) evaluated the aetiology of erectile dysfunction after radical prostatectomy with Duplex ultrasonography and intracavernosal injection in 60 men. They showed cavernosal dysfunction in 31 (52%) men, arteriogenic insufficiency in 19 (32%) and neurogenic dysfunction in seven (12%). Three men (5%) had mixed vascular dysfunction. Kawanishi et al (34) evaluated erectile function before and after surgery using intracavernosal injection, with colour Doppler ultrasonography and nocturnal penile tumescence monitoring. They found that of 123 patients scheduled for surgery only 21 patients (17%) were having normal erectile function before surgery. After radical prostatectomy, nine (43%) of these 21 men had preserved erectile function. Eight patients had a nerve-sparing operation of whom five were potent. The cause of erectile dysfunction after surgery was a neurogenic disorder in seven and a related vascular disorder in five. Kim et al. (35) found penile blood flow to be decreased on colour Doppler ultrasound after radical prostatectomy, especially on the side were the nerve bundle had been sacrificed. Cavernous artery diameter, PSV, EDV and RI were also decreased after surgery. These differences, however, were not statistically significant. No evidence for veno-occlusive dysfunction was found after radical

prostatectomy in the ten studied cases.
More prospective studies on vascular involvement are required for full understanding of its role in post-radical prostatectomy erectile dysfunction.

3.5.3. The role of the accessory pudendal arteries

Recently, the role of the accessory pudendal arteries was discussed by several investigators. Abosief et al (12) found a decrease in peak systolic flow velocity and diameter of the cavernosal arteries in 8/20 cases (40%) after radical prostatectomy. An explanation for this decrease was found in the cadaveric dissections of Breza et al. (41), who found accessory pudendal arteries present in 7/10 cases originating from the obturator artery, the inferior vesical artery or the superior vesical artery. These accessory pudendal arteries were found anterolateral to the prostatic surface and are usually sacrificed during dissection. They supply additional blood to the cavernous bodies: in two cases the accessory pudendal artery was the main supply to the penis. Droupy et al (42) demonstrated the functional role of accessory pudendal arteries in penile erection. During pharmacologically induced erection haemodynamic changes in accessory and internal pudendal arteries were similar to those described in cavernous arteries. In contrast, Blander et al (36) could not demonstrate any significant importance of the accessory pudendal artery in the maintenance of erections in the post-radical prostatectomy patients. Rogers et al (37) reported on the presence of accessory pudendal arteries in a series of 2399 radical prostatectomies and found the accessory artery present in only 84 (4%) men. Potency was preserved in 93% and 70% of men, after sparing one or both pudendal arteries and sacrificing the arteries, respectively. A bilateral nerve-sparing procedure was performed in all 84 men. Preservation of the accessory pudendal artery increased the likelihood of potency more than twofold and these patients show a significantly shorter median time to regain potency (6 versus 12 months).
We conclude that the role of preserving the accessory pudendal artery is still uncertain, as some investigators found significant hemodynamic changes after sacrificing the accessory pudendal artery where others could not confirm these observations.

3.6. Diagnostic techniques for post-prostatectomy erectile dysfunction

An evaluation of different diagnostic techniques has been published by Zimmern et al. (43) In a group of 45 potent men, candidates for radical prostatectomy, biothesiometry,

nocturnal penile tumescence registration (Rigiscan analysis) and colour Doppler ultrasound were performed before the operation. Only colour Doppler showed normal results in most patients (93%); both Rigiscan analysis and biothesiometry correlated poorly with the potency status of the investigated subjects. Rhee et al (44) demonstrated that the PSV, as measured by colour Doppler ultrasound, was an effective, reliable and non-invasive means of evaluating corporeal arterial function. Several studies have confirmed that penile Doppler ultrasonography correlates with selective arteriography in 90-95% of the cases. (45,46)

In practice a goal-directed approach, as proposed by Lue et al (47), is applied in most patients with ED after radical prostatectomy. Colour Doppler ultrasound studies in combination with administration of Papaverine, Prostaglandin E1, or PDE-5 inhibitors have shown to be a reliable test for vascular factors. We believe that invasive diagnostic procedures should be performed only if they influence the choice of therapy.

Conclusion

Bilateral nerve-sparing radical prostatectomy preserves potency in 31% - 86% of sexually active men with organ-confined disease. However, in most cases a nerve sparing procedure is not performed and potency is usually lost. Most important prognostic factors for recovery of sexual potency are the number of spared neurovascular bundles, age and sexual activity before the operation. The aetiology of impotence following radical prostatectomy is multifactorial, but neurogenic factors seem to play a major role. Vascular factors may be of importance in selective cases. Some investigators found that preservation of the accessory pudendal arteries may favourably influence the recovery of sexual function and decrease the time to recovery of spontaneous erections after radical prostatectomy. Arterial insufficiency and veno-occlusive dysfunction can be found in 32-59% and 26-52% of the patients after operation, respectively. The prognosis for the return of erectile function seems to be worst when venous leakage is present. More prospective studies on vascular involvement are required for full understanding of its role in post-radical prostatectomy sexual dysfunction, including an analysis of the vascular status before the procedure. Colour Doppler ultrasound appears to be the most reliable, non-invasive diagnostic test for erectile dysfunction after radical prostatectomy in patients who do not respond to pharmacotherapy.

References

[1] Aus G, Abbou CC, Bolla M et al. EAU guidelines on prostate cancer. Eur Urol 2005;48 :546-551.
[2] Walsh PC and Donker PJ. Impotence following radical prostatectomy: insight into aetiology and prevention. J Urol 1982;128:492-497.
[3] Walsh PC. Radical prostatectomy for localized prostate cancer provides durable cancer control with excellent quality of life. J Urol 2000;163:2030-2031.
[4] Catalona WJ, Carvalhal GF, Mager DE and Smith DS. Potency, continence and complication rates in 1870 consecutive radical retropubic prostatectomies. J Urol 1999;162:433-438.
[5] Fowler FJ, Barry MJ, Lu-Yao G, Roman A, Wasson J and Wennberg JE. Patient-reported complications and follow-up treatment after radical prostatectomy. Urology 1993;42: 622-629.
[6] Schover LR, Fouladi RT, Warnecke CL et al. Defining sexual outcome after treatment for localized prostate carcinoma. Cancer 2002;15:1773-1785.
[7] Penson DF, McLerran D, Feng Z et al. 5-Year urinary and sexual outcome after radical prostatectomy: results from the prostate cancer outcome study. J Urol 2005; 173:1701-1705.
[8] Kormann HJ, Sirls LT and Kirkemo AK. Success rate of modified Pereyra bladder neck suspension determined by outcome analysis. J Urol 1994;152:1453-1457.
[9] Kundu SD, Roehl KA, Eggener SE, Antenor JAV, Han M and Catalona WJ. Potency, continence and complications in 3477 consecutive radical retropubic prostatectomies. J Urol 2004;172:2227-2231.
[10] Quinlan DM, Epstein JI, Carter BS and Walsh PC. Sexual function following radical prostatectomy: influence of preservation of neurovascular bundles. J urol 1991;145:988-1002.
[11] Davidson PJT, Van Den Ouden D and Schroeder FH. Radical prostatectomy: prospective assessment of mortality and morbidity. Eur Urol 1996;29:168-173.
[12] Abosief SR, Shinohara K, Breza J and Narayan P. Role of penile vascular injury in erectile dysfunction after radical prostatectomy. Br J Urol 1994;73:75-82.
[13] Salonia A, Zanni G, Gallina A et al. Baseline potency in candidates for bilateral nerve-sparing radical retropubic prostatectomy. Eur Urol 2006 Aug;50(2):360-5.
[14] Geary ES, Dendinger TE, Freiha FS and Stamey TA. Nerve sparing radical prostatectomy: a different view. J Urol 1995;154: 145-149.
[15] Catalona WJ and Basler JW. Return of erections and urinary continence following nerve sparing radical retropubic prostatectomy. J Urol 1993;150:905-907.
[16] Korfage IJ, Essink-Bot ML, Borsboom GJJM et al. Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. Int J Cancer 2005;116 (2):291-296.
[17] Karakiewicz PI, Tanguay S, Kattan MW, Lhilali MM and Aprikian AG. Erectile and urinary dysfunction after radical prostatectomy for prostate cancer in Quebec: a population-based study of 2415 men. Eur Urol 2004;46:188-194.
[18] Potosky AL, Davis WW, Hoffman RM et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst 2004;96:1358-1367.
[19] Stanford JL, Feng Z, Hamilton AS et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer. JAMA 2000;283:354-360.
[20] Noldus J, Michl U, Graefen M, Haese A, Hammerer P and Huland H. Patient-reported sexual function after nerve-sparing radical retropubic prostatectomy. Eur Urol 2002;42:118-124.
[21] Walsh PC, Marschke P, Ricker D and Burnett AL. Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. Urology 2002;55:58-61.
[22] Tsujimura A, Matsumiya K, Miyagawa Y et al. Relation between erectile dysfunction and urinary incontinence after nerve-sparing and non-nerve-sparing radical prostatectomy. Urol Int 2004;73:31-35.

[23] McCammon KA, Kolm P, Main B and Schellhammer PF. Comparative quality of life analysis after radical prostatectomy or external beam radiation for localized prostate cancer. Urology 1999;54:509-516.
[24] Rabbani F, Stapleton AMF, Kattan MW, Wheeler TM and Scardino PT. Factors predicting recovery of erections after radical prostatectomy. J Urol 2000;164:1929-1934
[25] Roumequere T, Bollens R, Vanden Bossche M et al. Radical prostatectomy: a prospective comparison of oncological and functional results between open and laparoscopic approaches. World J Urol 2003;20:360-366.
[26] Janetschek G and Montorsi F. Open versus laparoscopic radical prostatectomy. Eur Urol 2006 (Suppl 5);377-384.
[27] Leandri P, Rossignol G, Gautier JR and Ramon J. Radical retropubic prostatectomy: morbidity and quality of life. Experience with 620 consecutive cases. J Urol 1992;147:883-887.
[28] Steineck G, Helgesen F, Adolfson J et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002;347:790-796.
[29] Arai Y, Okubo K, Aoki Y et al. Patient-reported quality of life after radical prostatectomy for prostate cancer. Int J Urol 1999;6:78-86.
[30] Bates TS, Wright MPJ and Gillatt DA. Prevalence and impact of incontinence and impotence following total prostatectomy assessed anonymously by the ICS-male questionnaire. Eur Urol 1998;33(2):165-169.
[31] Gralnek D, Wessells H, Cui H and Dalkin BL. Differences in sexual function and quality of life after nerve-sparing and nonnerve sparing radical retropubic prostatectomy. J Urol 2000;163;1166-1170.
[32] Mulhall JP, Slovick R, Hotaling J et al. Erectile dysfunction after radical prostatectomy: hemodynamic profiles and their correlation with the recovery of erectile function. J Urol 2002;167:1371-1375.
[33] Zelefsky MJ and Eid JF. Elucidating the etiology of erectile dysfunction after definitive therapy for prostate cancer. Int J Radiat Oncol Biol Phys 1998;40:129-133.
[34] Kawanishi Y, Lee KS, Kimura K, Kojima K, Yamamoto A and Numata A. Effect of radical retropubic prostatectomy on erectile function, evaluated before and after surgery using colour Doppler ultrasonography and nocturnal penile tumescence monitoring. BJU International 2001;88:244-247.
[35] Kim ED, Blackburn D and McVary KT. Post-radical prostatectomy penile blood flow: assessment with color doppler ultrasound. J Urol 1994;152:2276-2279.
[36] Blander DS, Broderick GA, Malkowicz SB, Van Arsdalen KN and Wein AJ. Retrospective review of flow patterns following retropubic prostatectomy. Int J Impot Res 1999;11:309-314.
[37] Rogers CG, Trock BP and Walsh PC. Preservation of accessory pudendal arteries during radical retropubic prostatectomy: surgical technique and results. Urology 2004;64(1):148-151.
[38] Moreland RB. Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. Int J Impot Res 1998;10:113-20.
[39] Montorsi F, Briganti A, Salonia A, Rigatti Pand Burnett AL. Current and future strategies for preventing and managing erectile dysfunction following radical prostatectomy. Eur Urol 2004;45:123-133.
[40] Lue TF, Hricak H, Marich KW, Tanagho EA. Vasculogenic impotence evaluated by high resolution ultrasonography and pulsed Doppler spectrum analysis. Radiology 1985;155:777-781.
[41] Breza J, Abosief SR, Orvis BR, Lue TF and Tana¬go EA. Detailed anatomy of penile neurovascular structures surgical significance. J Urol 1989;141:437-443.
[42] Droupy S, Hessel A, Benoit G, Blanchet P, Jardin A and Giuliano F. Assessment of the functional role of accessory pudendal arteries in erection by transrectal color Doppler ultrasound. J Urol 1999;162:1987-1991.
[43] Zimmern PE, Kaswick j and Leach GE. How potent is potent before nerve-sparing radical retropubic prostatectomy? J Urol 1995;154:1100-1101.
[44] Rhee E, Osborn A and Witt M. The correlation of cavernous systolic occlusion pressure with peak velocity flow using color duplex Doppler ultrasound. J Urol 1995;153:358-360.

[45] Velcek D, Sniderman KW, Vaughnan ED, Sos TA and Muecke EC. Penile flow index utilizing a Doppler pulse wave analysis to identify penile vascular insufficiency. J Urol 1980;123: 669-673.
[46] Lane RJ, Appleberg M and Williams W. A comparison of two techniques for the detection of the vasculogenic component of impotence. Surg Gynecol Obstet 1982;155:230-234.
[47] Lue TF. Impotence: a patient`s goal-directed approach to treatment. World J Urol 1990;8:67-74.

Penile vascular evaluation and sexual function before and after radical retropubic prostatectomy: 5 year follow-up.

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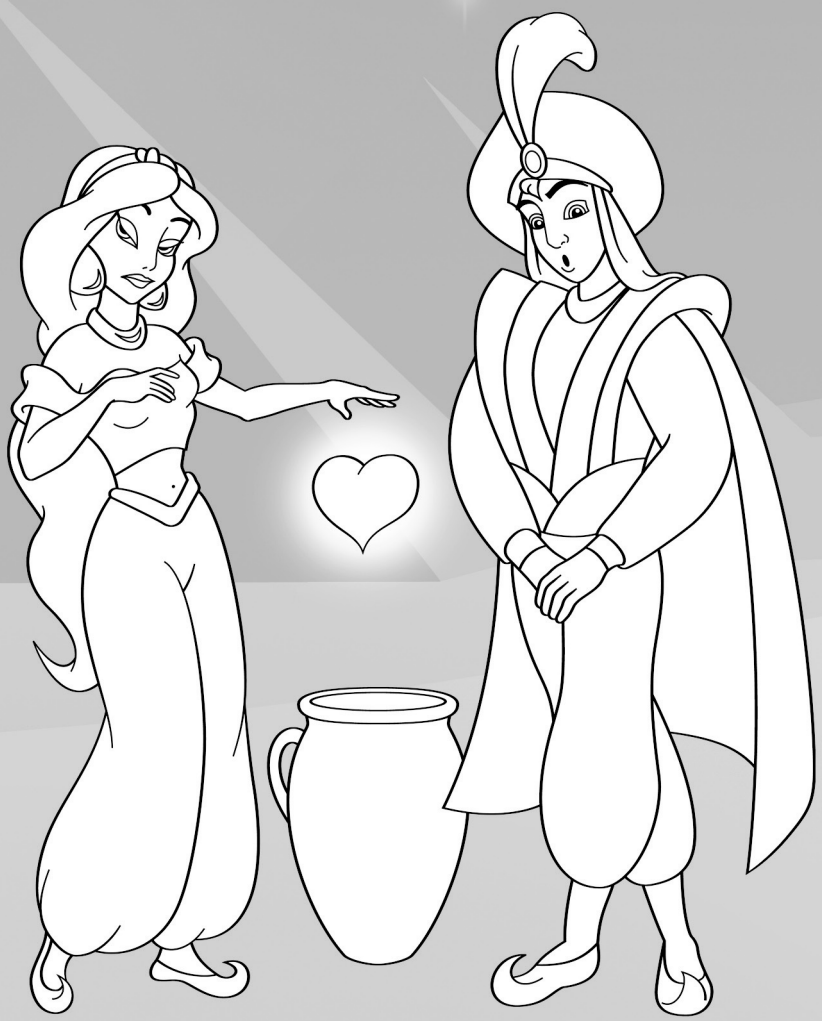

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Abstract

Objectives

Sexual dysfunction is common after surgery for prostate cancer. The aetiology of changes in sexual potency after radical prostatectomy is probably multifactorial, including neurogenic, vascular and psychosexual factors. A prospective study was designed to investigate hemodynamic and psychosexual changes before and after radical retropubic prostatectomy (RRP) for organ confined prostate cancer.

Methods

Penile hemodynamic evaluation and an assessment of sexual excitement were performed preoperatively and three months after RRP by colour Doppler ultrasonography(CDU) with visual erotic stimulation(VES) combined with a single intracavernous injection of a mixture of papaverine/phentolamine. Questionnaires on sexual function (International Index of Erectile Function), general health and quality of life were send to the patients preoperative, three months and five years after operation.

Results

Forty-eight men participated in the study. Mean age was 62.6 years (range 55-69). CDU did not show any significant reduction of mean peak systolic flow velocity and mean resistance index. From the men who preoperatively had normal arterial inflow 18% developed arteriogenic insufficiency. Some form of veno-occlusive insufficiency and low resistance indexes were already present in the majority of normal potent men preoperatively. Surgical technique did not influence penile arterial blood flow after the operation.

Three months and five years postoperatively, there was a highly significant reduction of erectile function, intercourse satisfaction, overall satisfaction, orgasmic function and sexual desire. However, with respect to the outcome at three months there was a significant improvement of orgasmic function five years after operation, especially after a bilateral nerve sparing procedure. Erections sufficient for vaginal penetration (question 3 + 4 of the IIEF, score $\geq$ 8) improved from 2 to 11% three months and five years after RRP, respectively. Total IIEF score was significantly better after a bilateral nerve sparing procedure compared with non nerve sparing.

Conclusion

No structural vascular changes were observed three months after operation. Vascular factors appear to be less important in the aetiology of ED after RRP. There seems to be a trend of a better improvement of sexual function over time, especially orgasmic function, in patients with bilateral nerve sparing surgery.

Introduction

Since the introduction of the anatomical approach of the penile neurovascular bundles by Walsh and Donker [1], sexual potency rates have increased after nerve sparing radical prostatectomy in potent and sexual active men with organ confined carcinoma of the prostate. However, despite the preservation of the neurovascular bundles a significant number of patients suffer from erectile dysfunction (ED). [2] The exact aetiology of changes in sexual potency after radical prostatectomy is suggested to be multifactorial. The impact of either psychosexual, vascular and neurogenic factors remains unclear. Neural integrity seems to be important to maintain penile homeostasis and to prevent fibrosis and subsequent loss in elasticity and function of erectile tissue. [3,4] The importance of preserving the accessory pudendal artery has not been confirmed, although significant hemodynamic changes after sacrificing these arteries have been reported.

Colour Doppler ultrasound (CDU) studies in combination with intracavernous injection of Papaverine or prostaglandin E1 or after Sildenafil administration has shown to be a reliable test for penile hemodynamics. [5-7] We performed a prospective study in men with organ confined prostate cancer, to evaluate hemodynamic function before and three months after radical retropubic prostatectomy by CDU in combination with visual erotic stimulation (VES), penile vibratory stimulation and a single intracavernous injection of a mixture of papaverine/phentolamine. We combined this evaluation with an analysis of sexual function by a validated questionnaire preoperatively, three months and five years after operation.

Patients and methods

We performed a prospective study between 1999 and 2005. All men, candidates for radical retropubic prostatectomy (RRP) who wanted to participate into the study, signed an informed consent. The study was approved by the institution's Ethical Committee. An assessment of sexual excitement and hemodynamic evaluation was performed preoperatively and three months after operation by a visual analogue scale(VAS), VES with penile vibratory stimulation and CDU. Penile circumference was measured with an erection meter around the base of the penis before and after the

VES procedure. The VES procedure was previously described by Slob et al [8]. During VES the patient was asked to report the level of sexual arousal and his own rating of genital response on a VAS. Penile vibratory stimulation was used to enhance sexual response during VES.

CDU of the cavernous arteries was performed using a 10mHz linear probe applied at the basis of the penile shaft after intracavernosal injection of 0,25 mg of a mixture of papaverine and phentolamine (R/Androskat). Doppler angle correction was adjusted to match the correct axis of flow in the cavernous arteries. Flow parameters included peak systolic velocity (PSV), end diastolic velocity (EDV) and resistance index (RI). The RI was calculated using the equation RI = (PSV-EDV)/PSV. High PSV on a CDU study suggests a good arterial inflow, a positive intracavernous injection test and low EDV with a high RI indicates intact veno-occlusive function. Based on our clinical experience and the literature [9] we used three categories to define normality. Cavernosal artery inflow was considered normal with PSV greater than 35 ml/s, a PSV < 30 ml/s indicates arterial insufficiency. The corporeal veno-occlusive mechanism was considered normal with an EDV value less then 4 cm/s and RI values greater than 0.90.

Also, patients were asked to fill out a validated questionnaire about sexual function, the International Index of Erectile Function (IIEF)[10], and a questionnaire about general health, medical history, the impact of ED on quality of life and the willingness to undergo the same treatment again (Appendix 1). The questionnaires were send to the patients one to six weeks before the operation. The questionnaires were returned on the day of admission in the hospital one day before the operation. On receipt of the questionnaires all patients were aware of their prostate carcinoma. All men were re-evaluated using the same questionnaires three months and five years after the operation. We used a 5-years follow-up period because further nerve recovery is not likely to occur anymore. Also, quality of life may be more important for the patients after a longer follow-up period than with a shorter follow-up period, when prostate cancer survival may be the dominant issue. With this longer follow-up time we hoped to get more reliable information about the definitive sexual function.

Potency was defined as the ability to have unassisted intercourse with successful vaginal penetration.

The severity of ED was classified according to the IIEF into five categories, as previously suggested by Cappelleri et al (11): no ED (EF score 30-26), mild (EF score

25 to 22), mild to moderate (EF score 21 to 17), moderate (EF score 16 to 11) and severe (EF score 10 to 1).

Pre- and operative information and pathologic outcomes were obtained from medical charts.

The Wilcoxon Rank test and the Kruskal Wallis H test were used for statistical analysis of two or more unrelated samples. A p-value <0.05 was considered statistically significant. Results are given as median values.

Results

From February 1999 till March 2000, 48 consecutive men with prostate cancer were scheduled for surgery and wanted to participate into the study. All men verbally reported that they were potent before the operation. Mean age was 62.6 years (range 55-69 years). One of the patients was excluded from the study because no radical retropubic prostatectomy was performed due to lymph node metastasis. Follow-up was available of the 47 patients who underwent RRP. A nerve-sparing procedure was performed depending on the preoperative and intra-operative assessment of the disease. The neuro-vascular bundles were preserved bilaterally (BNS) in 12 (26%) and unilaterally (UNS) in 15 (32%) men. A non-nerve-sparing (NNS) procedure was performed in 20 (42%) men. Pathological stage of the tumour was organ confined in 88%. Of the patients with non-organ confined disease none received adjuvant radiotherapy. Patients characteristics are listed in table 1.

Hemodynamic evaluation

Preoperatively, all patients were willing to undergo the CDU with visual and pharmacological stimulation. After the operation three patients refused the stimulation phase. During VES there was no difference in sexual arousability pre- and postoperatively. The subjective amount of erection decreased form 75 to 50% during VES with vibratory stimulation and intracavernosal injection. Maximal penile circumference, as measured with the erectionmeter, decreased from 29 to 21 mm ($p<0.0001$).

Preoperatively, according to the CDU investigations 39 (83%) of the men were classified as having a normal arterial inflow and 4 (8.5%) as having arteriogenic insufficiency already based upon a PSV of < 30 cm/s. From the men who preoperatively had normal

Table 1. Patient characteristics (N=47)

	Number	(%)
Preop. serum PSA (ng./ml.)		
< 4,0	13	(28)
4,0 – 10,0	26	(55)
10,1 – 20,0	7	(15)
> 20,0	1	(2)
Clinical stage (TNM'92)		
T1	26	(55)
T2	18	(38)
T3	3	(7)
Bioptie grade		
G1	36	(77)
G2	11	(23)
Type of operation		
Non-nerve sparing	20	(43)
Unilateral nerve sparing	15	(32)
Bilateral nerve sparing	12	(25)
Pathological stage		
T2	42	(89)
T3	5	(1)
Pathological grade		
G1	38	(81)
G2	8	(17)
missing	1	(2)

arterial inflow values 29 (74%) also showed normal values after the operation, 3 (8%) has a PSV between 30-35 cm/s and 7 (18%) had developed arteriogenic insufficiency. There was a slight mean reduction of PSV of 44.9 to 41.7 cm/sec. However, there were no significant changes in mean arterial cavernous flow after the operation as compared to before RRP. RI was normal in only ten and three men pre- and postoperative, respectively. Results of colour Doppler ultrasound investigation of the penis (median scores) before and after radical retropubic prostatectomy for the total group of patients and a subdivision to type of operation are shown in table 2. Stratifying the results according to the nerve-sparing procedure (none, unilateral and bilateral) and age did not result in differences of vascular evaluation outcome.

Table 2. Results of colour Doppler ultrasound investigation of the penis (median scores) before and after radical retropubic prostatectomy, for the total group of patients and segregated into type of operation.

	Total Before RRP*	NNS#	UNS†	BNS£	p-value nns vs uns	p-value nns vs bns	p-value uns vs bns	Total 3 mnd after RRP	NNS	UNS	BNS	p-value nns vs uns	p-value nns vs bns	p-value uns vs bns
PSV‡	43.2	42.7	41.7	44.7	0.74	0.48	0.35	42.4	44.1	37.2	46.9	0.19	0.52	0.07
EDV§	9.0	7.4	9.5	8.4	0.26	0.97	0.75	9.3	9.4	8.5	8.9	0.70	0.82	0.81
RI¶	0.8	0.81	0.8	0.81	0.24	0.64	0.24	0.79	0.78	0.78	0.80	0.60	0.41	0.19

* Radical retropubic prostatectomy; # Non-nerve sparing; † Unilateral nerve sparing;
£ Bilateral nerve sparing; ‡ Peak systolic velocity; § End diastolic velocity; ¶ Resistance index

Sexual function analysed by questionnaires

All patients filled out the questionnaires before surgery. Postoperatively, questionnaires were completed and returned by 47 (100%) and 42 (89%) patients at three months and five years, respectively. According to the IIEF questionnaire, 23 of 47 (49%) men had a normal IIEF score for erectile function (IIEF-EF score $\geq$ 26) before operation. Three months after the operation no one had a normal score. Five years later only one man had a normal score. According to the IIEF questionnaire, erections sufficient for vaginal penetration (question 3 + 4, score $\geq$ 8) were present in 36 of 47 men, preoperatively. Three months after the operation only 1 man had normal erections. However, 5 years after surgery potency had become normal in another 4 men; over time potency improved from 2 to 11%. According to the five categories of the IIEF, the severity of erectile dysfunction was classified as no, mild, mild to moderate, moderate and severe in 23, 9, 5, 2, and 9 men, preoperatively. Six of nine men with a score suggesting severe ED actually were not sexually active during the last four weeks before the operation. There were hardly any spontaneous firm erections three months and five years postoperatively. Of the men who were sexually active, orgasm was normal in 37 (90%), preoperatively. From these men 16.6% and 40.6% had normal orgasmic sensations three months and five years after the operation, respectively (question 9 and 10 of the IIEF). Statistically, according to the IIEF-questionnaire, sexual function showed a highly significant decrease in erectile function, orgasmic function, intercourse satisfaction, sexual desire and in overall

sexual satisfaction three months and 5 years postoperative. (Table 3) With respect to the outcome at three months there was a significant improvement of orgasmic function five years after operation.

Stratifying the results according to the nerve-sparing procedure sexual desire was significantly decreased postoperatively for the non-nerve sparing group only. Compared with the score at 3 months postoperative, patients with a bilateral nerve sparing operation the total IIEF score and the orgasmic function score significantly increased 5 years after operation from 22 to 40 (p=0.04) and from 2 to 6 (p=0.02), respectively. At 5 years, there was a significant difference between bilateral and non-nerve sparing procedure for the total IIEF score and sexual desire with a median score of 40 vs 21 (p=0.04) and a median score of 8 vs 5 (p=0.04), respectively. For erectile function and intercourse satisfaction there was a trend towards a better outcome for bilateral vs non-nerve sparing procedure with a median score of 8 vs 3 (p=0.06) and a median score of 5 vs 0 (p=0.06), respectively.

Age did not result in significant differences of sexual function outcome after operation.

Most men seemed to suffer from the persistent sexual dysfunction. The pleasure of having sex and sexual activity was significantly decreased after the operation (p<0.0001). However, with respect to the outcome at three months sexual activity increased again five years after the operation (p=0.013). Despite a decline in sexual performance levels 36 (77%) men were satisfied with the chosen treatment and 40 (85%) men would have the same procedure again.

Three months after operation no one was treated for the ED. Men were free to choose their own ED treatment. Five years after operation two men with a bilateral nerve sparing and one with a non-nerve sparing operation were successfully treated with intracavernosal injections. Two men with a non-nerve sparing operation were successfully using a vacuum device. One man with a non-nerve sparing and one man with a bilateral nerve sparing operation had used intracavernous injections and PDE-5 inhibitors without success, respectively.

Discussion

Lue et al [9] introduced CDU for the evaluation of ED as a non-invasive measurement for penile hemodynamics. Rhee et al [5] demonstrated that the PSV, as measured by

Table 3. The IIEF[#]-score (median values) before, 3 months and 5 years after radical retropubic prostatectomy, for the total group and segregated into type of operation. P-value for the total group.

	Score before RRP*				Score 3 months after RRP*				Score 5 years after RRP				p-value 3 months after vs before	p-value 5 years after vs before	p-value 5 years after vs 3 months after
	T[§]	NNS[¶]	UNS[†]	BNS[£]	T	NNS	UNS	BNS	T	NNS	UNS	BNS			
Total IIEF-score (0-75)	58	57	55	62	23	22	25	22	33	21	30	40	<0.0001	<0.0001	0.07
Erectile function (1-30)	24	25	24	26	5	6	5	5	5	3	6	8	<0.0001	<0.0001	0.27
Intercourse satisfaction (0-15)	10	10	10	11	0	0	0	0	0	0	0	5	<0.0001	<0.0001	0.69
Orgasm (0-10)	10	10	10	10	2	2	4	2	5	2	5	6	<0.0001	<0.0001	0.001
Sexual desire (2-10)	6	7	6	8	5	5	6	6	6	5	7	8	0.03	0.03	0.85
Overall sexual statisfaction (0-10)	8	8	8	8	5	5	3	5	6	7	6	6	<0.0001	0.001	0.13
Potency (IIEF 3+4) (0-10)	9	8	8	10	0	2	0	0	1	0	1	2	<0.0001	<0.0001	0.226

[#] International Index of Erectile Function; * Radical Retropubic Prostatectomy; ¶ Non-nerve sparing; † Unilateral nerve sparing; £ Bilateral nerve sparing; § Total group

CDU, was an effective, reliable and non-invasive means of evaluating corporeal arterial function. Several studies have confirmed that penile CDU correlates with selective arteriography in 90-95% of the cases. [6,7] However, Meuleman et al [12] found no difference in the arterial response measured by CDU between impotent men and normal controls. He also reported abnormal findings in the arterial response in men with a normal sexual function. Mills et al reported on CDU as a poorly reproducible technique for assessing vascular status in patients with impotence. [13] In the present study CDU was used before and after RRP and showed normal penile arterial inflow in most of the sexually potent men, preoperatively. After the operation, some of the men with a normal penile arterial inflow preoperatively, had developed arteriogenic insufficiency. Despite, the low potency rate after the operation, mean changes in arterial cavernous flow were not statistically different before and after the operation. Only a few studies used CDU for erectile function tests and vascular evaluation after radical prostatectomy. Mulhall et al [14] performed a vascular evaluation, including penile cavernosometry or duplex ultrasonography in 96 patients after bilateral nerve-sparing radical prostatectomy. They found arterial insufficiency in 59% and venous leakage in 26% of the men. Return of erectile function with vaginal intercourse was present in 47% of men with a normal evaluation, in 31% with arteriogenic insufficiency and in only 9% of men with venous leakage, 12 months post-operatively. They also found that a longer duration of ED after RRP resulted in a greater risk for venous leakage. Zelefsky et al [15] evaluated the aetiology of erectile dysfunction after RRP with duplex ultrasonography and intracavernosal injection tests in 60 men. They showed cavernosal dysfunction in 31 (52%), arteriogenic dysfunction in 19 (32%) and neurogenic dysfunction in seven (12%). Three men (5%) had mixed vascular dysfunction. No information about the preoperative vascular status of these men was presented in these studies. In our study, some form of veno-occlusive insufficiency and low resistance indexes were already present in the majority of normal potent men preoperatively. One explanation for this could be the non-physiologic circumstance of the tests. It has been suggested that the hemodynamic stimulus following a vasoactive intracavernous injection can vary considerably according to the patient's sympathetic activity at the time of injection. Another reason could be the amount of sexual excitement during the erotic videotape. Most men were moderately excited during the videotape in our study. This could be the reason for an insufficient smooth muscle relaxation and a suboptimal resistance index. We demonstrated that most

of the postoperative abnormal values found with CDU are already present before the operation in men who reported to have a normal sexual potency preoperatively. Care must be taken when interpreting outcomes of studies performed only after the operation.

The recovery of sexual potency after RRP varies widely between different studies. From the literature potency rates of 11-40% probably reflects the results of sexual function after RRP in a general urological practice. [16-18] In the present study all patients had a subjectively reported normal sexual performance prior to surgery. However, only half of the men had a normal IIEF score for erectile function preoperatively, suggesting various degrees of baseline ED. Salonia et al [19] reported on discrepant results between verbally obtained information from the patient and information from questionnaires. Of three hundred men who reported full potency during the patient-physician interview only 43% had a normal erectile function according to the IIEF questionnaires score. They concluded that incorrect timing of the administration of the questionnaire, the potential influence of the patient's preoperative psychosexual distress and the implication of the partner's psychological and sexual health may be contributing factors to the contradictory findings.
We found less favourable outcomes for erectile function 3 months and 5 year after RRP. One reason for this poor outcome can be the high proportion of men having a non-nerve sparing procedure. Another reasons can be the fact that the operations were done by different urological surgeons and residents in training. Nevertheless, our findings were comparable with Penson et al, who recently reported a low potency rate of 28% 5 years after operation as well. [2]
Our data suggests that sexual function according to the IIEF in patients with a bilateral nerve sparing procedure is more likely to improve compared to patients with a non-nerve sparing procedure. Recently, Michl et al reported on a stronger decrease in IIEF score in patients undergoing UNS RRP compared to patients undergoing BNS procedure. [20]
In our study orgasm was the only sexual function that significantly improved over years. In almost half of the men orgasm recovered to normal five years after operation. The remaining men had persistent absent or decreased experience of orgasmic function. These data are comparable with the study of Steineck et al. [21] They reported orgasm to be absent or reduced in intensity in 62% men one year after

operation. In contrast, Noldus et al [22] reported on the capability of orgasm after operation and found that in only 11% of men orgasmic function was decreased. A likely explanation for the return of orgasmic function may be nerve regeneration and confident feeling of being cured of prostate cancer. None of the studies mentioned if there was a correlation between orgasmic function and the number of neurovascular bundles spared. We analysed the effect of surgical technique on orgasm and found a trend towards a better recovery of orgasm in patients with bilateral nerve sparing surgery over years.
Results about bother of severe sexual dysfunction after RRP vary widely between 2 and 72% in literature. [17,18,23,24] In the present study, most men were disappointed about their sexual function, postoperatively. However, five years after operation sexual activity slowly returned despite the persistence of ED. Many men seemed to accept the situation and found alternative methods for sexual satisfaction. Although most men suffered from sexual dysfunction the majority was satisfied with their chosen treatment.

We realise that our study has some limitations: first, the three months time interval between surgery and vascular assessment could be discussed. Studies on post-prostatectomy ED pathophysiology showed that prolonged penile ischemia could cause penile structural changes (such as fibrosis), which in turn may cause venous leakage. The loss of smooth muscle fibers after denervation is another explanation for this phenomenon. Such structural changes represent a continuous process, which might not be detectable three months after surgery. However, the fact that there was no significant change in hemodynamic indices at three months after surgery, can be important, in that it suggests that observal structural changes have not taken place by that point. This has implications for research on rehabilitation therapy.
Second, the small cohort can be a reason for the lack of a statistically significant difference between pre- and postoperative erectile function and prognostic factors.

Conclusions

We conclude that although many studies have confirmed the importance of both neurogenic and vascular factors in the aetiology of sexual dysfunction after RRP, our prospective study suggest that vascular factors are less important in the aetiology

of ED after RRP. No structural vascular changes had taken place in a time period of three months after operation. For evaluating hemodynamic changes it is necessary to perform CDU before and after surgery. Orgasm may recover several years after operation, especially in patients with bilateral nerve sparing surgery.

References

[1] Walsh PC and Donker PJ. Impotence following radical prostatectomy: insight into aetiology and prevention. J Urol 1982;128:492-497.
[2] Penson DF, McLerran D, Feng Z et al. 5-Year urinary and sexual outcome after radical prostatectomy: results from the prostate cancer outcome study. J Urol 2005; 173:1701-1705.
[3] User HM, Hairston JH, Zelner DJ, McKenna KE and McVary KT. Penile weight and cell subtype specific changes in a post-radical prostatectomy model of erectile dysfunction. J Urol 2003;169:1175-1179.
[4] Iacono F, Giannella R, Somma P, Manno G, Fusco F and Mirone V. Histological alterations in cavernous tissue after radical prostatectomy. J Urol 2005;173:1673-1676.
[5] Rhee E, Osborn A and Witt M. The correlation of cavernous systolic occlusion pressure with peak velocity flow using color duplex Doppler ultrasound. J Urol 1995;153:358-360.
[6] Velcek D, Sniderman KW, Vaughnan ED, Sos TA and Muecke EC. Penile flow index utilizing a Doppler pulse wave analysis to identify penile vascular insufficiency. J Urol 1980;123: 669-673.
[7] Lane RJ, Appleberg M and Williams W. A comparison of two techniques for the detection of the vasculogenic component of impotence. Surg Gynecol Obstet 1982;155:230-234.
[8] Slob AK, Blom JHM and van der Werff ten Bosch JJ. Erection problems in medical practice: differential diagnosis with relatively simple method. J Urol 1990;143:46-50.
[9] Lue TF, Hricak H, Marich KW and Tanagho EA. Vasculogenic impotence evaluated by high resolution ultrasonography and pulsed Doppler spectrum analysis. Radiology 1985;155:777-781.
[10] Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J and Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile function. Urology 1997;49:822-830.
[11] Cappelleri JC, Rosen RC, Smith MD, Mishra A and Osterloh IH. Diagnostic evaluation of the erectile function domain of the international index of erectile function. Urology 1999;54:346-351.
[12] Meuleman EJ, Bemelmans BL, van Asten WN, Skotnicki SH and Debruyne FM. Assessment of penile blood flow by duplex ultrasonography in 44 men with normal erectile potency in different phases of erection. J Urol 1992;147(1):51-6.
[13] Mills RD and Sethia KK. Reproducibility of penile arterial colour duplex ultrasonography. Brit J Urol 1996;78:109-112.
[14] Mulhall JP, Slovick R, Hotaling J et al. Erectile dysfunction after radical prostatectomy: hemodynamic profiles and their correlation with the recovery of erectile function. J Urol 2002;167:1371-1375.
[15] Zelefsky MJ and Eid JF. Elucidating the etiology of erectile dysfunction after definitive therapy for prostate cancer. Int J Radiat Oncol Biol Phys 1998;40:129-133.
[16] Korfage IJ, Essink-Bot ML, Borsboom GJJM et al. Five-year follow-up of health-related quality of life after primary treatment of localized prostate cancer. Int J Cancer 2005;116
(2):291-296.
[17] Potosky AL, Davis WW, Hoffman RM et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst 2004;96:1358-1367.
[18] Stanford JL, Feng Z, Hamilton AS et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer. JAMA 2000;283:354-360.
[19] Salonia A, Zanni G, Gallina et al. Baseline potency in candidates for bilateral nerve-sparing radical retropubic prostatectomy. Eur Urol 2006;50:360-365.
[20] Michl UHG, Friedrich MG, Graefen M, Haese A, Heinzer H, Huland H. Prediction of postoperative sexual function after nerve sparing radical retropubic prostatectomy. J of Urol 2006;176:227-231.
[21] Steineck G, Helgesen F, Adolfson J et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002;347:790-796.

[22] Noldus J, Michl U, Graefen M, Haese A, Hammerer P and Huland H. Patient-reported sexual function after nerve-sparing radical retropubic prostatectomy. Eur Urol 2002;42:118-124.
[23] Gralnek D, Wessells H, Cui H and Dalkin BL. Differences in sexual function and quality of life after nerve-sparing and nonnerve sparing radical retropubic prostatectomy. J Urol 2000;163;1166-1170.
[24] Arai Y, Okubo K, Aoki Y et al. Patient-reported quality of life after radical prostatectomy for prostate cancer. Int J Urol 1999;6:78-86.

Appendix 1.

Non-validated questionnaire for quality of life.

Question 1

Has your current status of sexuality changed compared with the situation before operation?

5= Yes, much better
4= Yes, improved
3= Unchanged
2= No, become worse
1= No, much worse

Question 2

How would you feel if your current sexual situation remains unchanged the rest of your life?

5= Very satisfied
4= Moderately satisfied
3= About equally satisfied and dissatisfied
2= Moderately dissatisfied
1= Very dissatisfied

Question 3

How satisfied are you with the result of the chosen treatment?

5= Very satisfied
4= Moderately satisfied
3= About equally satisfied and dissatisfied
2= Moderately dissatisfied
1= Very dissatisfied

Question 4

If you have to choose your final treatment for prostate cancer again, with your current knowledge about the outcome, would you still choose the same treatment?

4= Yes
3= Probably yes
2= Only if the urologist strongly advises this treatment
1= No

Orgasmic dysfunction after open radical prostatectomy: clinical correlates and prognostic factors.

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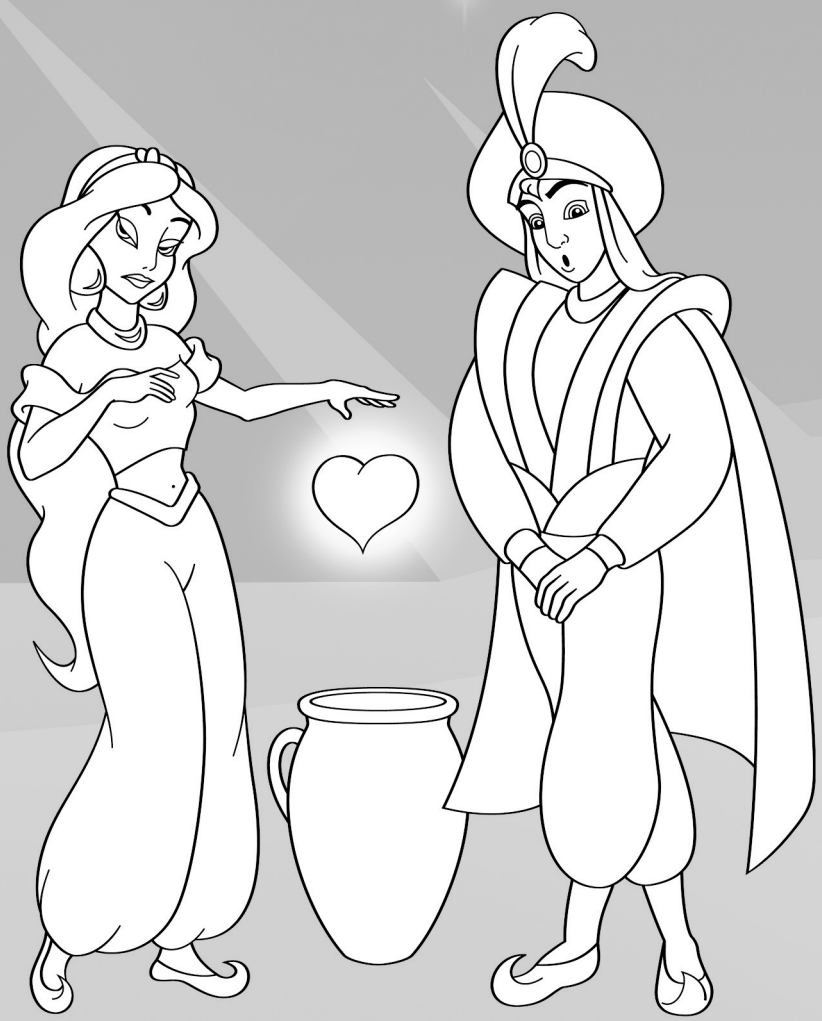

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Abstract

Introduction
Erectile function after radical retropubic prostatectomy (RRP) is extensively discussed in literature. However, less is known about orgasm after RRP.

Aim
To analyse sexual function, in particularly orgasmic function, in men before and after RRP.

Methods
Between 1977 and 2007 a RRP was performed in 1021 men. All men were interviewed by their follow-up physician using a standardised interview about sexual function before and after RRP at regular intervals during a 2 years follow-up. The questions were related to sexual interest, sexual activity, spontaneous erections and orgasmic function.

Main outcome measures
Sexual function, in particularly orgasmic function, before and after RRP. Factors potentially influencing orgasmic function, such as patients age, type of operation, pathological stage and continence status were analysed for their predictive value.

Results
Information about preoperative and postoperative sexual activity and spontaneous erection was available in 596 and 698 men, respectively. Additional questions were asked on sexual interest (n=425) and orgasmic function (n = 458).
Pre-operatively, sexual interest, sexual activity, spontaneous erections and orgasmic function were normal in 99%, 82.1%, 90.0% and 90% of men, respectively. After operation these values decreased to 97.2%, 67.3%, 29.4% and 66.8%, respectively. Orgasmic function was preserved in 141 of 192 men (73.4%) after a bilateral nerve sparing procedure, in 90 out of 127 men (70.9%) after a unilateral nerve-sparing procedure and in 75 of 139 men (54.0%) after non-nerve sparing technique. Postoperatively, orgasm was present in 123 (77.4%) men below the age of 60 years and in 183 (61.2%) men of 60 years and older ($p<0.0001$). Orgasmic function was significantly affected by age $\geq$ 60 years, non-nerve sparing procedure and severe incontinence (more than two pads/day).

Conclusions
After RRP, orgasmic function is still present in the majority of men. A non-nerve sparing operation, age and severe urinary incontinence are risk factors for orgasmic dysfunction after RRP.

Introduction

Several studies have been performed to analyse sexual function in the ageing male. Also for men between 70-80 years of age sex seems important. An intact sexual desire, erection and orgasm are common even in ageing men and is considered important to preserve. [1,2]

Sexual function, especially erectile function, is decreased in most men after radical retropubic prostatectomy (RRP). [3-6] With the introduction of the nerve sparing technique more favourable outcomes have been reported. [7] Little information is available on orgasmic function, another important aspect of sexual function, just like sexual activity and desire. Only a few investigators reported on these items in selected groups of patients. [8,9] The effect of the RRP on the orgasmic function can be total absence of orgasm, reduction of intensity, pain during orgasm (dysorgasmia) and urine loss during orgasm (climacturia). [10,11] With RRP the prostate, seminal vesicles and ejaculatory ducts are removed and consequently ejaculation is absent. This may affect orgasm. In contrast, despite the absence of erections, orgasmic function can still be normal after the operation, although not all patients are aware of this.

Sexual dysfunction and alterations in orgasm, in particular its absence, are associated with significant reductions in emotional and physical satisfaction, which in turn may lead to sexual-avoidance behaviour and secondarily to discord in relationships. [12-15] We performed a prospective study, analysing sexual function, including orgasmic function, by a standardised, non-validated interview of patients before and after RRP. Factors potentially influencing orgasmic function, such as patient's age, type of operation, pathological stage and continence status were analysed for their predictive value.

Material and methods

Between 1977 and 2007, in 1021 patients with clinically localised prostate cancer a radical retropubic prostatectomy was performed at Erasmus MC. The operations were performed by different urological surgeons and residents in training. A nerve-sparing procedure following the technique described by Walsh et al [7] was performed depending on the preoperative and intra-operative assessment of the

extent of the disease. All men were interviewed by their follow-up physician using a non-validated standardised interview, including questions on sexual function (appendix). Information about sexual function was collected before and after surgery. Since only data were collected from patient charts, according to the Dutch law no IRB approval was required. Information about preoperative and postoperative sexual activity and spontaneous erection was available in 596 and 698 men, respectively. In a subset of patients additional questions were asked on sexual interest (n = 425) and orgasmic function (n=458). Information about age of the patient, preservation of the neurovascular bundles, pathological stage of the tumour and continence status was collected from the patients records. The first interview was performed 6 weeks to 3 months before the operation. The next interviews were performed every 3 months after the operation in the first year of follow-up and every 6 months in the following years. Evaluation was performed after 2 years.

The results of sexual and orgasmic function were correlated to age, preservation of the neurovascular bundles, pathological stage of the tumour and continence status. Incontinence was defined as mild to moderate when 2 or fewer pads were used and severe when more than 2 pads were necessary. Prognostic indicators were analysed in a univariate and multivariate analysis by a logistic backward regression analysis. The Pearson Chi-Square test was used for univariate statistical analysis. All variables mentioned above were included in the logistic regression analysis. A p-value at the 5% level was considered to reflect a statistically significant difference.

Results

Baseline characteristics

Mean patient age was 63 years (range 43-79 years). Twenty-eight percent of the men had an age below 60 years. The neurovascular bundle was preserved unilaterally or bilaterally in 63.2% of the men (645/1021). A non-nerve-sparing procedure was performed in 36.8% of the men (376/1021). Pathological stage of the tumour was organ confined in 58.3% of the men (594/1019). Postoperative urinary continence (defined as no pad use) was achieved in 73.4% of the men (713/972), while severe incontinence was present in 9.6% ot the men (93/972). Table 1 shows the patients characteristics according to age, surgical approach, pathological stage and continence status.

Table 1. Baseline characteristics (n=1021)

	Number of patients (%)	
Age (yrs)		
< 60	282	(27.6)
≥ 60	739	(72.3)
Pathological stage		
pT0	10	(1.0)
pT1	1	(0.1)
pT2	593	(58.1)
pT3	344	(33.7)
pT4	71	(7.0)
missing	2	(0.2)
Type of surgery		
Non-nerve sparing	376	(37.0)
Unilateral nerve sparing	261	(25.5)
Bilateral nerve sparing	384	(37.5)
Continence status		
Continent	713	(69.8)
Incontinent ≤2 pads	166	(16.3)
Incontinent >2 pads	64	(6.3)
Sphincter prostheses	29	(2.8)
missing	49	(4.8)

Basic sexual characteristics

Sexual activity

Preoperatively, 82.1% of the men (714/870) were sexually active. In 596 patients who were sexually active before the operation, postoperative information about sexual activity was collected. In 32.7% of these men (195/596) sexual activity was absent after the operation. In case of age <60 years, a bilateral nerve sparing procedure and continence status of 2 or fewer pads per day normal sexual function was more likely to occur postoperatively ($p<0.0001$, $p<0.0001$ and $p=0.038$, respectively). (Table 2,3,4) In a multivariate logistic regression analysis age and non-nerve sparing RRP were factors for absence of sexual activity after RRP. (Table 5)

Table 2. Sexual evaluation after radical retropubic prostatectomy in preoperatively potent and sexual active men according to type of surgery.

Parameter	Post-operative	Total group (%)	BNS (%)†	UNS(%)∞	NNS (%)£	p-value
Sexual active (n=596)	Yes No	401 (67.3%) 195	186 (74.7%) 63	118 (67.8%) 56	97 (56.1%) 76	<0.0001
Spontaneous erections (n=698)	Yes No	205 (29.4%) 493	119 (41.9%) 165	55 (27.8%) 143	31 (14.4%) 185	<0.0001
Sexual interest (n=425)	Yes No	413 (97.2%) 12	191 (99.0%) 2	120 (96.8%) 4	102 (94.4%) 6	0.072
Orgasmic function (n=458)	Yes No	306 (66.8%) 152	141 (73.4%) 51	90 (70.9%) 37	75 (54.0%) 64	0.001

£ non-nerve sparing; † bilateral nerve sparing; ∞ unilateral nerve sparing
The chi-square test was used for testing statistical significance.

Table 3. Sexual evaluation after radical retropubic prostatectomy in preoperatively potent and sexual active men according to age.

Parameter		Total group (%)	< 60 yrs (%)	≥ 60 yrs (%)	p-value
Sexual activity (n=596)	Yes No	401 (67.3%) 195	161 (79.3%) 42	240 (61.1%) 153	<0.0001
Spontaneous erections (n=698)	Yes No	205 (29.4%) 493	84 (39.6%) 128	121 (24.9%) 365	<0.0001
Sexual interest (n=425)	Yes No	413 (97.2%) 12	164 (98.8%) 2	249 (96.1%) 10	0.107
Orgasmic function (n=458)	Yes No	306 (66.8%) 152	123 (77.4%) 36	183 (61.2%) 116	<0.0001

The chi-square test was used for testing statistical significance.

Spontaneous erections

Preoperatively, 90.0% of the men (786/873) had spontaneous erections. In 698 patients with spontaneous erections before operation, postoperative information about spontaneous erections was available. In 70.6% of the men (493/698) spontaneous erections disappeared after surgery. However, overtime, due to improved operation techniques the percentage of men who lost their spontaneous erections after operation decreased to 38%. Patients with an age of ≥60 years were more likely to

develop erectile dysfunction (p<0.0001). (Table 3) There was a significant difference between a non-nerve sparing and a nerve-sparing approach and between unilateral and bilateral nerve-sparing approach. In case of a non-nerve sparing operation, an unilateral and a bilateral nerve-sparing procedure 31/216 men (14.5%), 55/198 men (27.8%) and 119/284 men (41.9%) had spontaneous erections, respectively. (p<0.0001). (Table 2) In multivariate logistic regression analysis age and surgical approach were prognostic factors for the absence of spontaneous erections after RRP. (Table 5)

Table 4. Sexual evaluation after radical retropubic prostatectomy in preoperatively potent and sexual active men according to continence status.

Parameter		Total group (%)	continent (%)	≤2 bandages (%)	>2 bandages (%)	Sphincter prostheses (%)	p-value
Sexual activity (n=596)	Yes	401 (67.3%)	308 (69.2%)	76 (65.5%)	13 (56.5%)	4 (33.3%)	0.038
	No	195	137	40	10	8	
Sexual interest (n=425)	Yes	413 (97.2%)	313 (98.1%)	83 (93.3%)	13 (100%)	4 (100%)	0.089
	No	12	6	6	0	0	
Orgasmic function (n=500)	Yes	335 (67.0%)	252 (68.7%)	71 (68.3%)	8 (47.1%)	4 (33.3%)	0.021
	No	165	115	33	9	8	

The chi-square test was used for testing statistical significance.

Additional questions on sexual interest and orgasm

Sexual interest

Ninety-nine percent of men (719/723) were sexually interested preoperatively. In 425 patients who were sexually interested before operation, postoperative information was gathered. After operation almost all of these men were still sexually interested (n=413; 97.2%). There were no significant differences in univariate analysis for the subcategories: age, surgical approach, continent status or pathological stage. (Table 2,3,4) However, there was a trend towards a slight decrease of sexual interest in men with a non-nerve sparing procedure. (Table 2) In multivariate logistic regression analysis non nerve-sparing RRP was a prognostic factor for a decrease in sexual interest (p=0.037) (Table 5)

Table 5. Logistic regression analysis of different risk factors of sexual function after radical retropubic prostatectomy.

Erectile function	Risk factor	odds	95% CI	p-value
Sexual activity	Age	2.282	1.529-3.405	<0.0001
	NNS[#] vs BNS [†]	0.473	0.311-0.721	0.001
	UNS[∞] vs BNS	0.728	0.472-1.123	0.151
Spontaneous erections	age	1.792	1.256-2.557	0.001
	NNS vs BNS	0.247	0.157-0.387	<0.0001
	UNS vs BNS	0.532	0.359-0.789	0.002
Sexual interest	NNS vs BNS	0.178	0.035-0.898	0.037
	UNS vs BNS	0.314	0.057-1.741	0.185
Orgasmic function	age	2.003	1.284-3.126	0.002
	NNS vs BNS	0.454	0.284-0.725	0.001
	UNS vs BNS	0.865	0.522-1.432	0.573

[#] non-nerve sparing; [†] bilateral nerve sparing; [∞] unilateral nerve sparing

Orgasm

Ninety percent of men had orgasmic function before surgery. (664/734) In 458 patients with an orgasmic function before operation, postoperative information about orgasmic function was recorded. In the majority of men (66.8%; 306/458) orgasm was present after surgery. There was an age-related decline. Orgasmic function was preserved in 77.4% of the men (123/159) with an age below 60 years and in 61.2% of the men (183/299) of 60 years and older. (p<0.0001). (Table 3) Men with a non-nerve sparing procedure were more likely to have orgasmic dysfunction compared to nerve-sparing procedure (54.0% [75/139] versus 70.9-73.4% [90/127 and 141/192]), respectively; p=0.001) Severe incontinence after surgery showed a negative effect on orgasmic function; 47.1% of the men (8/17) who needed more than two pads/day had a normal orgasmic function compared to 68.3% of the men (71/104) who needed two or fewer pads/day (p=0.021). In multivariate logistic regression analysis age and surgical approach were prognostic factors for impairment of orgasmic function. (Table 5)

Discussion

The male sexual response cycle consists of the following phases: desire, arousal, plateau phase, orgasm, and resolution. [16] The orgasmic phase is characterized by seminal emission and ejaculation and the accompanying sensations. Emission of semen into the urethra depends on sympathetic nerves that elicit contractions of smooth muscles in the vas deferens, seminal vesicles, and prostate. Rhythmic contractions of pelvic floor striated muscles (M. bulbospongiosus and M. ischiocavernosus) result in seminal emission from the urethra (ejaculation). [17] Helgason et al studied sexual functions and their importance in elderly Swedish men. In men between 50-59 and 60-69 years of age sexual desire was present in 98 and 94%, erection was present in 97 and 89% and orgasm was present in 98 and 92% respectively. For men between 50-59 years and 60-69 years of age the ability to maintain the pre-operative level of sexual function was either important or very important for sexual desire in 75 and 48%, for erectile capacity in 84 and 59% and for orgasmic pleasure in 91-63%, respectively. Authors concluded that an intact sexual desire, erection and orgasm are common in elderly men and it is considered important to preserve them [1]. Nicolosi et al reported on sexual function in almost 14000 men between 40 –80 years of age. They found erection difficulties, lack of interest in sex and inability to achieve orgasm in 8-22%, 6-20% and 5-15%, respectively. The results of the study indicate that sexual desire and activity are widespread among middle-age and elderly men worldwide and persist into old age. [2]

We showed, in a prospective study, that in patients who had orgasmic function preoperatively, orgasm was preserved in 66.8% of men after RRP. Prognostic factors for orgasmic dysfunction are not evaluated in literature. We found that orgasm is negatively affected by sacrificing the neurovascular bundles, severe incontinence and age. In multivariate analysis surgical approach and age were prognostic factors. These factors are comparable with the most important prognostic factors for erectile function after RRP in literature. [3,18-21]

Most studies on sexual outcome after RRP focus on the ability to achieve erections sufficient for unassisted intercourse. We also analysed orgasm, sexual interest and sexual activity. Although almost all men were sexually interested two years after surgery 70.6% of men had erectile dysfunction and sexual activity was absent in

32.7%. Younger age and nerve-sparing technique were factors associated with a more favourable sexual outcome.

Only a few studies concentrated on orgasmic function after RRP. However these were retrospective studies with small numbers of patients and studies in which only postoperative questionnaires were used. [8,9,22] The outcomes of these studies are less favourable than ours, perhaps due to the lack of pre-operative information.

In a prospective study, Hollenbeck et al. reported on long-term sexual health in 671 men after RRP. [22] They used a postoperative questionnaire for this analysis. Outcomes were compared to a control group. One item of sexual health was the ability to achieve orgasm. Patient with an age below 58 years were able to achieve orgasm in 84%, 68% and 67% after bilateral, unilateral and non-nerve sparing procedure, respectively, compared to 94% of the men in the control group. Patients with an age above 69 years achieve orgasm in 58%, 58% and 30% respectively, compared to 77% in the control group. Factors independently associated with better sexual health outcome included: younger age, nerve-sparing technique, time since prostatectomy, smaller prostate size, higher education level and higher household income. In controls only age and having a partner were factors associated with better sexual health.

In a retrospective study Koeman et al, investigated the ability to attain orgasm and the quality of orgasm after RRP in 20 men [8]. They used a semi-structured interview and a self-administered questionnaire. None of the patients had normal erections after the operation, but 5 patients had tumescence sufficient for intercourse. Diminished sexual desire was present in 50%. None experienced the exquisite sensation of inevitability, the so-called "point of no return". In seven of 14 patients orgasmic sensation was weakened. Only 4 men reported normal pleasure and sensation similar to the situation before the operation. In 5 men there was involuntary loss of urine during orgasm and avoidance of sexual contact with their partner. Barnas et al. evaluated in a retrospective study the type of orgasmic dysfunction after RRP [9]. They used a questionnaire on erectile and orgasmic function in 239 patients after surgery. Twenty-two percent of the men had no change in orgasm intensity, 37% a complete absence, 37% a decreased orgasm intensity and 4% reported a more intense orgasm since the operation. Dysorgasmia occurred in 14% of the patients. In these men the pain occurred always (i.e. with every orgasm) in 33%, frequently in 13%, occasionally in 35% and rarely in 19%. Most patients (55%) had an orgasm-associated pain duration of less than 1 min.

In studies analysing potency after nerve-sparing procedures, orgasm was present in 66-80% of patients postoperatively, whether potency was normal or absent. [6,23-25] Van der Aa et al. analysed the effect of unilateral nerve sparing surgery on potency after RRP in 46 men. [23] They found that 30.4% of men regained full potency after surgery. Eighty-four percent reported the ability to achieve orgasm postoperatively. Madeb et al. reported on functional outcomes after robotic-assisted nerve sparing radical prostatectomy. [24] They used a post-operative questionnaire. Potency was present in 32 %, including non nerve and nerve sparing operations, and more than 80% of the men were able to attain an orgasm. Steineck et al. reported orgasm to be absent or reduced in intensity in 34% and 30% after operation, respectively. [25] Noldus et al. reported on the capability of orgasm after nerve-sparing operation and found that 80% of men had an unchanged, 9% improved, and 11% decreased experience of orgasmic function whether they were potent or not. [6]

Another feature of orgasm observed after RRP that diminish the sexual pleasure and activity is climacturia. Choi et al. evaluated the rate of occurrence of orgasm associated incontinence following radical pelvic surgery and found it to be present in 20% after open RRP. Orgasm associated incontinence was more likely to occur within 12 months following surgery, in patients with orgasm associated pain and in case of loss of penile length. It was not associated with daytime continence, patient age, degree of nerve sparing, surgical margin status, seminal vesicle and lymph node involvement, preoperative erectile function, nocturnal erections and disturbances in libido. [10] Lee et al. found that 19 (45%) of 42 patients experienced climacturia following RRP. [11] Of these men 21% reported that it occurred most of the time or always. Age, Gleason score and time since surgery were not predictors of climacturia.

The cause of dysorgasmia is not well understood. It is postulate that the physiological bladder neck closure that occurs during orgasm in men who underwent a RRP translates into spasm of the vesico-uretral anastomosis or pelvic floor musculature dystonia. [9] The muscle spasm concept is supported by the experience with the amelioration of dysorgasmia using the alpha-blocker tamsulosine. [26] Other suggestions are intraoperative neurapraxia of the cavernous nerves and the psychological distress that men experience with a diagnosis of prostate cancer for which they had major radical pelvic surgery. For treatment options of dysorgasmia alpha-blockers and phosphodiesterase type 5 (PDE-5) inhibitors are recommended [26]. Treatment with PDE-5 inhibitors seems to improve orgasmic function after

nerve sparing radical prostatectomy. Nehra et al. reported on a randomised, placebo controlled, double blind trial with Vardenafil, and found the drug significantly superior to placebo in the International Index of Erectile Function domains for intercourse satisfaction, orgasmic function and overall satisfaction with sexual experience. [27] Lowentritt et al. reported a significant improvement of the orgasmic function after radical retropubic prostatectomy in patients taking Sildenafil citrate. [28]

We realise that our study has some limitations. First, we collected data from a long period (1977-2007) in which the operations were performed by different surgeons: this possibly could give some form of bias. Secondly, we did not use a self-administered questionnaire, but different physicians were the interviewers of the standardized non-validated questionnaires. This could possibly gives some overestimations of the outcomes since we know from literature that for example incontinence rates after radical prostatectomy based on mailed questionnaires are higher than results verbally obtained by the follow-up physician. Third, the lack of available follow-up information. In spite of this limitations we feel that these data are of interest and may be useful in counselling men candidates for radical prostatectomy.

Beside the different treatment options for sexual dysfunction after RRP, pre-operative sexual counselling seems to be important and should addresses the ability to reach an orgasm even with a flaccid penis and without emission and ejaculation. Furthermore, pre-operative information about potential changes in the quality of the orgasm and climacturia is important. This counselling may contribute to a better sexual health in men after radical prostatectomy.

Conclusion

After radical prostatectomy sexual interest was still present in the majority of men. Orgasm and sexual activity disappeared in one third of the men after the operation. A non-nerve sparing operation, age and severe incontinence after the operation are significant risk factors for orgasmic dysfunction after RRP.

References

[1] Helgason AR, Adolfsson J, Dickman P et al. Sexual desire, erection, orgasm and ejaculatory functions and their importance to elderly Swedish men; a population-based study. Age and aging 1996;25:285-291.
[2] Nicolosi A, Laumann EO, Glasser DB et al. Sexual behavior and sexual dysfunctions after age 40: the global study of sexual attitudes and behaviors. Urology 2004;64:991-997.
[3] Karakiewicz, P.I., Tanguay, S., Kattan, M.W., Ihilali, M.M. and Aprikian, A.G. Erectile and urinary dysfunction after radical prostatectomy for prostate cancer in Quebec: a population-based study of 2415 men. Eur. Urol.2004;46,188-194.
[4] Stanford, J.L., Feng, Z., Hamilton, A.S., Gilliland, F.D., Stephenson, R.A., Eley, J.W., Albertsen, P.C., Harlan, L.C. and Potosky, A.L. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer. JAMA 2000;283,354-360.
[5] Walsh, P.C., Marschke, P., Ricker, D. and Burnett, A.L. Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. Urology 2000;55,58-61.
[6] Noldus, J., Michl, U., Graefen, M., Haese, A., Hammerer, P. and Huland, H. Patient-reported sexual function after nerve-sparing radical retropubic prostatectomy. Eur. Urol 2002;42,118-124.
[7] Walsh, P.C. and Donker, P.J. Impotence following radical prostatectomy: insight into aetiology and prevention. J. Urol 1982;128,492-497.
[8] Koeman, M., van Driel, M.F., Schultz, W.C. and Mensink, H.J. Orgasm after radical prostatectomy. Br J Urol. 1996, jun;77(6):861-4
[9] Barnas, J.L., Pierpaoli, S., Ladd, P., Valenzuela, R., Aviv, N., Parker, M., Waters, W.B., Flanigan R.C. and Mulhall, J.P. The prevalence and nature of orgasmic dysfunction after radical prostatectomy. BJU Int 2004,sep;94(4):603-5.
[10] Choi, J.M., Nelson, C.J., Stasi, J. and Mulhall, J.P. Orgasm associated incontinence (climacturia) following radical pelvic surgery: rates of occurrence and predictors. J Urol, 2007,jun;177(6):2223-6.
[11] Lee J, Hersey K, Lee CT and Fleshner N. Climacturia following radical prostatectomy: prevalence and risk factors. J Urol 2006;176(6Pt1):2562-5.
[12] Perez MA, Skinner EC, Meyerowitz BE. Sexuality and intimacy following radical prostatectomy: patient and partner perspectives. Health Psychol 2002;21:288-93.
[13] Snyder DK, Berg P. Determinants of sexual dissatisfaction in sexually distressed couples. Arch Sex Behav 1983;12:237-46.
[14] Aroujo AB, Durante R, Feldman HA et al. the relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from the Massachusetts Male Aging Study. Psychosom Med 1998;60:458-465.
[15] Rust J, Golombok S and Collier J. Marital problems and sexual dysfunction: How are they related? Br J Psychiatry 1988;152:629-631.
[16] Kaplan HS Hypoactive sexual desire. J Sex Marital Ther 1977;3:3-9.
[17] deGroat, W.C. and Booth, A.M. Physiology of male sexual function. Ann Intern Med 1980, Feb;92(2Pt2):329-31.
[18] Geary, E.S., Dendinger, T.E., Freiha, F.S. and Stamey, T.A. Nerve sparing radical prostatectomy: a different view. J.Urol 1995;154, 45-149.
[19] Kundu, S.D., Roehl, K.A., Eggener, S.E., Antenor, J.A.V., Han, M. and Catalona, W.J. Potency, continence and complications in 3477 consecutive radical retropubic prostatectomies. J. Urol 2004 ;172,2227-2231.
[20] Quinlan, D.M., Epstein, J.I., Carter, B.S. and Walsh, P.C. (1991). Sexual function following radical prostatectomy: influence of preservation of neurovascular bundles. J.Urol 1991;145,988-1002.
[21] Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy:

a meta-analysis. J Sex Med 2009;6(9):2538-46.
[22] Hollenbeck BK, Dunn RL, Wei JT, Montie JE, Sanda MG. Determinants of long-term sexual health outcome after radical prostatectomy measured by a validated instrument. J Urol 2003(169):1453-1457.
[23] Van der Aa F, Joniau S, De Ridder D and Van Poppel H. Potency after unilateral nerve sparing surgery: a report on functional and oncological results of unilateral nerve sparing surgery. Prostate Cancer Prostatic Dis.2003;6(1):61-5.
[24] Madeb R, Golijanin D, Knopf J, Vicente I, Erturk E, Patel HRH, Hons BMSc, Joseph JV. Patient-reported validated functional outcome after extraperitoneal robotic-assisted nerve-sparing radical prostatectomy. JSLS 2007;11:443-448.
[25] Steineck, G., Helgesen, F., Adolfson, J. et.al. Quality of life after radical prostatectomy or watchful waiting. N. Eng. J. Med. 2002;347,790-796.
[26] Barnas, J., Parker, M., Guhring, P. and Mulhall, J.P. The utility of tamsulosin in the management of orgasm-associated pain: a pilot analysis. Eur Urol 2005,Mar;47(3):361-5.
[27] Nehra, A., Grantmyre, J., Nadel, A., Thibonnier, M. and Brock, G. Vardenafil improved patient satisfaction with erectile hardnesss, orgasmic function and sexual experience in men with erectile dysfunction following nerve sparing radical prostatectomy. J Urol 2005,Jun;173(6):2067-71.
[28] Lowentritt, B.H., Scardino, P.T., Miles, B.J., Orejuela, F.J., Schatte, E.C., Slawin, K.M., Elliott, S.P. and Kim, E.D. Sildenafil citrate after radical retropubic prostatectomy. J Urol 1999,Nov;162(5):1614-7.

Appendix

Questions on sexual function:

- are you interested in sex (0=no, 1=yes)
- are you sexually active, inclusive masturbation and sex with and without coitus (0=no, 1=yes)
- do you have spontaneous erections (without stimulus or aid) (0=no, 1= yes)
- do you reach an orgasm (0=no, 1=yes)


indy

Part III

Continence status after radical retropubic prostatectomy

Chapter 6 The recovery of urinary continence after radical retropubic prostatectomy: a randomized trial comparing the effect of physiotherapist guided pelvic floor muscle exercises with guidance by an instruction folder only.
British Journal of Urology International, 2010; 106(4): 515-22

Chapter 7 Quantification of changes in detrusor function and pressure-flow parameters after radical prostatectomy: relation to postoperative continence status and the impact of intensity of pelvic floor muscle exercises.
Neurourology and Urodynamics, 2012; 31(5): 637-41

Chapter 8 Urodynamic quantification of decrease in sphincter function after radical prostatectomy: relation to postoperative continence status and the effect of intensive pelvic floor muscle exercises.
Neurourology and Urodynamics, 2012; 31(5): 646-51

Chapter 9 Urethral sphincter function before and after radical prostatectomy; systematic review of the prognostic value of various assessment techniques.
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The recovery of urinary continence after radical retropubic prostatectomy:

a randomized trial comparing the effect of physiotherapist guided pelvic floor muscle exercises with guidance by an instruction folder only.

6

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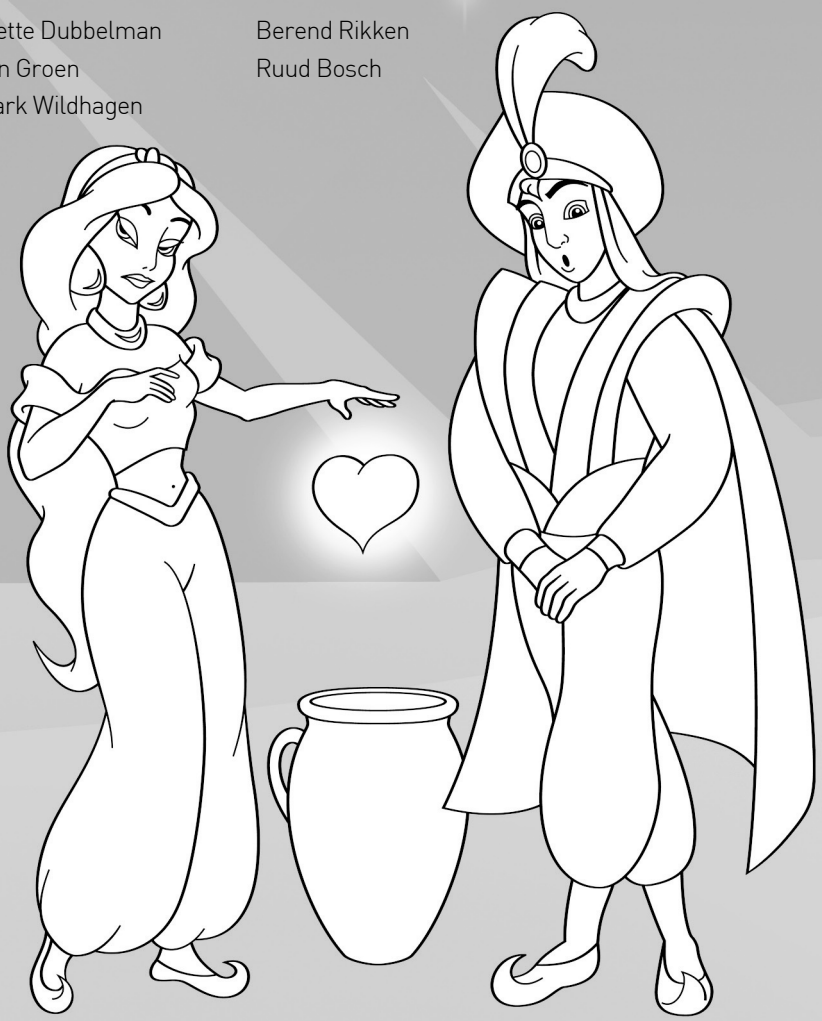


British Journal of Urology International, 2010; 106(4): 515-22

Abstract

Objective

To compare the effect on the recovery of post radical prostatectomy incontinence (PRPI) of intensive physiotherapist-guided pelvic floor muscle excercises (PG-PFME) in addition to an information folder, with PFME explained to patients by an information folder only (F-PFME). And to determine independent predictors of failure to regain continence after radical retropubic prostatectomy (RRP).

Material and methods:

We postulated that a 10% increase in the proportion of men who regained continence at 6 months with PG-PFME as compared to men treated with F-PFME only, would constitute a clinically relevant effect.

To show statistical significance of this difference with a power of 80%, 96 men should be randomized to each of the two arms. One day before operation, all patients received verbal instruction and an information folder on PFME. Patients randomized to the F-PGME arm received no further physiotherapist guidance whereas those in the PG-PFME arm received a maximum of 9 sessions with the physiotherapist. A 1h pad-test was performed at 1, 12 and 26 weeks and the 24h pad-test at 1, 4, 8, 12 and 26 weeks after catheter removal. We defined "continence" as urine loss of less than 1 g at the 1h and of less than 4 g at the 24h pad-test.

Results

During the 2-year recruitment period, the number of patients randomized fell short of the target determined by the sample size calculation owing to limitations of resources and unexpected changes in treatment preferences. In spite of this, we analyzed the data. Of the 82 randomized patients 70 completed the study. Of these, 34 and 36 men had been assigned to thePG-PFME and the F-PFME group, respectively. Six months after operation, ten (30%) and nine (27%) men were completely dry on both 1h and 24h pad-test in the PG-PFME and the F-PFME group, respectively (difference not significant). In a multivariate analysis the amount of urine loss 1 week after catheter removal seemed to be an independent prognostic factor for failure to regain continence.

Conclusion

PG-PFME seems to have no beneficial effect on the recovery of continence within the first six months after RRP, over an instruction folder guided approach. However, due to underpowering there is a high risk of type II error. Nevertheless, this finding can be added to the knowledge base for availability in meta-analyses and can serve as a starting point for the design of new randomized studies.

Introduction

Urinary incontinence occurring after radical retropubic prostatectomy (RRP) remains one of the most troubling side effects of the operation. Incontinence rates following RRP vary widely among different series due to disparities in patient selection, the inclusion of bother in the definition of incontinence and in the methodology used to determine the continence status of the patient. Reported incontinence rates six months after surgery vary between 10-87%. [1-3] Greater understanding of the anatomy of the prostatic apex and the pelvic floor, as well as attention to details of surgical techniques, like nerve sparing techniques, have all contributed to improvements in continence rates. [4-7] In most men a stable continence level is achieved within 6 months [1,8], and almost all men who will achieve complete urinary continence will have done so within 1 year after operation. [9]

Studies of the effect of pelvic floor muscle exercises (PFME) on the recovery of continence after radical prostatectomy have led to conflicting conclusions. [10-16] At the time of the design of our study, several randomized studies comparing control groups with groups receiving PFME with or without biofeedback, for treatment of post-radical prostatectomy incontinence, had been reported in the English language peer-reviewed literature. [12,13,17,18] Most of these studies, involved small numbers of men in each treatment arm (generally less than 20) and had not shown a beneficial effect of PFME. However, van Kampen et al, in a well-designed and well-conducted study, found a clear positive effect of PFME versus no treatment i.e. "ineffective" electrical stimulation through skin patches. [13] We aimed to confirm these results and additionally wanted to show that physiotherapist-guidance was essential for success by comparing a PG-PFME group with a control group receiving verbal and written instructions about self-administered PFME (instruction folder).

Since the start of our study several other reports on PFME in PRPI have been published and manuscripts published before 2006 have been included in a recent Cochrane review. [19] In this review, 15 randomized trials of conservative management of post-prostatectomy incontinence were found to be eligible for inclusion; of these, 7 involved trials of PFME. In only 1 of these, a beneficial effect of PFME was demonstrated. [13] Apart from performing a prospective randomized study to compare the effect of guidance by a physiotherapist combined with instructions using an information

folder (PG-PFME arm) versus an information folder only (F-PFME arm), we tried to determine independent predictors of failure to regain continence.

Materials and methods

We performed a randomized IRB approved study, on the effect of PFME guided by an instruction folder plus intensive post-operative guidance by a physiotherapist versus guidance by an instruction folder only, on the recovery of urinary continence after RRP.

All patients listed for RRP and living within about 75 km from our hospital were asked to participate and subsequently screened. Inclusion criteria for the study were: completed RRP because of prostate cancer, informed consent and urinary incontinence one week after catheter removal i.e. loss of at least 1g during the 1h pad-test as recommended by the International Continence Society. [20] Exclusion criteria were: incontinence before RRP. All patients reported that they were fully continent and had complete urinary control before the operation. One day before surgery, a physiotherapist discussed post-operative exercises with all consenting patients and an instruction folder was handed out. The instruction folder contained information about urogenital tract anatomy, consequences of the operation and exercises to strengthen the pelvic floor (Appendix 1). The instruction folder was in Dutch language; the appendix gives a short summary of the items discussed and explained in the folder. The full text of the folder is available on request. Patients were randomized into one of both arms if they were incontinent (urine-loss of at least 1g during the 1h pad-test) one week after removal of the trans-urethral catheter. The estimated percentage of incontinent men at six months after RRP is about 25%, based on data from previous studies. [13,21] We postulated that a 10% increase in the proportion of men who regained continence at 6 months with PG-PFME as compared to men treated with F-PFME only, would constitute a clinically relevant effect. To show statistical significance of this difference with a power of 80%, 96 men should be randomized to each of the two arms. We used a random number generator to determine the randomisation outcome in a 1:1 ratio. The outcome was printed on a piece of paper and put in a sealed, non-opague envelope. The envelopes, which contained the treatment allocation were sequentially numbered and were stored in the urology trial bureau and opened by the trial nurse after the result of the pad

test (one week after catheter removal) had indicated eligibility for inclusion. The timing of randomization and the start of the intervention were comparable with Van Kampen et al [13]. The data for outcome assessment (e.g. pad-tests, voiding diaries) were collected and entered in a database by a trial nurse who was not involved in the treatment or intervention. The physiotherapist who guided men in the PG-PFME group, was blinded to the outcome data of both treatment groups. Patients who were randomized to the F-PFME arm did not receive any further guidance or instruction by the physiotherapist. Only patients who were randomized in the PG-PFME arm were invited for a maximum of 9 sessions of physiotherapist-guided PFME after surgery. The duration of each session was 30 min. The exercises were reviewed and approved by several professional physiotherapy organizations (Appendix 2).

We chose to do a monocenter study to assure constant quality of physiotherapy guidance; at the time of the design of the study, resources and numbers of patients undergoing RRP seemed to be adequate to complete recruitment within a 2-year period.

The primary outcome measure, "urinary continence", was defined as a loss of < 4 g urine on the 24 h pad tests AND of < 1 g on the 1h pad test. We also graded incontinence according to the amount of urine loss during the 1h pad-test as dry (<1g), mild (1-10g), moderate (11-50g) and severe (>50g). Voiding dairies (frequency-volume-pad use charts, 24 hour) were completed for 24 hour in week 1, 4, 8, 12 and 26 weeks after catheter removal. The 1h pad-test was repeated 12 and 26 weeks after catheter removal. The 24h pad-test was performed at 1, 4, 8, 12 and 26 weeks after catheter removal.

We analysed the results for the total group of patients and for the F-PFME arm versus the PG-PFME arm; we also compared the group of patients who regained continence with those who remained incontinent. The concept of an intent-to-treat analysis was not applied, for the following reasons: In the PG-PFME arm and the F-PFME arm 1and 2 men dropped out because of an anastomotic stricture that required treatment that led to more incontinence, respectively; these men were not be available for the 26-weeks evaluation. In the folder group 6 more men dropped out because of withdrawal of consent (5) and lack of understanding. (1) To further evaluate the effect of dropouts, we conducted a sensitivity analysis. Participants were analysed in the group to which they were allocated at randomization.

Because of the non normal distribution of the data we used non-parametric statistics.

Results are given as median values and interquartile ranges (25^{th}-75^{th} percentile range) unless stated otherwise. We used the t-test and the Mann-Whitney U-test to test for significance, where applicable. We used univariate analysis to determine the effect of a number of variables on the persistence of incontinence after RRP. Prognostic factors considered for inclusion in the model were: age, clinical tumor stage, prostate volume, body mass index, PSA, operation time, bloodloss, nerve-sparing technique, bladder neck sparing technique, amount of urine loss 1 week after catheter removal and physiotherapy. Variables that achieved a p-value below 0.2 on univariate analysis were included in a multivariate logistic regression analysis. A p-value at the 5% level was considered to reflect a statistically significant difference. Odds ratios and 95% confidence intervals are reported.

Results

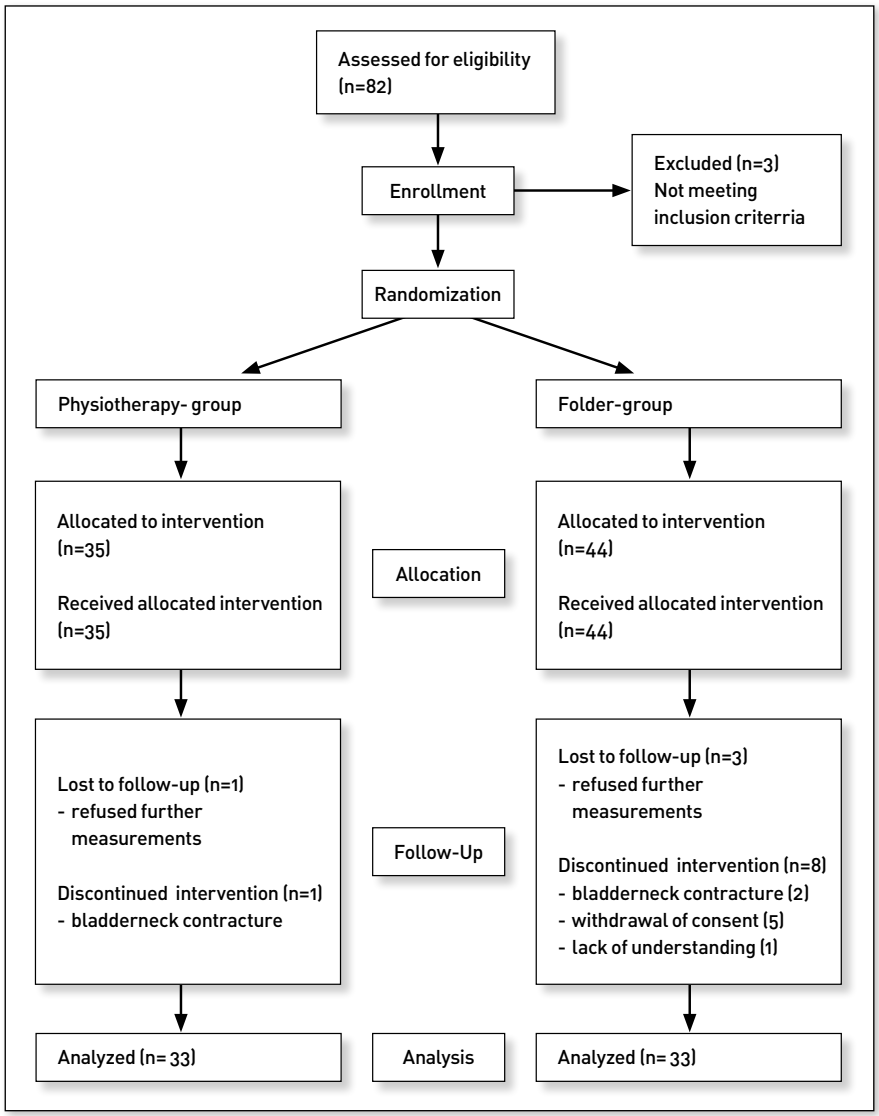
During the 2-year recruitment period, the number of patients randomized fell short of the target determined by the sample size calculation owing to limitations of resources and unexpected changes in treatment preferences. In spite of this, we analysed the collected data, representing about a third of the calculated sample size.

Eighty-two men with clinically localized prostate cancer were recruited (Figure 1). Three patients had positive lymph nodes on frozen section and were excluded, because the operation was cancelled. The remaining 79 patients underwent RRP and were randomised into one of the two study-arms. All 79 men had urine loss>1g on the 1h pad-test that was performed 1 week after catheter removal. Thirty-five and 44 men, were randomized to the PG-PFME arm and the F-PFME arm, respectively.

During follow-up, nine patients dropped out: 3 because of bladder neck contracture (one of the PG-PFME arm and two of the F-PFME arm), 5 withdrew consent (all from the F-PFME arm) and 1 illiterate man, because of lack of understanding (from the F-PFME arm). Of the nine patients that were lost to follow-up or dropped out 5, 2, 1 and 1 dropped out in week 1, 4, 8 and 12, respectively.

Urine loss during 1h and 24h pad-test one week after catheter removal was between 2-20g and 22-94g, respectively in those drop-outs. Thirty-four and 36 men in the PG-PFME arm and the F-PFME arm, respectively, completed the study. The median age of the 70 men at the time of surgery was 64 (range 46-73) years. Table 1 shows that there were no statistically significant differences between the baseline characteristics

Figure 1. Trial profile



of the different patients groups. Complete follow-up was available in 66 patients. Four men, 1 in the PG-PFME arm and 3 in the F-PFME arm, insisted verbally that they were continent. However, they refused to do a 1h and 24 h pad-test for objective measurements six months after surgery, because they did not see the value of these tests in addition to their verbal report.

Table 1. Baseline characteristics (n=66) for the complete group and subdivided for the physiotherapist guided and the folder group and for the men who regained continence and those who remained incontinent; median values (interquartile ranges).

	Total group	Physiotherapy group	Folder group	p-value	Continent n= 19	Incontinent n= 47	p-value
Age	64 (60-67)	64 (60-66)	64 (61-67)	0.55	62 (61-67)	64(60-67)	0.90
Prostate volume	52 (42-62)	50 (40-61)	55 (43-64)	0.16	50(43-60)	52(42-66)	0.64
PSA	6.4 (4.1-11)	5.3 (3.4-9.9)	7.6 (4.9-11.5)	0.07	4.4 (3.4-8.9)	6.6(4.8-11.0)	0.07
Operation time	261(240-293)	260(230-283)	268 (240-295)	0.60	270 (230-295)	259(240-283)	0.47
Bloodloss	2150 (1500-2800)	2000 (1500-2500)	2400 (1500-2900)	0.25	2100 (1650-2800)	2200 (1500-3000)	0.64
BMI†	25.0 (23.7-27.1)	24.8 (23.1-26.8)	25.4 (24.3-27.6)	0.33	26.1 (24.7-27.4)	24.6 (23.1-26.7)	0.09
pT∞ 2 **3** **4**	51 16 3	24 8 2	27 8 1	0.80	14 5 -	35 9 3	0.31
PG# 1 **2** **3**	41 20 9	19 11 4	22 9 5	0.90	12 5 2	18 13 6	0.90
Type of operation*							
BNS	22	12	10	0.23	6	15	0.70
UNS	19	6	12		6	10	
NNS	28	15	14		7	21	
unknown	1	1	0		-	1	

† Body mass index; ∞ pT: pathological stage; # pG: pathological grade;
* BNS: bilateral nerve sparing; UNS: unilateral nerve sparing; NNS: non-nerve sparing.

Incontinence rate after operation

Six months after surgery, 19 of 66 patients (29%) were continent during both the 1h and 24h pad-test. Analyzing the PG-PFME group (n=33) and the F-PFME group (n=33) group, ten (30%) and nine men (27%), respectively, were completely continent during

both the 1h and 24h pad-test after six months; this difference of 3% was statistically not significant (p= 0.786). In terms of a sensitivity analysis we have determined the outcome in both arms if we had considered all 6 dropouts from the F-PFME group to be incontinent at the 26 weeks evaluation. In that case, the continence rate of the F-PFME group would change from 9/33 (27%) to 9/39 (23%). Statistically, the difference with the PG-PFME group (30% continence) is still not significant.

Table 2. Number (%) of incontinent men according to the amount of urine loss during the 1h pad test: dry (<1g), mild (1-10g), moderate (11-50g) and severe (>50g) for the total group, the physiotherapy and the folder group six months after surgery.

	< 1 g N (%)	1-10 g N (%)	11-50 g N (%)	> 50 g N (%)
Total group (66)	29 (44)	27 (41)	3 (4)	7 (11)
Physiotherapy (33)	16 (49)	12 (36)	1 (3)	4 (12)
Folder (33)	13 (39)	15 (46)	2 (6)	3 (9)

Taking only the 1h pad-test into account 49%, 36%, 3% and 12% of the patients in the PG-PFME arm and 39%, 46%, 6% and 9% of the patients in the F-PFME arm had no, mild, moderate or severe incontinence, respectively (no significance was found, Table 2). Median urine loss during the 24h pad-test decreased from 207 (55-609) ml and from 211 (55-475) ml at 1 week after catheter removal to 11 (0-42) ml and 4 (0-20) ml at 26 weeks in the PG-PFME arm and the F-PFME arm, respectively (Table 3). There were no significant differences between the two groups.

The amount of urine loss 1 week after catheter removal for men who had become continent and men who remained incontinent was 30 (16-220) ml and 320 (100-648) ml, respectively (p<0.001; Table 3).

Time to regain continence

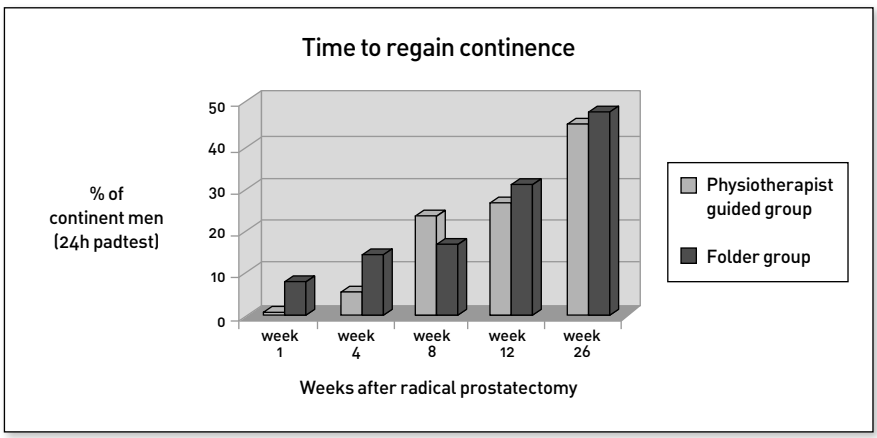
In those who became continent, mean time to regain continence was 14,8 versus 15,1 weeks for the PG-PFME arm and the F-PFME arm, respectively (p=0.97). We also analyzed the impact of physiotherapist-guided exercises on the recovery of continence in the sub-groups of patients with mild incontinence. Again, no beneficial effect of intensive guidance by a physiotherapist was found (p=0.768). Figure 2 shows the

percentage of men who became fully continent in the physiotherapist-guided and the folder-group at different time-points during follow-up.

Table 3. Results of the 24h pad test (in grams) 1 and 26 weeks after RRP. Median values (interquartile ranges) are given. In brackets the percentage of men losing < 10 grams.

	1 Week		26 Weeks		Improvement
All [n=66]	207 (57-508)	[6%]	6 (0-22)	[55%]	187 (31-463)
Physiotherapy-group [n=33]	207 (55-609)	[6%]	11 (0-42)	[47%]	160 (30-496)
Folder-group [n=33]	211 (55-475)	[6%]	4 (0-20)	[63%]	201 (40-426)
p-value	0.72		0.36		0.71
Continent [n=19]	30 (16-220)	[12%]	0	[100%]	30 (16-220)
Incontinent [n=47]	320 (100-648)	[0%]	18(6-38)	[14%]	268 (72-540)
p-value	<0.001		<0.001		0.003

Figure 2. Time to regain continence: percentage of patients who became continent in the physiotherapist-guided and the folder group at different time points after surgery. (Continence was defined as < 4 g urine loss during the 24h pad test).



Prognostic factors

Univariate and multivariate logistic regression analysis showed that the amount of urine loss 1 week after catheter removal, as a continuous variable, was a significant prognostic factor for the persistence of incontinence six months after RRP (Odds ratio 1.008 [95%CI 1.000-1.016], p=0.046; Table 4).

Table 4. Univariate and multivariate logistic regression analysis enter method of prognostic factors for incontinence after radical retropubic prostatectomy.

	Univariate Odds Ratio (95%CI)	p-value	multivariate Odds Ratio (95%CI)	p-value
Age	1.007 (0.908-1.116)	0.899		
Clinical stage 1 versus 3 2 versus 3	0.000 (0.000-0.001) 0.000 (0.000-0.001)	0.999 0.999		
Prostate volume	1.006 (0.976-1.038)	0.682		
BMI	0.899 (0.742-1.089)	0.275		
PSA	1.112 (0.984-1.258)	0.089	1.107 (0.980-1.251)	0.103
Operation time	0.997 (0.992-1.003)	0.371		
Bloodloss	1.000 (1.000-1.001)	0.396		
Surgical approach BNS versus NNS UNS versusNNS	 0.833 (0.233-2.985) 0.556 (0.148-2.090)	 0.779 0.385		
Bladder neck sparing technique	0.750 (0.244-2.308)	0.616		
Physiotherapist guided exercises (yes or no)	0.862 (0.297-2.506)	0.786		
Urine loss 1 h pad test 1 week after catheter removal	1.008 (1.000-1.015)	0.043	1.008 (1.000-1.016)	0.046

BMI: body mass index.
NNS: non-nerve sparing; BNS: bilateral nerve sparing; UNS: unilateral nerve sparing

Discussion

Our sample size calculation was based on the assumption that men in the PG-PFME arm would do better than men in the F-PFME arm. Unfortunately, the number of patients recruited fell short of the target determined by the sample size calculation. Furthermore, when analysing the available data we unexpectedly did not find an advantage for the men in the PG-PFME arm.

Based on numbers of RRP's performed in previous years, we assumed that an inclusion of 100 men undergoing RRP per year would be feasible. The inclusion period of the study was therefore planned to be two years. To achieve a constant high quality of the physiotherapeutic treatment we opted for a monocenter study. Unfortunately, after initiation of our study the technique of open RRP was gradually being replaced with laparoscopic RP, which delayed the recruitment. In spite of this we decided not to include patients who were scheduled to undergo a laparoscopic RP since this would add the confounding factor of the learning curve of the laparoscopic surgeons. Furthermore, we clearly overestimated the willingness of men to be randomized and run the chance that physiotherapist-guidance would not be available to them. Perhaps we underestimated the participant burden of the repeated measurements for the patients. Obviously, our study (like most of the other available studies comparing PG-PFME with other modalities [11,22]) was not powered to show equivalence of the 2 approaches. In spite of the fact that the sample size was not achieved we feel that the results of our study are significant from a clinical point of view and should be added to the available data base of this topic and be available for the purpose of meta-analysis. The results of our study together with other reports that have become available recently [22], indicate that future studies should be designed to show equivalence between PG-PFME and F-PFME or verbally instructed PFME. Such an equivalence trial would be difficult to do because of the large number of men that would have to be randomized to each arm. We performed an example power calculation and found that 757 men would have to be randomized to each of the two arms, to show equivalence in the primary outcome measure with a power of 80%.

The majority of men who undergo RRP have some level of urine loss immediately after urinary catheter removal. Because of a variable use of definitions it is difficult to establish expected continence rates. We defined continence by both the 1h and

the 24h pad-test, to get a reliable estimate of the continence status. We used the pad test because it is an inexpensive and simple form of assessment in patients with bothersome incontinence. Additionally, it allows documentation of improvement over time. [21] Six months after surgery, 29% and 44% of our patients were objectively continent on both the 1h and 24h pad-tests and on the 1h pad-test only, respectively. The seemingly less favourable overall continence rate in our study is probably due to the definition of continence and the methods used in the study. When we take the results for "no" and "mild" incontinence together our "continence rate" is 85% what is comparable with other reports. Others have shown that the recovery of continence is time dependent. [4] About 75-90% of the patients achieve continence within six months. [2,3] Beside the variable use of definitions it has been reported that incontinence rates based on mailed questionnaires are higher than results verbally obtained by the surgeon [13]. In physician reported studies, the incidence of total incontinence is 0-5% and the incidence of stress incontinence requiring protection is 5-30%. [2, 5, 10-12, 23] In a study based on patient self-report, the incidence of any degree of incontinence is 66% and the incidence of pad use was 33%. [24] Incontinence rates based on strict urodynamic criteria are as high as 87%. [1]

The role of PFME with or without biofeedback is still controversial. The main research questions of our study were: can we confirm the reported beneficial effect of physiotherapist-guided PFME [13] and what are possible predictors of failure to regain continence in randomized controlled treatment setting? In our study, 48% and 39% of the patients in the PG-PFME arm and the F-PFME arm respectively, were continent after six months according to the 1h pad-test. This suggests a benefit for PG-PFME arm. However, when analysing continence rate by both 1h and 24h pad-tests, there was no significant difference between the groups (30% versus 27%).

After the report of van Kampen et al [13] and since the initiation of our study others have shown mixed results with conflicting conclusions. Comparison of the various trials is difficult because of variable study designs.

Moore et al recently reported on the effect of postoperative PFME versus supportive telephone contact by a urology nurse on the return of continence after RRP. [22] Continence was defined as 8g or less of urine loss on a 24h pad-test. They did not find a significant difference between the two groups: at 28 weeks after surgery 50% of the control group and 47% of the PFME group were continent; at 52 weeks 64% and 60% were continent, respectively. They concluded that less-intense therapy may be

more cost-effective, but their study (like ours) was not powered to show equivalence between the two arms. Their findings are in agreement with ours.

Parekh et al evaluated the relevance of preoperative and early postoperative biofeedback enhanced PFME on the early return of continence. [11] The intervention group received PFME guided by a physiotherapist before as well as, up to three months after surgery. The control group received no formal instruction on PFME pre-operatively, only telephone or face to face follow-up at least monthly. Continence was defined as the use of 0 pads or 1 precautionary pad. PFME was of limited benefit to patients with severe urinary incontinence 16 weeks after surgery. Furthermore, continence rates at 1 year were similar in the two groups. Unlike our study, Parekh et al started with PFME before surgery. Perhaps this is the reason for the better result in the early post-operative period. In the longterm there was no significant effect of PFME on the recovery of continence.

Filocamo et al investigated the effectiveness of early pelvic floor rehabilitation treatment for post-prostatectomy incontinence in 300 patients. [14] One group took part in a structured early postoperative PMFE-program while the other group was not formally instructed. Incontinence was assessed objectively using the 1h and the 24h pad-test. Continence was defined as 0-1 pad per day. After three months, continence was achieved in 74% (111 patients) and 30% (45 patients) for the treated group and the control group respectively. The differences between the groups declined between 6-12 months. Like the study of Parekh et al PFME seems to have limited benefit in the longterm follow-up.

Van Kampen et al, reported on the effect of postoperative PFME in 102 patients. [13] Urine loss was measured by 24h and 1h pad tests. Continence was defined as a loss of no more than 2g urine on both the 24h and 1h pad-test. They found a beneficial effect of pelvic floor re-education on urinary incontinence recovery after surgery. The duration and degree of incontinence had significantly decreased in the physiotherapy treatment group compared with the control group. The primary end point of the study was the incontinence rate at 3 months, which showed a significant benefit for the PFME group. Differences had decreased at 1-year follow-up.

Overgard et al, reported a significant beneficial effect of intensive PFME instructed by a physiotherapist throughout a one-year period, compared to patients training on their own after having received oral and written instructions. [16] Although they did not find a statistically significant difference in continence rate (defined as no use of pads)

between the two groups at three and six months after surgery, they found that one year after surgery continence was achieved in 92% and 72% of the physiotherapist-guided and the control group, respectively. They suggested that follow-up instructions by a physiotherapist increase long-term adherence to PFME and thereby improve continence rates over time more than information provided to patients for training on their own. The frequency of PFME was kept significantly higher in the PFME group than in the control group. Perhaps the results in the control group would have been better if the patients would have been verbally motivated as well.

Several prognostic factors of failure to regain continence have been reported in observational retrospective surveys, including age, prostate size, anastomotic stricture, preoperative urodynamic abnormalities and details of the surgical technique. [25-27] However, other investigators did not find a prognostic value of factors like age, preoperative urinary leakage, postoperative pelvic floor exercises, anastomotic strictures, BMI, severity of lower urinary tract symptoms, Gleason score, nerve sparing status or blood loss. [2,28-29] Majoros et al found that age represented a risk factor only for delayed continence, but not for a permanent incontinence. [30]

Based on a multivariate logistic regression analysis we show that the amount of urine loss 1 week after catheter removal is a significant prognostic factor for persisting incontinence six months after RRP.

Conclusion

Physiotherapist-guided PFME seems to have no beneficial effect on the recovery of continence within the first six months after RRP over an instruction folder-guided approach. A time-consuming and therefore expensive program of intensive guidance by a physiotherapist does not seem to be necessary. Because our sample size was not achieved our results should be regarded with caution since the fact that the study is underpowered may result in a high risk of finding no difference where in fact this might exist (Type II error). Nevertheless, these findings can be added to the knowledge base for availability in meta-analyses and can serve as a starting point for the design of new randomized studies.

PFME can have its role in selected patients, especially if they have difficulty to understand and implement the instructions described in the folder. A higher amount of urine loss 1 week after catheter removal seems to be a significant predictor of

persistence of incontinence six months after radical RRP. Future studies should be designed to show equivalence between PG-PFME and F-PFME or verbally instructed PFME.

Acknowledgement

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References

[1] Minervini R, Felipetto R, Morelli G et al. Urodynamic evaluation of urinary incontinence following radical prostatectomy: our experience. Acta Urol Belg 1996;64:5-8.
[2] Lepor H, Kaci L.The impact of open radical retropubic prostatectomy on continence and lower urinary tract symptoms: a prospective assessment using validated self-administered outcome instruments. J Urol 2004;171;1216-1219.
[3] Rudy DC, Woodside JR, Crawford ED. Urodynamic evaluation of incontinence in patients undergoing modified Campbell radical retropubic prostatectomy: a prospective study. J Urol 1984;132(4):708-12.
[4] Steiner MS, Morton A, and Walsh PC. Impact of anatomical radical prostatectomy on urinary incontinence. J Urol 1991;145:512-515.
[5] Catalona WJ, and Basler JW. Return of erections and urinary continence following nerve sparing radical retropubic prostatectomy. J Urol 1993;150:905-7
[6] O'Donnell PD and Finan BF. Continence following nerve-sparing radical prostatectomy. J Urol 1989;142:1227-8.
[7] Eastham JA, Kattan MW, Rogers E. Risk factors for urinary incontinence after radical prostatectomy. J Urol 1996;156:1707-13.
[8] Milam DF and Franke JJ. Prevention and treatment of incontinence after radical prostatectomy. Semin Urol Oncol 1995;13:224-37.
[9] Smither AR, Guralnick ML, Davis NB, See WA. Quantifying the natural history of post-radical prostatectomy incontinence using objective pad test data. BMC Urol 2007;5;7:2.
[10] Wille S, Sobottka A,Heidenreich A, et al. Pelvic floor exercises, electrical stimulation and biofeedback after radical prostatectomy: results of a prospective randomised trial. J Urol 2003;170:490-493.
[11] Parekh AR, Feng MI, Kirages D, et al. The role of pelvic floor exercises on post-prostatectomy incontinence. J Urol 2003;170:130-133.
[12] Franke JJ, Gilbert WB, Grier J et al. Early post-prostatectomy pelvic floor biofeedback. J Urol 2000;163:191-193.
[13] Van Kampen M, De Weerdt W, Van Poppel H, et al. Effect of pelvic-floor re-education on duration and degree of incontinence after radical prostatectomy: a randomised controlled trial. Lancet 2000;355:98-102.
[14] Filocamo MT, Li Marzi V, Del Popolo G, et al. Effectiveness of early pelvic floor rehabilitation treatment for post-prostatectomy incontinence. Eur Urol 2005;Nov;48(5):734-8.
[15] Burgio KL, Goode PS, Urban DA, et al. Preoperative biofeedback assisted behavioural training to decrease post-prostatectomy incontinence: a randomised, controlled trial. J Urol 2006 Jan;175(1):196-201.
[16] Overgard M, Angelsen A, Lydersen S, Morkved S. Does physiotherapist-guided pelvic floor muscle training reduce urinary incontinence after radical prostatectomy? Randomised controlled trial. Eur Urol 2008;54:438-448.
[17] Floratos DL, Sonke GS, Rapidou CA, et al. Biofeedback vs verbal feedback as learning tools for pelvic muscle exercises in the early management of urinary incontinence after radical prostatectomy. BJU Int 2002; May;89(7):714-9.
[18] Moore KN, Griffiths D, Hughton A. Urinary incontinence after radical prostatectomy: a randomised controlled trial comparing pelvic muscle exercises with or without electrical stimulation. BJU Int 1999;83(1):57-65.
[19] Hunter KF, Moore KN, Glazener CMA. Conservative management for postprostatectomy urinary incontinence (Review). Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD001843. DOI: 10.1002/14651858.CD001843.pub3.
[20] Abrams P, Blaivas JG, Stanton SL and Andersen JT. The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology. Scand

J Urol Nephol 1988,suppl.,114:5-19.
[21] Donnellan SM, Duncan HJ, MacGregor RJ, et al. Prospective assessment of incontinence after radical retropubic prostatectomy: objective and subjective analysis. Urology 1997;49:225-230.
[22] Moore KN, Valiquette L, Chetner MP, Byrniak S, Herbison GP. Return of continence after radical retropubic prostatectomy: a randomised trial of verbal and written instructions versus therapist-directed pelvic floor muscle therapy. Urology 2008;72(6):1280-6.
[23] Chao R, Maye ME. Incontinence after radical prostatectomy: detrusor or sphincter causes. J Urol 1995;154:16-18.
[24] Kao TC, Cruess DF, Garmer D, et al. Multicenter patient selfreporting Questionnaire on impotence, incontinence and stricture after radical prostatectomy. J Urol 2000;163:858-864.
[25] Kundu SD, Roehl KA, Eggener SE, Antenor JAV, Han M and Catalona WJ. Potency, continence and complications in 3477 consecutive radical retropubic prostatectomies. J Urol 2004;172:2227-2231.
[26] Karakiewicz PI, Tanguay S, Kattan MW, Lhilali MM and Aprikian AG. Erectile and urinary dysfunction after radical prostatectomy for prostate cancer in Quebec: a population-based study of 2415 men. Eur Urol 2004;46:188-194.
[27] Sacco E, Prayer-Galetti T, Pinto F, Fracalanza S, Betto G, Pagano F, Artibani W. Urinary incontinence after radical prostatectomy: incidence by definition, risk factors and temporal trend in a large series with a long-term follow-up. BJU Int 2006 jun;97(6):1234-41.
[28] Fontaine E, Izadifar V, Barthelemy Y, Desgrippes A, Beurton D. Urinary continence following radical prostatectomy assessed by a self-administrated questionnaire. Eur Urol. 2000 feb;37(2):223-7.
[29] Muhlholland TL, Huynh PN, Huang RR, Wong C, Diokno AC, Peters KM. Urinary incontinence after radical retropubic prostatectomy is not related to patient body mass index. Prostate Cancer Prostatic Dis. 2006;9(2):153-9.
[30] Majoros A, Bach D, Keszthelyi A, Hamvas A, Mayer P, Riesz P, Seidl E, Romics I. Analysis of risk factors for urinary incontince after radical prostatectomy. Urol Int 2007;78 (3):202-7.

Appendix 1

Summary of the content of the information folder that was handed out to all men on the day before surgery.

1. Explanation of the anatomy of the prostate, the sphincter and the pelvic floor.
2. Description of the anatomical and functional changes that occur after surgery.
3. Explanation of cause(s) of postradical prostatectomy incontinence.
4. Description of the postoperative period until 1 week after removal of the stenting transurethral catheter.
5. Explanation on how to keep a voiding-incontinence diary and measure urine loss in pads.
6. Life style advice for the early postoperative period.
7. Explanation on how to localize the pelvic floor muscles, how to exercise these

muscles and how to perform a contraction.
8. Description of the exercise program:
   One series of 10 contractions performed during a period of 1-3 minutes.
   Series should be repeated hourly for 15 times i.e. 150 contractions per 24 hrs.
   Explanation of the optimal timing of contractions.
9. Description of prospects for regaining continence.

Appendix 2

Physiotherapeutic treatment protocol for PG-PFME arm.

1. PERFECT model to test pelvic floor musculature by rectal examination.
   P : power, muscle strength
   E : endurance, time of the contraction
   R : repetition of the muscle contraction
   F : fast / fasttwitch
   E : every
   C : contraction
   T : is timed

2. Instruction and information about pelvic floor anatomy and pelvic floor muscle exercises

3. Practical treatment in the outpatient clinic: 9 sessions of 30 minutes in week 2, 3, 4, 6, 8, 12, 16, 20, 26. Treatment is based on propriocepsis combined with exercises to increase muscle strength.

4. Functional treatment in daily activities.

5. Instructions at home: at least 150 pelvic floor contractions per day.

Quantification of changes in detrusor function and pressure-flow parameters after radical prostatectomy:

relation to postoperative continence status and the impact of intensity of pelvic floor muscle exercises

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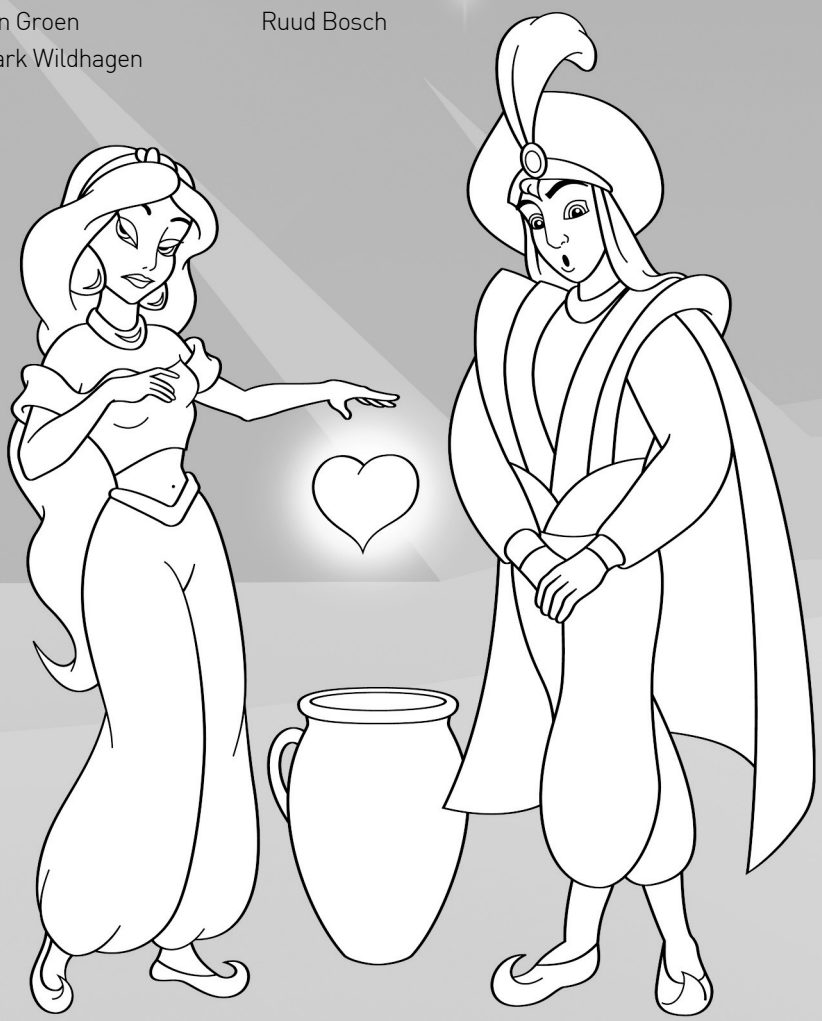

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Abstract

Objectives

We aim to quantify changes in detrusor function and pressure-flow parameters after radical retropubic prostatectomy (RRP) and to determine the impact of the level of intensity of pelvic floor muscle exercises (PFME) on these changes. We also tried to identify preoperative urodynamic factors, predictive of postoperative continence status.

Methods

Sixty-six patients were included in the study. An urodynamic examination was performed before surgery and 26 weeks after catheter removal. All patients were instructed in PFME. However the intensity of PFME varied between instructions based on an information folder only (F-PFME) and intensive guidance by a physiotherapist, in addition to the folder (PG-PFME).

Results

In 66 men pre as well as postoperative urodynamic studies were available for analysis. Overall, Q_{max} increased, $p_{detQmax}$ and the urethral resistance factor URA decreased significantly after surgery. At baseline, detrusor overactivity was found in 34% and 5.3% of the men who were still incontinent 6 months postoperatively and those who regained continence, respectively (p=0.015). Postoperatively, Q_{max} was significantly higher (p=0.04) and URA significantly lower (p=0.047) in the physiotherapist-guided group. No prognostic standard urodynamic factors for post RP incontinence (PRPI) were identified.

Conclusion

In univariate analysis, preoperative detrusor overactivity is associated with a higher risk of remaining incontinent after surgery. However, in multivariate analysis, urodynamic parameters predictive of PRPI could not be identified. Therefore, standard preoperative filling cystometry and pressure-flow studies seem to have no role as preoperative predictors of PRPI in patients with localized prostate cancer. More intensive PFME might have a lowering effect on bladder outflow resistance after RRP.

Introduction

Urinary incontinence is one of the most devastating complications of a radical prostatectomy for localized prostate cancer, and has a negative impact on quality of life. [1,2]

Most studies that have urodynamically analyzed lower urinary tract function before and after radical prostatectomy have reported sphincter incompetence as the predominant cause of incontinence. However, bladder dysfunction (de novo detrusor overactivity, decreased bladder compliance and impaired detrusor contractility) seems to play an additional role [3-6], but the prevalence and time frame for resolution of the bladder dysfunction is still not clear. In a review about voiding dysfunction after radical prostatectomy, Porena et al [7] described that detrusor overactivity was a "de novo" occurring dysfunction in 2-77% of patients. Decreased bladder compliance was present at baseline in 8-39% of patients and occurred de novo in about 50%. Impaired detrusor contractility was found in 29-61% of patients; this problem occurred de novo in 47% but disappeared after radical prostatectomy in about 50% of patients. These authors concluded that data on urodynamic parameters are scarce and often contradictory. Furthermore, the lack of studies with routinely performed preoperative urodynamic studies makes it difficult to assess the exact role of the operation in causing these dysfunctions.

Pelvic floor muscle exercises (PFME) have been suggested as an effective treatment for post radical prostatecomy incontinence (PRPI). [8-10] This implies that a measurable effect on lower urinary tract function can be anticipated. However, the effect of PFME on the urodynamic parameters has not yet been described. We analysed (1) the impact of radical retropubic prostatectomy (RRP) on detrusor function and bladder outflow resistance and its relation to post-radical prostatectomy continence status; (2) the effect on lower urinary tract function of intensive physiotherapist guided PFME (PG-PFME) as compared to PFME with an information/instruction folder (F-PFME); (3) the prognostic value of the bladder function on continence outcome after RRP in a prospective study in men who did recover and men who did not recover from PRPI.

Materials and methods

This study was part of the randomized controlled trial [RCT]:" The recovery of urinary continence after radical retropubic prostatectomy: a randomized trial comparing the effect of physiotherapist guided pelvic floor muscle exercises with guidance by an instruction folder only". [12] Analysis of the effect of RRP on detrusor function and bladder outflow resistance and its relation to post-radical prostatectomy continence status, and the effect of intensive pelvic floor muscle exercises (PFME) on detrusor function and bladder outflow resistance were secondary outcomes of the study mentioned above.

From the study mentioned above [12] 66 patients were available for the present study. All patients underwent an open RRP (bilateral nerve sparing proceure in 21, unilateral in 16 and a non-nerve sparing procedure in 28 men; data missing from one man) and were incontinent one week after removal of the stenting transurethral catheter. Incontinence was defined as urine loss of at least 1 gram during a 1-hour pad test performed according to the recommendations of the International Continence Society (ICS). [11] All patients were instructed in PFME. However, the intensity of PFME varied since one group of patients received instructions based on an information folder (F-PFME) only, and another group received intensive guidance by a physiotherapist (PG-PMFE), in addition to the instruction folder. [12] The instruction folder contained information about urogenital tract anatomy, consequences of the operation and exercises to strengthen the pelvic floor. Patients in the PG-PFME arm were invited for a maximum of 9 sessions of physiotherapist-guided PFME and started within 2 weeks after randomization. The duration of each session was 30 min. After the start of PFME, one patient randomized to the PG-PFME and two men from the F-PFME group, respectively, were subsequently excluded and therefore not available for the present study, because treatment of an anastomotic stricture interfered with the execution of the PFME protocol. From the original RCT [12], an additional number of one and seven men in the PG-PFME and the F-PGME group, respectively, were lost to follow-up and not available for 6 months urodynamic evaluation. The exercises were reviewed and approved by several professional physiotherapy organizations.

Finally, both the preoperative and postoperative urodynamic investigations were of

technically good quality in 66 men.

An urodynamic examination including free uroflowmetry, filling cystometry and pressure flow studies was performed before surgery and 26 weeks after catheter removal. Two 5F transurethral feeding tubes were used for bladder filling (rate 50 ml/min) and for measuring intravesical pressure during the cystometries and pressure flow studies, while an 8F tube was used for measuring rectal pressure. The flow rate was measured with a rotating disk flowmeter. In every man two filling and emptying cycles were studied (except uroflowmetry). The primary outcome parameters derived from the cystometric studies were: maximum cystometric capacity, bladder volume at first involuntary detrusor contraction, detrusor pressure at highest involuntary detrusor contraction and bladder compliance. Filling phase bladder dysfunction was defined as the occurrence of a low compliance (< 20 ml/cmH_2O) or detrusor overactivity at volumes below 400 ml. The primary outcome parameters derived from the pressure flow studies were: maximum flow rate Q_{max}, and the associated detrusor pressure $p_{detQmax}$, bladder contraction strength parameter w_{max} and w_{Qmax}, the urethral resistance factor URA and residual volume. The urodynamic measurements and analyses were done with AUDACT equipment and software (Andromeda medizinische Systeme GmbH, Taufkirchen, Germany).

No formal sample size calculation could be performed for this study, since this is an observational study of the urodynamic effects of RRP; this was a secondary aim of the aforementioned randomized study for which the sample size was calculated.

Statistical analysis was done for the total group of patients, and separately for the F-PFME group, the PG-PFME group, the group of patients who regained continence and those who were still incontinent. We used a severe definition of "urinary continence": loss of < 4 g urine on the 24-h pad tests AND of < 1 g on the 1-h pad test. The Mann-Whitney U-test, the Pearson Chi-Square-test and the Kruskall-Wallis test were used for the analysis. Results are given as median values and interquartile ranges (25^{th}-75^{th} percentile range). We used a multivariate backwards logistic regression model to determine the effect of several variables on the persistence of incontinence after RRP. Using a backward model fit, those variables with a p-value < 0.10 in univariate analysis were selected for the multivariate logistic regression analysis. A p-value at the 5% level was considered to reflect a statistically significant difference.

Results

Good quality pre- as well as post-operative urodynamic investigations were available in 66 men. Median age was 64 (range 60-67) years. Thirty-three men each had been assigned to the PG-PFME and the F-PFME group, respectively. According to our severe definition, 19 of the 66 men had regained continence six months after RRP.

Urodynamics during the filling phase before and after operation

Median values of urodynamic parameters before and after RRP are listed in Table 1. Bladder capacity decreased from 473 ml preoperatively to 435 ml six months after RRP (p=0.065). Overall, preoperative detrusor overactivity (DOA) was present in 26% (17/66) and de novo DOA in 12% of men. In men who were still incontinent and men who regained continence after the operation, preoperative DOA was noticed in 34% (16/47) and in 5% (1/19) of men, respectively (p=0.015) Table 1; de novo DOA occurred in 8.5% (4/47) and 21% (4/19), respectively, (p=0.157).

Table 1. Detrusor function parameters measured before (0) and after (26 weeks) RRP. Comparison between the PG-PFME versus F-PFME group and between men who regained continence versus men who remained incontinent.

	Complete group	Physiotherapy (PG-PFME) group	Folder (F-PFME) group	p-value	Continence regained	Persistently incontinent	p-value
DOA + (0)	17/66 (26%)	11/33 (33%)	6/33 (18%)	0.16	1/19 (5%)	16/47 (34%)	0.015
DOA + (26)	14/66 (21%)	5/33 (15%)	9/33 (27%)	0.22	5/19 (26%)	9/47 (19%)	0.51
Compliance < 20ml/cm H_2O (0)	8/65 (12%)	5/32 (16%)	3/33 (9%)	0.42	2/18 (11%)	6/47 (13%)	0.86
Compliance < 20ml/cm H_2O (26)	12/65 (18%)	5/32 (16%)	7/33 (21%)	0.56	3/18 (17%)	9/47 (19%)	0.82
W_{max} ≤ 10 W/m² (0)	48/64 (75%)	23/31 (74%)	25/33 (76%)	0.89	15/18 (83%)	33/46 (72%)	0.34
W_{max} ≤ 10 W/m² (26)	45/64 (70%)	21/31 (68%)	24/33 (73%)	0.66	12/18 (67%)	33/46 (72%)	0.50

DOA detrusor overactivity; W_{max} bladder contraction strength (bladder contractility)

Information on bladder compliance was available in 65 men. Preoperatively, bladder compliance was decreased in 12% of the men (8/65). Postoperative de novo decrease of the bladder compliance was present in 11% of men (7/65). The percentage of patients with a preoperatively decreased bladder compliance was not significantly different between the men who were still incontinent and the men who regained continence after the operation (12.8% [6/47] vs 11.1% [2/18]; p = 0.856), Table 1.

Urodynamics during the voiding phase before and after RRP

Table 2 shows the results of the urodynamic studies performed before and after RRP. Q_{max} increased from a pre-operative median value of 8.4 ml/s to 11.9 ml/s (p=0.002), $p_{detQmax}$ and URA decreased significantly after surgery from 50.5 to 36.8 cm H_2O (p=0.001) and from 29.0 to 16.5 cm H_2O (p=0.001), respectively. Overall bladder outlet obstruction (BOO) (defined as URA>29 cm H_2O) was present in 31 of 63 men (49%) and in 18 of 63 men (29%) preoperatively and postoperatively, respectively (p=0.018). Pre-operatively, W_{qmax} was significantly lower in the men who regained continence after the operation. Urodynamic parameters of the voiding phase were not significantly different after surgery. (Table 2)

Effect of intensity of PFME on urodynamic parameters

There were no significant urodynamic differences before surgery between the PG-PFME and the F-PFME group. Preoperative DOA was found in 18% (6/33) and 33% (11/33) of the men in the F-PFME and PG-PFME subgroup, respectively (p= 0.159; Table 2). The percentage of patients with a preoperatively decreased bladder compliance was not significantly different between the PG-PFME and the F-PFME group (15.6% [5/32] vs 9.1% [3/33]; p = 0.423).

Surprisingly, de novo DOA was present in 21% (7/33) in the F-PFME and in 3% (1/33) in the PG-PFME subgroup (p=0.024). Six months after operation Q_{max} was higher (p=0.044) and URA was lower (p=0.047) in the PG-PFME compared to the F-PFME group. However, the relative decrease in URA was not significantly different between the two groups (p=0.40).

Prognostic factors:

Variables considered for inclusion in the multivariate backward logistic regression model were: preoperative bladder capacity, DOA, bladder compliance, W_{max} and

urethral resistance (URA). In multivariate logistic regression analysis none of the factors were significant prognostic factors for the persistence of incontinence six months after radical retropubic prostatectomy (Table 3).

Table 2. Pressure flow study parameters before (0) and after (26 weeks) RRP in the complete group and in the physiotherapy, folder, continent and incontinent subgroups; median values (interquartile ranges).

	Complete group	Physiotherapy (PG-PFME) group	Folder (F-PFME) group	p-value	Continence regained	Persistently incontinent	p-value
Cap[§] 0 (ml)	473 (385-561)	475 (405-590)	463 (382-553)	0.73	505 (418-630)	450 (379-543)	0.08
Cap 26 (ml)	435 (350-547)	470 (338-570)	415 (358-530)	0.72	450 (363-560)	430 (355-530)	0.89
Q_{max}[*] 0 (ml/s)	8.4 (6.2-11.6)	8.5 (6.3-11.6)	8.4 (6.1-11.5)	0.94	10.1 (6.8-12.6)	8.2 (6.0-10.9)	0.38
Q_{max} 26 (ml/s)	11.9 (6.9-20.0)	13.9 (8.8-23.7)	10.9 (4.7-15.9)	0.04	11.9 (7.4-16.1)	12.3 (5.5-20.3)	0.62
$p_{detQmax}$[¶] 0 (cm H_2O)	50.5 (40.5-62)	45.0 (37-57)	56.8 (41-63.5)	0.24	42.8 (32-62)	56.5 (41.5-64.5)	0.06
$p_{detQmax}$ 26 (cm H_2O)	36.8 (25-47.8)	34.5 (23-42.5)	43.0 (26.5-53)	0.08	34.5(28.3-52)	36.8 (25-47)	0.67
Ura[†] 0 (cm H_2O)	29.0 (19.8-37.5)	25.8 (17.8-36)	30.5 (21-39)	0.48	22.5 (16-33.5)	31.0 (20.8-39.3)	0.08
Ura 26 (cm H_2O)	16.5(10.5-28.5)	15.3 (9.8-22)	21.0 (13-30)	0.047	17.0 (12-29.5)	16.5 (9.8-29)	0.36
W_{max}[#] 0 (W/m²)	9.0 (7.8-10.3)	8.1 (7.1-10.8)	9.4 (8.3-10.2)	0.11	8.0 (6.6-9.6)	9.3 (8.0-10.8)	0.05
W_{max} 06 (W/m²)	8.8 (7.1-10.5)	8.8 (7-10.8)	8.8(7.6-10.3)	0.94	8.1 (7.1-10.5)	8.9 (7.2-10.4)	0.67
W_{qmax}[‡] 0	7.9 (6.2-9.2)	7.0 (6.1-8.7)	8.4 (6.9-9.3)	0.12	6.1 (5.5-8.6)	8.3 (7.1-9.3)	0.01
W_{qmax} 26	7.7 (5.9-9.1)	7.0 (5.7-8.9)	7.8 (6.6-9.1)	0.51	7.5 (5.8-8.1)	7.8 (6.2-9.2)	0.51
Residual[£] 0 (ml)	15.0 (0-86)	15.0 (0-71)	15.0 (0-97.5)	0.98	25.0 (0-63.5)	15.0 (0-110)	0.75
Residual 26 (ml)	0.0 (0-30)	0.0 (0-30)	0.0 (0-40)	0.78	0.0 (0-12.5)	0.0 (0-40)	0.52

[†] Urethral resistance factor ; [*] Maximum flow rate; [¶] Detrusor pressure at maximum flow; [§] Bladder capacity; [#] Bladder contraction strength parameter; [£] Residual volume; RRP radical retropubic prostatectomy. [‡] Bladder contraction strength parameter at maximum flow.

Table 3. Multivariate logistic regression analysis of prognostic factors for persisting incontinence after radical retropubic prostatectomy.

	Odds Ratio (95%CI)	p-value
W_{max}*	1.234 (0.885-1.723)	0.215
Capacity	0.998 (0.993-1.004)	0.563
URA†	1.019 (0.956-1.086)	0.561
Detrusor overactivity	0.048 (0.002-1.325)	0.073
Bladder compliance	22.987 (0.751-703.910)	0.073

† Urethral resistance factor; * Bladder contraction strength parameter

Discussion

Radical prostatectomy is a well-established therapeutic option for men with organ confined prostate cancer. However, 10-25% of the patients will not achieve urinary continence six months after surgery. [13,14]

During the operation continence nerves contained in the neurovascular bundles can be damaged and seminal vesical dissection can injure the pelvic plexus. [15]

Surgical damage (denervation and/or devascularization injuries) to the detrusor muscle, trigone, bladder neck, posterior urethra and external sphincter probably also has a negative impact on lower urinary tract function in as much as detrusor overactivity, reduced bladder capacity and reduced bladder compliance are often seen after RRP. [3-6]

Zermann et al [16] evaluated pelvic floor function before and after RRP using clinical neurourological investigations (by inspection and palpation regarding reflex integrity), urodynamics and electromyography. Sacral reflexes, voluntary pelvic floor contractions and relaxation and needle EMG did not show significant changes after surgery. Fine motor changes of pelvic floor muscle function was the main finding in patients without pre-existing bladder dysfunction. The authors contended that neurophysiological events, like a barrage of nociceptive information, caused by surgical dissection and an inflammatory reaction due to the healing process, contribute too altered processing within the central nervous system.

The impact of the surgical dissection on the filling phase or the voiding phase of the micturition reflex is still not clear, due to a paucity of data on detrusor function after RRP. [7]

In addition to the surgical effects on the bladder function, pre-existing bladder dysfunction in the aging male probably also has a negative impact on continence after RRP. Decreased bladder perfusion due to longstanding elevation of voiding detrusor pressure as a result of bladder outlet obstruction, can initiate a reduction in bladder compliance. [17] Impaired detrusor contractility can be related to transient bladder denervation.

We report on the analysis of the urodynamic investigation before and after RRP. We found a significant rise of Q_{max} due to a significant decrease of bladder outflow resistance; this is most likely attributable to the removal of the prostate. We also found that, preoperatively, detrusor overactivity was less often present in men who regained continence after RRP. This implies that these men probably had less bladder outlet obstruction and bladder damage before surgery and therefore a better regenerative capacity after surgery. The preoperative URA was 22.5 and 31.0 cm H_2O for men who regained continence and men who remained incontinent, respectively. But, this difference was not statistically significant (p=0.08). Furthermore, in the PG-PFME group Q_{max} was significantly higher and URA significantly lower than in the F-PFME group, postoperatively. The significance of these findings is unclear but one wonder whether the higher Q_{max} and the lower URA might be due better pelvic floor relaxation.

De novo DOA at six months postoperatively, was significantly more often present in the F-PFME group (p=0.024). This difference may be due either to an unidentified [perioperative] factor that led to less de novo DOA in the PG-PFME group even before PFME were started, which seems unlikely, or to a positive effect of more intensive PFME on bladder function i.e. decreasing the chance that de novo DOA persists at 6 months follow-up. Previously, we showed that the intensity of PFME was not associated with a greater chance of regaining continence [12].

In literature, there are a few urodynamic studies before and after RRP, mostly with a small number of patients. We compare our data with other prospective studies with a minimum of 40 patients. (Table 4) Kleinhans et al [3] performed urodynamic studies before and after surgery in 44 men. Before surgery DOA was already present in 44% (16/44) of the patients. In 14 of these 16 patients DOA disappeared after surgery. Mean

flow rate increased significantly from 18 to 29 ml/sec ((p=0.03) and $p_{detQmax}$ decreased significantly from 88 to 58 cm H_2O (p=0.0009) after operation.

Giannantoni et al [5] reported about bladder and urethral sphincter function after RRP in 54 men. Before and 8 months after RRP pressure flow studies and valsalva leak point pressure measurements were performed. Thirty-two men were studied again 3 years later. At baseline on VLPP examination no patients showed ISD. Eight months after RRP de novo reduced bladder compliance was present in 32.3% of men and persisted in 28.1 % 3 years after RRP. De novo hypocontractility was present in 51% of men and persisted in 25% 3 years after RRP. ISD was observed in 74% (40/54) and in 59.3% (19/32) of men, 8 months and 3 years after RRP, respectively. Detrusor hypocontractility, decreased bladder compliance and intrinsic sphincter deficiency became established conditions over time in 30% of patients. Nevertheless, these men did not develop voiding symptoms.

Song et al [6] analysed bladder function and voiding pattern before RRP and 3, 6 en 36 months after RRP in 72 men. They assessed the maximum cystometric capacity, maximum detrusor pressure, DOA, and maximum urethral closure pressure. They found a reduction in bladder capacity, detrusor and sphincter activity up to three years after surgery. The incidence of detrusor overactivity increased from 37.5% to 51.4%. The maximum flow rate continued to improve up to 3 years. Although voiding symptoms improved in most men, the significant deterioration in storage symptoms became a source of overall urinary bother in the long term.

Our data are comparable with the studies mentioned above. In these prospective urodynamic studies, baseline detrusor overactivity and impairment of bladder compliance ranges from 25-62% and from 2-37%, respectively. De novo detrusor overactivity and de novo impairment of bladder compliance ranges from 2 to 16% and from 10 to 20% of men, respectively. After RRP the maximum flow rate improves (3 of 3 studies), $p_{detQmax}$ decreases (4 of 4 studies) and bladder capacity decreases (2 of 3 studies) (Table 4).

Ribeiro et al [8] analyzed the effect of biofeedback-pelvic floor muscle training in men with PRPI. They found that early biofeedback-pelvic floor muscle training not only hastens the recovery of urinary continence but also allows for significant improvements in the severity of incontinence, voiding symptoms (analysed by questionnaire) and pelvic floor muscle strength 12 months postoperatively. We showed that intensive PFME might have a positive impact on Q_{max} and URA 6 months after surgery.

Table 4. Comparison of urodynamic parameter values before and after radical prostatectomy, in 4 prospective studies.

Study	Pt (N)	Follow-up (months)	Capacity [ml]	DOA$^{\infty}$ (%)	Decreased compliance [ml/cm H_2O] (%)	$Q_{max}$$^{\#}$ [ml]	$P_{detQmax}$$^{£}$ [cm H_2O]
Song[6]	72	Baseline 3 36	393 - 322	27 (38) (45.8) (51.4)	2 (3) - -	15.3 -	54.1* - 45.3
Kleinhans[3]	66 44	Baseline 3-10	375 428	21 (32) 1 (2) §	- -	18 29	88 58*
Giannantoni[5]	54 54 32	Baseline 8 36	- - -	33 (61.2) 8 (14.8) § 5 (16) §	20 (37.1) 11 (20.4) § 5 (16) §	9.7 13.2 14.6	71.4* 30.8 35.5
Present	66	Baseline 6	473 435	17 (25.7) 8 (12) §	8/55 (14.5) 7/55 (13) §	8.4 11.9	50.5 36.8

§ De novo; # Maximum flow rate; $^{\infty}$ Detrusor overactivity; £ Detrusor pressure at maximum flow;
* detrusor pressure parameter

Risk factors for post-radical prostatectomy incontinence as defined by the 4th International Consultation on Incontinence include: age, radiation, functional sphincteric length, membranous urethral length, surgical technique, preoperative incontinence and certain medical comorbidities. [18] Little is known about possible urodynamic prognostic indicators. We did not find any significant prognostic factor among standard urodynamic parameters.

Conclusion

Standard preoperative filling cystometry and pressure-flow studies seem to have no role as preoperative predictors of PRPI in patients with localized prostate cancer. More intensive PFME might have a lowering effect on bladder outflow resistance after RRP, and may decrease the chance of de novo DOA 6 months after the RRP.

References

[1] Sacco E, Prayer-Galetti T, Pinto F, Fracalanza S, Betto G, Pagano F, Artibani W. Urinary incontinence after radical prostatectomy: incidence by definition, risk factors and temporal trend in a large series with a long-term follow-up. BJUI 2006;97:1234-41

[2] Liss AN, Osann K, Canvasser N, Chu W, Chang A, Gan J, Li R, Santos R, Skarecky D, Finley DS, Ahlering TE. Continence definition after radical prostatectomy using urinary quality of life: evaluation of patient reported validated questionnaires. J Urol 2010 183(4): 1464-8.

[3] Kleinhans B, Gerharz E, Melekos M, et al: Changes of urodynamic findings after radical retropubic prostatectomy. Eur Urol 1999;35:217-222

[4] Giannantoni A, Mearini E, Di Stasi SM, Mearini L, Bini V, Pizzirusso G and Porena M. Assesment of bladder and urethal sphincter function before and after radical retropubic prostatectomy. J Urol 2004;171,1563-1566.

[5] Giannantoni A, Mearini E, Zucchi A, Costantini E, Mearini L, Bini V and Porena M. Bladder and urethral sphincter function after radical retropubic prostatectomy: a prospective long-term study. Eur Urol 2008;54: 657-664

[6] Song C, Lee J, Hong JH, Choo MS, Kim CS and Ahn H. Urodynamic interpretation of changing bladder function and voiding pattern after radical prostatectomy: a long-term follow-up. BJU Int 2010;106(5):681-6.

[7] Porena M, Mearini E, Mearini L, Vianello A, Giannantoni A. Voiding dysfunction after radical retropubic prostatectomy : more than external urethral sphincter deficiency. Eur Urol. 2007;52(1):38-45.

[8] Ribeiro LHS, Prota C, Gomes CM, de Bessa J, Boldarine MP, Dall'Oglio MF, Bruschini H and Srougi M. Long-term effect of early postoperative pelvic floor biofeedback on continence in men undergoing radical prostatectomy: a prospective, randomized, controlled trial. J Urol 2010;184:1034-1039.

[9] Centemero A, Rigatti L, Giraudo D, Lazzeri M, Lughezzani G, Zugna D, MOntorsi F, Rigatti P, Guazzoni G. Preoperative pelvic floor muscle exercises for early continence after radical prostatectomy: a randomised controlled study. Eur Urol 2010;57:1039-43.

[10] Van Kampen M, De Weerdt W, Van Poppel H, et al. Effect of pelvic-floor re-education on duration and degree of incontinence after radical prostatectomy: a randomised controlled trial. Lancet 2000;355:98-102.

[11] Abrams P, Blaivas JG, Stanton SL and Andersen JT. The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology. Scand J Urol Nephol 1988;114: 5-19

[12] Dubbelman Y, Groen J, Wildhagen M, Rikken B and Bosch R. The recovery of urinary continence after radical retropubic prostatectomy : a randomized trial comparing the effect of physiotherapist-guided pelvic floor muscle exercises with guidance by an instruction folder only. BJU Int 2010;106(4):515-22

[13] Rudy DC, Woodside JR, Crawford ED. Urodynamic evaluation of incontinence in patients undergoing modified Campbell radical retropubic prostatectomy: a prospective study. J Urol 1984;132:708–12

[14] Lepor H, Kaci L.The impact of open radical retropubic prostatectomy on continence and lower urinary tract symptoms: a prospective assessment using validated self-administered outcome instruments. J Urol 2004;171;1216-1219.

[15] Hollabaugh Jr RS, Dmokowski RR, Kneib TG, Steiner MS. Preservation of putative continence nerves during radical retropubic prostatectomy leads to more rapid return of urinary continence. Urology 1998; 51:960-7

[16] Zermann Dh, Ishigooka M, Wunderlich H, Reichelt O, Schubert J. A study of pelvic floor function pre and postradical prostatectomy using clinical neurourological investigations, urodynamics and electromyography. Eur Urol 2000;37(1):72-8.

[17] Kershen RT, Azadoi KM, Siroky MB. Blood flow pressure and compliance in the male human bladder. J Urol 2002;168:121-5

[18] Herschorn S, Bruschini H, Comiter C, Grise P, Hanus T, Kirschner-Hermanns R. Surgical treatment of urinary incontinence in men. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. "Incontinence -4th International Consultation on Incontinence". 4th edition; Pp. 1121-1190. Paris, France: Health Publications Ltd; 2009

Urodynamic quantification of decrease in sphincter function after radical prostatectomy:

relation to postoperative continence status and the effect of intensive pelvic floor muscle exercises

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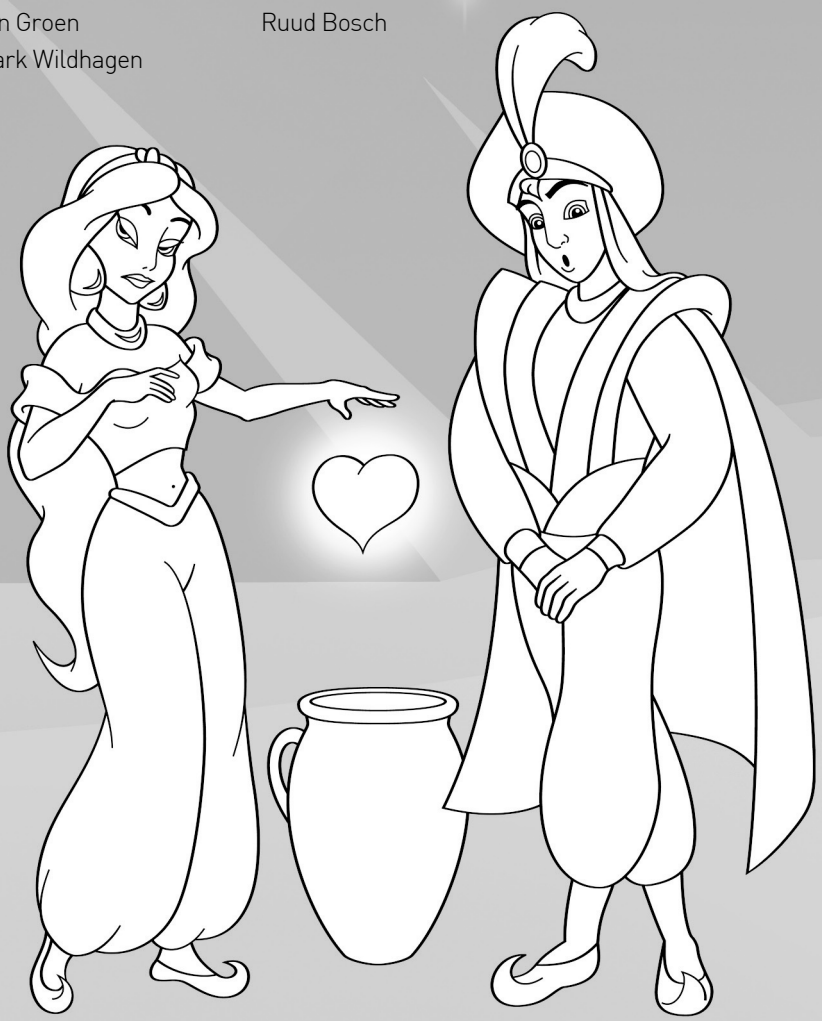

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Abstract

Aims

We analysed the impact of radical retropubic prostatectomy (RRP) on the urethral sphincter function as assessed by urethral pressure profilometry (UPP) and its relation to post-radical prostatectomy continence status. Furthermore we analysed the effect of intensive pelvic floor muscle exercises (PFME) on the urethral sphincter function.

Methods

Sixty-six patients were included in the study. UPP was performed before RRP and 26 weeks after catheter removal. All patients were instructed in PFME, however the intensity of PFME varied between instructions based on an information folder only (F-PFME) and intensive guidance by a physiotherapist, in addition to the folder (PG-PFME).

Results

In 66 patients pre as well as postoperative UPP was evaluable. After surgery, the functional profile length (FPL) and the maximum urethral closure pressure (MUCP) showed a median decrease of 64% and 41%, respectively. For men who had regained continence after six months the median MUCP was significantly higher both before and after operation as compared to men who were still incontinent. In multivariate analysis non-nerve sparing approach was a prognostic factors for a higher relative decrease of the MUCP after RRP. Comparing the PG-PFME group with the F-PFME group there were no significant differences in changes in UPP parameters.

Conclusions

A poor preoperative MUCP seems to be an important prognostic factor for persistent incontinence after RRP. Non-nerve sparing approach seems to be an important prognostic factor for impairment of the urethral sphincter function as measured by UPP. More intensive physiotherapy seems to have no additional effect on the postoperative urethral sphincter function as measured by UPP.

Introduction

Potential explanations for urinary incontinence after radical retropubic prostatectomy (RRP) are detrusor dysfunction (impaired contractility, overactivity or decreased compliance), sphincter incompetence and treated bladder outlet obstruction. [1,2]
Only a few studies performed standard urodynamic investigation both before and after RRP and little is known about possible urodynamic prognostic indicators for post-radical prostatectomy incontinence (PRPI). [1,3] In a recent analysis, we could not identify standard filling and voiding cystometry parameters predictive of PRPI. [4]
Several studies have shown that sphincter incompetence, due to the disruption of the sphincteric innervation, hypoperfusion or direct damage to the sphincteric muscles, rather than bladder overactivity is the predominant factor causing PRPI. [5,6] Both the pre- and postoperative sphincter quality seems to be important in regaining continence after RRP. [7] This suggests that a good preoperative sphincter muscle mass will protect against PRPI for the usual range of sphincteric length that will inevitably be sacrificed at RRP. [8]
Because we could not identify any standard urodynamic parameter predicting PRPI in the study mentioned above, we analysed urethral sphincter function. We studied the impact of radical retropubic prostatectomy (RRP) on the urethral sphincter function as assessed by urethral pressure profilometry (UPP) and its relation to PRPI status. We also studied whether age, nerve sparing or non-nerve sparing technique or bladder neck sparing approach were prognostic factors for the difference in changes in the maximum urethral closure pressure (MUCP) and functional profile length (FPL) between men who did recover and men who did not recover from PRPI 6 months after RRP.
Pelvic floor muscle exercises (PFME) have been suggested as an effective treatment for PRPI. [9,10] This indicates that a measurable effect on sphincter function/ urethral closure function might be anticipated. Therefore, the intensity of PFME i.e. physiotherapist-guided PFME (PG-PFME) versus PFME based on an information/ instruction folder (F-PFME) was also considered as a potential prognostic factor in the univariate analysis. A possible effect of PFME on the UPP has not been studied before.

Materials and Methods

We present an analysis of UPP measurements in 66 men, that were performed as part of our prospective randomized controlled trial: "The recovery of urinary continence after radical retropubic prostatectomy, comparing the effect of physiotherapist guided pelvic floor muscle exercises with guidance by an instruction folder only". The randomization process is described in that report. [11] The effect of RRP on the urethral sphincter function and its relation to PRPI, and the effect of the intensity of PFME on the urethral sphincter function as measured by UPP, were secondary outcomes of the randomized study. [11]

Sixty–six consecutive patients were available for the present study. An open RRP was performed because of localized prostate cancer. The operations were performed by urologists who had performed at least 50 RRP's before the start of this study. A nerve-sparing RRP as described by Walsh et al [12] was performed depending on the preoperative and intra-operative assessment of the extent of the disease.

All included patients were incontinent one week after removal of the transurethral catheter. Incontinence was defined as urine loss of at least 1 gram during the 1-hour pad test according to the recommendations of the International Continence Society. [13] Before the operation, all men were fully continent and had full urinary control. Preoperatively, all patients were instructed in PFME; however the intensity of PFME varied since one group of patients received instructions based on an information folder only (F-PFME) and the other group of patients received intensive guidance by a physiotherapist, in addition to the instruction folder (PG-PFME). [11] The instruction folder contained information about urogenital tract anatomy, consequences of the operation and exercises to strengthen the pelvic floor. Patients in the PG-PFME arm were invited for a maximum of 9 sessions after surgery. The duration of each session was 30 min. The exercises were reviewed and approved by several professional physiotherapy organizations.

Static UPP was performed before surgery and 26 weeks after catheter removal. The postoperative UPP measurement was performed at 26 weeks because most men who will regain continence will have regained continence at 6 months [10] and to capture the maximum effect of PFME; it seemed appropriate to study this relatively soon after completion of the PG-PFME sessions.

The Brown-Wickham method as modified by Griffiths was used for measuring the UPP, since it provides an accurate assessment of urethral pressures, not confounded by orientation and catheter-thickness artifacts. [14,15] An open-ended 5F catheter, perfused at a rate of 3 ml/minute, was withdrawn from the bladder and the urethra at a speed of 2 mm/second. The bladder volume was 100 ml. Rectal pressure was monitored with an 8F tube. Two subsequent UPP measurements were performed. Parameters derived from the UPP 's were the FPL and the MUCP. The mean value of both measurements of each of these parameters was used for statistical analysis. All UPP's before and after RRP were performed by one and the same urodynamicist (JG). The urodynamic measurements and analyses were done with AUDACT equipment and software (Andromeda Medizinische Systeme GmbH, Taufkirchen, Germany).

Additionally, the UPP 's were retrospectively analysed using self-written programs in Matlab® (version 5.1; The Math Works, Inc., Natick, MA) to visualize the effect of the RRP. An average UPP was constructed from the pre- and post-operatively measured UPP's using one measurement per patient. The measurement with the best appearance (least artefacts) was chosen without considering its amplitude or length (Figure 1). The construction included the following steps: (i) selection of the most relevant part of each UPP, that is, the part from the bladder neck to the point (in x direction) at two times the distance bladder neck – location of maximum of UPP; thus, each selected part started at the bladder neck and at least contained the prostatic part of the UPP (naturally only in the pre-operative measurement) and its sphinteric part, (ii) identification of the UPP with the largest distance bladder neck – location of maximum of UPP, (iii) scaling (in x direction) of all other selected parts in such a way that their maxima coincided with the maximum of the UPP identified in the previous step, that is , the distance bladder neck – location of maximum of UPP was made equally long for all selected UPP parts, (iv) calculation of the average pressure (y) value of the UPP's at each distance (x) value, (v) rescaling (in x direction) of the resulting average UPP in such a way that the location of its maximum became equal to the mean value of the locations of the maxima of the individual UPP's, that is, the length of the average UPP was reduced to the correct value.

In brief, the average urethral pressure of the UPP's was calculated as a function of the distance from the bladder neck after re-scaling each UPP (in x direction) in such a way that the position of its maximum coincided with the average of the position of all maxima.

Continence at 26 weeks follow-up was assessed by 1-hour and 24-hour pad tests. We defined "urinary continence", as a loss of < 4g urine on the 24-h pad tests AND of < 1g on the 1-h pad test. Subjective measurements of incontinence were not used.
Statistical analysis was done for the total group of patients, and separately, comparing the F-PFME group versus the PG-PFME group, as well as the group of patients who regained continence and those who remained incontinent.
The Mann-Whitney U-test, the Pearson Chi-Square-test and the Kruskall-Wallis test were used for the analysis, where appropriate. Results are given as median values and interquartile ranges (25^{th}-75^{th} percentile range). Prognostic indicators were analysed by multivariate logistic regression analysis. Using a backward model fit, those variables with a p-value < 0.10 in univariate analysis were selected for the multivariate logistic regression analysis. A p-value at the 5% level was considered to reflect a statistical significance.

Results

Good quality pre- as well as post-operative UPP's were available in 66 men.
Median age was 64 (range 60-67) years. Thirty-three and 33 men had been assigned to the PG-PFME and the F-PFME group, respectively. A bilateral, an unilateral and a non-nerve sparing RRP was performed in 21, 16 and 28 patients, respectively (1 unknown). The bladder neck was spared in 21 of 66 patients. According to our strict definition, 19 of the 66 men had regained continence six months after RRP.

Changes of the urethral pressure profile after operation

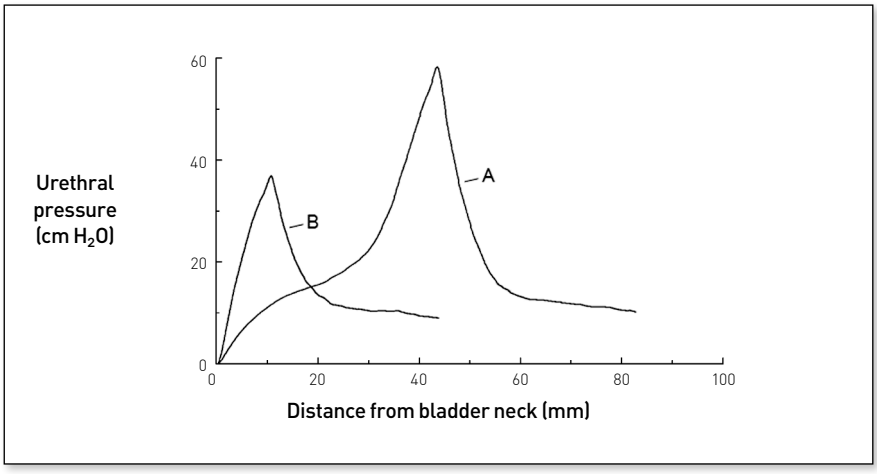
Overall, there was a median relative decrease in FPL and MUCP of 64% and 41%, respectively. Parameter values of the entire group and the respective subgroups are given in Table 1. Compared to those who still were incontinent after 6 months, the MUCP of the men who had regained continence was significantly higher both before and after operation. The median preoperative value of MUCP for the entire group was 53.1 cm H_2O. Of the men who regained continence, 13/19 men (68%) had a preoperative MUCP $\geq$ 53,1 cm H_2O; of those who did not regain continence, 28/47 men (60%) had a MUCP < 53.1 cm H_2O.
We used the UPP's before and after surgery to create an averaged curve of the urethral pressure profile. Figure 1 represents the averages of preoperative UPP (A) and post-operative UPP (B) of 78 and 67 men, respectively.

Table 1. Urethral pressure profile parameters before [0] and after [26 weeks] radical retropubic prostatectomy in the complete group (N=66) and segregated into the continent and incontinent subgroups. Values are medians with interquartile ranges.

	Complete group	Continent subgroup (N=19)	Incontinent subgroup (N=47)	p-value*
MUCP‡ [0] (cm H_2O)	53.1 [44.8-65.3]	66.2 [57.9-76.0]	49.7 [42.9-58.7]	0.001
MUCP [26] (cm H_2O)	30.6 [25.5-43.0]	41.3 [35.9-50.7]	29.2 [23.1-40.2]	0.01
Relative decrease in MUCP (%)	41% [26%-52%]	39% [19%-51%]	41% [27%-54%]	0.50
FPL# [0] (cm)	5.8 [4.8-6.5]	5.8 [4.8-6.3]	5.8 [5.0-6.3]	0.93
FPL [26] (cm)	2.1 [1.5-2.5]	2.1 [1.9-2.6]	2.0 [1.5-2.4]	0.1
Relative decrease in FPL (%)	64% [54%-73%]	62% [52%-66%]	67% [57%-74%]	0.12

* Mann – Whitney U test for the difference between the continent versus the incontinent subgroup.
# Functional profile length (cm); ‡ Maximum urethral closure pressure (cm H_2O)

Figure 1.
Curves representing the average of 78 pre-operative (A) and 67 post-operative urethral pressure profiles (B) in men treated with radical retropubic prostatectomy.



Effect of intensity of PFME on urethral pressure profile parameters

Comparing the PG-PFME group with the F-PFME group there were no significant differences in the changes in UPP parameters. However, there was a [counterintuitive] trend towards a higher relative decrease of the MUCP in the PG-PFME group versus the F-PFME group (45% versus 36%, respectively, p=0.05).

Univariate and multivariate analysis

We analysed the prognostic value of the variables age, intensity of PFME, type of nerve sparing and bladder neck preservation, for a relative decrease of the MUCP that was greater than the median relative decrease of 40.5% (found for the total group). In univariate analysis, nerve sparing approach and bladder neck sparing approach showed a trend towards a positive effect on the relative decrease of the MUCP (p=0.085 and p=0.066 respectively) (Table 2).

Table 2. Univariate analysis of prognostic factors for a greater than 40.5% relative decrease of the MUCP after RRP; 40.5% is the median decrease of MUCP for the complete group of men (N=66) evaluated pre- as well as post-operatively.

Prognostic factor	Percentage with relative decrease of MUCP > 40.5%	p-value
Age ≤ 60 yrs	44%	0.564
> 60 yrs	52%	
Intensive physiotherapy		
Yes	43%	0.316
No	56%	
Surgical approach*		
BNS	32%	0.085
UNS	47%	
NNS	67%	
Bladder neck sparing approach		
Yes	32%	0.066
No	57%	

NNS: non-nerve sparing; BNS: bilateral nerve sparing; UNS: unilateral nerve sparing
RRP: radical retropubic prostatectomy
* missing data in 1 case

Type of nerve sparing and bladder neck sparing approach were entered in a multivariate logistic regression analysis. The impact of these variables was assessed by calculating an adjusted odds ratio and 95% confidence intervals (CI). Non-nerve sparing approach (Odds ratio 0.149;p=0.007) and bladder neck sparing approach (Odds ratio 4.586;p=0.021) were prognostic factors for a higher relative decrease of the MUCP after RRP (Table 3).

Table 3. Multivariate logistic regression analysis of prognostic factors for a greater than 40.5% relative decrease of the MUCP after RRP; 40.5% is the median decrease of MUCP for the complete group of men evaluated pre- as well as post-operatively.

Prognostic factor	Odds Ratio (95%CI)	p-value
Surgical approach		
BNS vs NNS	0.149 (0.037-0.595)	0.007
UNS vs NNS	0.383 (0.097-1.517)	0.172
Bladder neck sparing approach		
Yes vs No	4.586 (1.263-16.656)	0.021

NNS: non-nerve sparing; BNS: bilateral nerve sparing; UNS: unilateral nerve sparing
RRP: radical retropubic prostatectomy
CI: 95% confidence intervals

Discussion

The major cause of PRPI is impaired function of the external urethral sphincter, although detrusor overactivity and/or decreased compliance may be additional factors. [5,16] We found a median loss of 64% [IQR:54-73] of the FPL and 41% [IQR:26-52] of the MUCP after RRP and visualized the effect of the operation on the UPP in Figure 1. The characteristic clear transition between the prostatic and the sphincteric part of the UPP that is usually observed has disappeared due to the averaging process, making it impossible to exactly determine the amplitude and length of the prostatic part. In spite of this, the average effect of RRP on the MUCP and the FPL is clear (Figure 1). A limited number of investigators have analysed sphincteric function before and after RRP using UPP (Table 4). [2, 7, 16, 17] The variability of MUCP baseline values

Table 4. Overview of clinical studies reporting urethral pressure profile (UPP) parameter values (means) before and after radical retropubic prostatectomy.

Author	Age (range)	Pts with baseline and follow-up UPP [N]	Timing of follow-up UPP	Catheter type/ method of urethral pressure profilometry	MUCP at baseline [cm H_2O]	MUCP at follow-up [cm H_2O]	FPL at baseline [mm]	FPL at follow-up [mm]	Relative decrease MUCP [%]	Relative decrease FPL [%]
John [2]	-	34	6 mo	6F double lumen catheter / withdrawal speed and perfusion rate not specified; bladder volume 200 ml	49	38.6	50	25	21	50
Rudy [16]	64.2	14	6 mo	5F triple lumen catheter (complete 11F), Water perfused; withdrawal speed not specified, 4 ml/min perfusion rate; 100 ml bladder volume	95	94	43	16	1	63
Majoros [7]	61.9 +/- 6.24	63	2 mo	Microtip transducer catheter, size not specified; 1 mm/s withdrawal speed; at 150 ml bladder volume	64	52	-	-	19	-
Hammerer [17]	63.5 (44-73)	82	6-8wks	Water perfused catheter, size not specified; 1 mm/s withdrawal speed; 2 ml/min perfusion rate; bladder volume not specified	89.6**	65.2**	61	26	24	57
Present*	64 (60-67)	66	6 mo	5F water perfused catheter; 2mm/s withdrawal speed; 3 ml/min perfusion rate; at 100 ml bladder volume	53.1	30.6	58	21	41	64

* UPP values are medians; ** MUP (maximal urethral pressure)

among the different studies shown in Table 4 can probably be explained by the variable methodology used when performing UPP. We used the Brown-Wickham method as modified by Griffiths and used an open-ended 5F catheter. For measuring the urethral pressure we think this is the best available method, because it is the least subject to orientational and thick-catheter artifacts and therefore (presumably, though not checked experimentally) the most reproducible method of measuring urethral pressure. [15] Other methods, including the 'classical'B-W method using a sidehole or –holes are more subject to orientational and thick-catheter artifacts and so may not give identical results.

We found that the pre- and post-prostatectomy MUCP was significantly lower in persistently incontinent men compared to the men who regained continence. However, the relative decrease in MUCP was almost identical in both groups. So, a low preoperative MUCP seems to predispose to persistent incontinence.

A decrease of the MUCP and/or FPL after surgery was a common finding in the reports mentioned in Table 4. John et al [2] and Majoros et al [7] demonstrated a significantly lower postoperative MUCP in incontinent men compared to men who regained continence. Majoros et al [7] performed an urodynamic study 3-7 days before and 2 months after RRP in 63 patients. Men who were immediately continent following catheter removal had significantly higher preoperative and postoperative MUCP than those who became continent later on. They concluded that immediate continence after the removal of the catheter is mainly caused by a good "passive" sphincteric function (high urethral closure pressure at rest), while the continence, which was reached later on was caused by a good "active" sphincteric function (high voluntary sphincteric closure pressure). However, the measurement of the UPP was done 2 months after RRP. This period is probably too short for definitive conclusions. Since we could not demonstrate a positive effect of intensive PFME on the UPP, and previously were unable to show a positive effect on continence by more intensive PFME [11], their conclusion that "continence, which was reached later on was caused by good " active " sphincter function, is not supported by our findings.

Biofeedback assisted behavioural training procedures might improve PRPI. However, the impact of these training procedures on the urethral sphincter function is not clear. Training might improve the strength and duration of contraction of the pelvic floor musculature and perhaps the FPL and the MUCP might improve due to these exercises. [18,19] However, we found a trend towards a higher relatively decrease of

the MUCP in the patients with intensive PFME. Perhaps, physiotherapy will delay the recovery of the involuntary sphincteric function. As far as we know there are no other published studies about the impact of the intensity of PFME on sphincter function as measured by profilometry. We analysed the effect of intensive physiotherapy on the FPL and the MUCP and we did not find any measurable effect. Mayby, PFME mainly have an effect on voluntary [fatigueable] pelvic floor muscles. Our results at least show that more intensive PFME do not result in improved involuntary sphincter function. Perhaps other aspects of the pelvic floor muscles are important. Song et al [20], in a study in 94 men who underwent magnetic resonance imaging of the pelvic organs and urodynamic studies before RRP, concluded that patients with better developed pelvic diaphragm and levator ani muscles achieve earlier recovery of continence.

Perhaps pelvic floor muscle exercises can have a role in the pre-operative period to strengthen the pelvic floor muscles before RP. Centemero et al [21] performed a randomised controlled study in 118 men to determine the benefit of starting PFME 30 d before RP. At 3 months 59.3% of the patients who received PFME before and after RP were continent versus 37.3% of the patients who received PFME postoperatively only. They concluded that preoperative PFME may improve early continence after RP.

In multivariate analysis, a non-nerve sparing approach was a prognostic factor for a higher relative decrease of the MUCP. However, we have previously shown that nerve sparing is not a prognostic factor for persisting incontinence after RRP. [11] It should also be mentioned that some characteristics like prostate volume, tumor stage and surgical skill might introduce some bias. Several studies have suggested that preservation of the neurovascular bundles may be important for the continence mechanism. [20,22,23] However, if nerve sparing RRP improves continence rates, the question about the mechanism of action remains. Probably, other intra-pelvic structures such as the pudendal nerve (which may be partly responsible for the function of the striated sphincter, as well as for the function of pelvic floor muscles), extrinsic pelvic floor muscle function or bladder properties may help to maintain closure function in particular, and urinary continence in general.

Bladder neck preservation (BNP) was a second prognostic factor for a higher relative decrease of the MUCP after RRP. However, it should be emphasized that BNP was neither a prognostic factor for persisting incontinence nor for recovery of continence in the analysis of the randomized study. [11] Srougi et al [24] performed a prospective randomized study to compare continence rate (defined as using 1 or no pad per day)

after RRP in patients with bladder neck resection versus bladder neck preservation. They did not find any statistically significant differences between the 2 groups in PRPI. So, it seems at least that continence after RRP depends more on urethral sphincter function than on bladder neck function. These findings also emphasize that the relative decrease of MUCP after RRP is less relevant for the final continence status than the absolute preoperative MUCP value. The less relevant role of a relative decrease is also underlined by the wide range [1%-41%] of relative decreases of MUCP values among the different studies in table 4.

Conclusions

We showed that UPP parameter values deteriorate in all men after RRP. Furthermore, a poor preoperative MUCP seems to be the most important prognostic factor for persistent PRPI. More intensive physiotherapy did not have a positive effect on the postoperative urethral sphincter function.

A good preoperative sphincter muscle mass and function seems to protect against PRPI. A 100% continence rate after RRP probably will not be achievable since there will always be some men with a low preoperative MUCP that will end up with an insufficient sphincter mass in spite of meticulous and expert operative technique.

In our patients, using our technique of performing UPP, the median preoperative value of 53.1 cm H_2O is a value below which there is an increased chance of persistent PRPI. However, because of the variability of UPP technique among the different urodynamic labs, every lab should determine its own cut-off value; to do this, the methodology that we have described can be used.

UPP's probably can have a role as preoperative predictor of PRPI when counselling patients with localized prostate cancer.

Men with a low pre-operative MUCP that may be at increased risk for PRPI represent a specific group on which to focus future research.

References

[1] Kleinhans B, Gerharz E, Melekos M, Weingartner K, Kalble T and Riedmiller H. Changes of urodynamic findings after radical retropubic prostatectomy. Eur Urol 1999; 35: 217-22

[2] John H, Sullivan MP, Bangerter U, Hauri D and Yalla SV. Effect of radical prostatectomy on sensory threshold and pressure transmission. J Urol 2000; 163(6): 1761-6

[3] Giannantoni A, Mearini E, Zucchi A, Costantini E, Mearini L, Bini V and Porena M. Bladder and urethral sphincter function after radical retropubic prostatectomy: a prospective long-term study. Eur Urol 2008;54: 657-664

[4] Dubbelman Y, Groen J, Wildhagen M, Rikken B and Bosch R. Quantification of changes in detrusor function and pressure-flow parameters after radical prostatectomy: relation to postoperative continence status and the impact of intensity of pelvic floor mucle exercises. Neurourol Urodynam 2012; 31(5): 637-41.

[5] Chao R, Maye ME. Incontinence after radical prostatectomy: detrusor or sphincter causes. J Urol 1995; 154:16-18

[6] Desautel MG, Kapoor R, Badlani GH. Sphincteric incontinence: the primary cause of post-prostatectomy incontinence in patients with prostate cancer. Neurourol Urodyn 1997; 16:153-60

[7] Majoros A, Bach D, Keszthelyi A, Hamvas A, Romics I. Urinary incontinence and voiding dysfunction after radical retropubic prostatectomy (prospective urodynamic study) Neurourol Urodyn 2006; 25:2-7

[8] Myers RP. Male urethral sphincteric anatomy and radical prostatectomy. Urol Clin N Am 1991; 18(2): 211-27

[9] Ribeiro LHS, Prota C, Gomes CM, de Bessa J, Boldarine MP, Dall'Oglio MF, Bruschini H and Srougi M. Long-term effect of early postoperative pelvic floor biofeedback on continence in men undergoing radical prostatectomy: a prospective, randomized, controlled trial. J Urol 2010;184:1034-1039

[10] Van Kampen M, De Weerdt W, Van Poppel H, et al. Effect of pelvic-floor re-education on duration and degree of incontinence after radical prostatectomy: a randomised controlled trial. Lancet 2000;355:98-102.

[11] Dubbelman Y, Groen J, Wildhagen M, Rikken B and Bosch R. The recovery of urinary continence after radical retropubic prostatectomy : a randomized trial comparing the effect of physiotherapist-guided pelvic floor muscle exercises with guidance by an instruction folder only. BJU Int 2010 ;106(4) :515-22

[12] Walsh, P.C. and Donker, P.J. Impotence following radical prostatectomy: insight into aetiology and prevention. J Urol 1982;128,492-497.

[13] Abrams P, Blaivas JG, Stanton SL and Andersen JT. The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology. Scand J Urol Nephol 1988; suppl: 114: 5-19

[14] Brown M, Wickham WEA. The urethral pressure profile. Br J Urol 1969; 51: 211-7

[15] Griffiths D. The pressure within a collapsed tube, with special reference to urethral pressure. Phys Med Biol 1985 ; 30(9) :951-63

[16] Rudy DC, Woodside JR, Crawford ED. Urodynamic evaluation of incontinence in patients undergoing modified Campbell radical retropubic prostatectomy: a prospective study. J Urol 1984; 132(4): 708-12

[17] Hammerer P, Huland H. Urodynamic evaluation of changes in urinary control after radical retropubic prostatectomy. J Urol 1997 ; 157: 233-6

[18] Meaglia JP, Jose ph AC, Chang M and Schmidt JD. Postprostatectomy urinary incontinence: response to behavioral training. J Urol 1990; 144(3): 674-6

[19] Burgio KL, Stutzman RE and Engel BT. Behavioral training for postprostatectomy urinary incontinence. J Urol 1989; 141(2): 303-6

[20] Song C, Doo CK, Hong JH, Choo MS, Kim CS, Ahn H. Relationship between the integrity of the pelvic floor muscles and early recovery of continence after radical prostatectomy. J Urol 2007 ; 178 :208-211

[21] Centemero A, Rigatti L, Giraudo D, Lazzeri M, Lughezzani G, Zugna D et al. Preoperative pelvic floor muscle

exercise for early continence after radical prostatectomy : a randomised controlled study. Eur Urol 2010 ; 57(6) :1039-43

[22] Burkhard FC, Kessler TM, Fleischmann A, Thalmann GN, Schumacher M, Studer UE. Nerve sparing open radical retropubic prostatectomy-does it have an impact on urinary continence? J Urol 2006; 176(1): 189-95

[23] Stanford JL, Feng Z, Hamilton A.S, Gilliland FD, Stephenson RA, Eley JW et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. JAMA 2000 ; 283(3): 354-60

[24] Srougi M, Nesrallah LJ, Kauffmann JR, Nesrallah A and Leite KRM. Urinary continence and pathological outcome after bladder neck preservation during radical retropubic prostatectomy : a randomized prospective trial. J Urol 2001; 165 : 815-8

Urethral sphincterfunction before and after radical prostatectomy:

systematic review of the prognostic value of various assessment techniques

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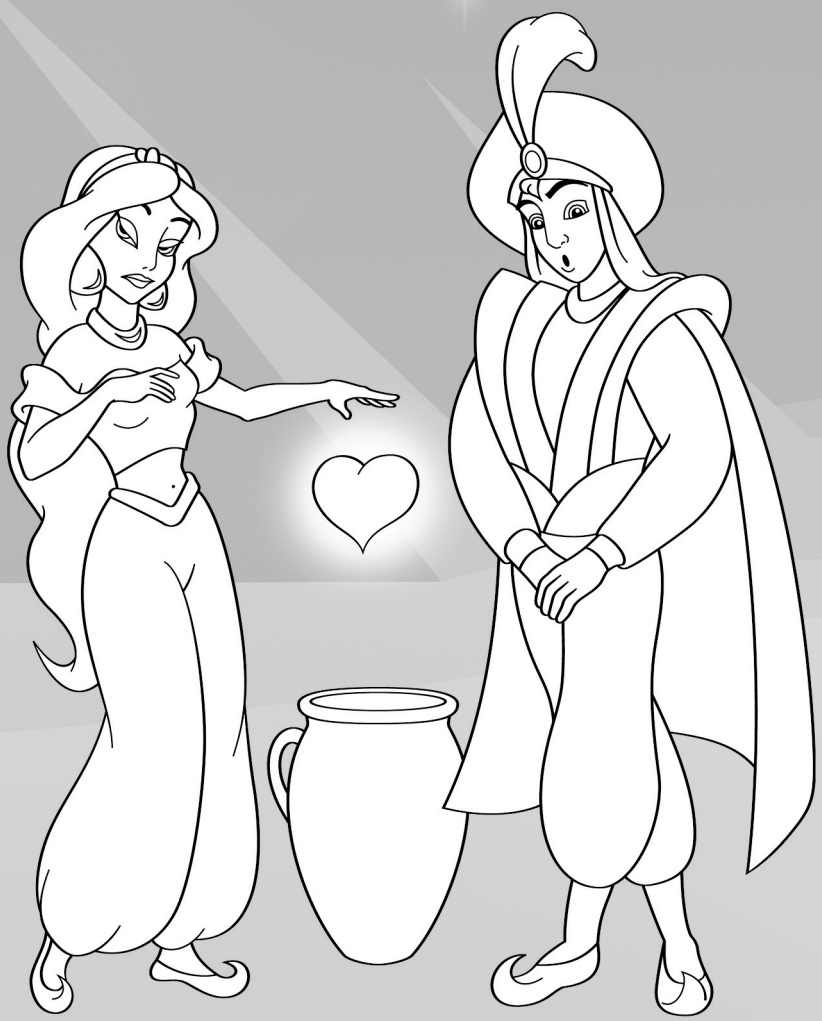

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Abstract

Aims

Urethral sphincter incompetence is generally considered to be the most important contributing factor to post- radical prostatectomy incontinence (PRPI). The value of various assessment techniques used to objectify urethral sphincter function before and/or after RP is unclear. Our review addresses the following questions: In men having to undergo RP, which measurement techniques that assess preoperative and postoperative urethral sphincter function have predictive value for the postoperative continence status or correlate with the postoperative continence status.

Methods

A systematic and comprehensive search was performed using the terms: urethral sphincter, radical prostatectomy and urinary incontinence. Results were restricted to English–language papers published between 1980 and March 2012. Only techniques described by at least 2 studies were included.

Results

Several assessment techniques for urethral sphincter function and anatomy were identified: sphincter electromyography, magnetic resonance imaging (MRI), perfusion sphincterometry and urethral pressure profilometry (UPP).

A shorter urethral sphincter length on preoperative endorectal MRI might be associated with an increased risk of PRPI as well as longer time to achieve continence.

UPP showed that both maximum urethral closure pressure (MUCP) and functional profile length (FPL) decrease significantly after RRP. Low preoperative MUCP and FPL are associated with an increased risk of PRPI.

The other mentioned assessment techniques are not usable as preoperative diagnostic tools.

Conclusions

MRI and UPP might be valuable preoperative diagnostic tools in patients waiting for RRP. However, more and larger studies are needed to show the exact role of MRI and UPP in the preoperative management of patients waiting for RRP and for whom postoperative incontinence is a big concern.

Introduction

Urinary incontinence is one of the two most important complications of radical prostatectomy (RP). Preservation of urinary continence is an important outcome measure. In literature, urethral sphincter incompetence and bladder dysfunction are both mentioned as causes of post-prostatectomy incontinence. Knowledge of the functional anatomy of the sphincter is important. Various techniques, including cadaveric dissection and magnetic resonance imaging, have been used to describe normal urethral sphincter anatomy. [1-3]

Myers et al [2] suggested that the part of the urethra that extends from the apex of the prostate to the bulb of the penis, which is surrounded by the striated sphincter, should be termed the sphincter urethra rather than the membranous urethra. However, in most other studies the length of this part of the urethra is called the membranous urethra length. It is innervated by autonomic (somatic) branches of the pelvic plexus, which partly run with the neurovascular bundle and partly derive from branches of the pudendal nerve by parasympathetic and sympathetic fibers. [1-3]

Damage of the muscle fibers and/or the nerve supply due to anatomical dissection during RRP may result in urethral sphincter deficiency and cause urinary incontinence.

Many studies have examined the effect of RP on urethral sphincter function. However, the exact impact of the external sphincter on the continence status after RRP is still controversial.

We reviewed the literature to determine the value of the different measurement techniques used for urethral sphincter function assessment and tried to answer the following questions: "In men having to undergo radical prostatectomy, which measurement techniques that assess preoperative and postoperative urethral sphincter function have predictive value for the postoperative continence status or correlate with the postoperative continence status".

Materials and Methods

A systematic and comprehensive Pubmed search of articles published between 1980 and March 2012, was performed using the following keywords: urethral sphincter,

radical prostatectomy, urinary incontinence. Results were restricted to English language papers.

One hundred twenty-four articles were found. From these articles we selected those with measurements both before and after RRP or articles which compared patients with and without post radical prostatectomy incontinence (PRPI). Eventually, we selected 25 articles about urethral sphincter function in patients who underwent radical prostatectomy which contained at least the following information: age, objective urethral sphincter measurements before and/or after operation, follow-up time, number of patients by study group, information about correlation among measurement and continence status (Figure 1). Papers on the following assessment techniques were found and discussed separately: sphincter electromyography (2 studies) [4,5], magnetic resonance imaging (6 studies) [6-11], urethral pressure profilometry (10 studies) [12-21], perfusion sphincterometry (7 studies) [22-28]. Only techniques described by 2 or more studies were included. When more than 5 studies were available for a certain measurement technique we selected the articles with both pre- and postoperative measurement. If available the sensitivity, specificity, the positive and negative predictive value and test –retest reliability of different objective urethral sphincter function assessments in finding ISD in patients with stress-incontinence after RRP were noted. Evidence summary, levels of evidence and grade of recommendations of the various techniques were determined according to the methods described by the EAU incontinence panel of the European association of urology 2012. [29]

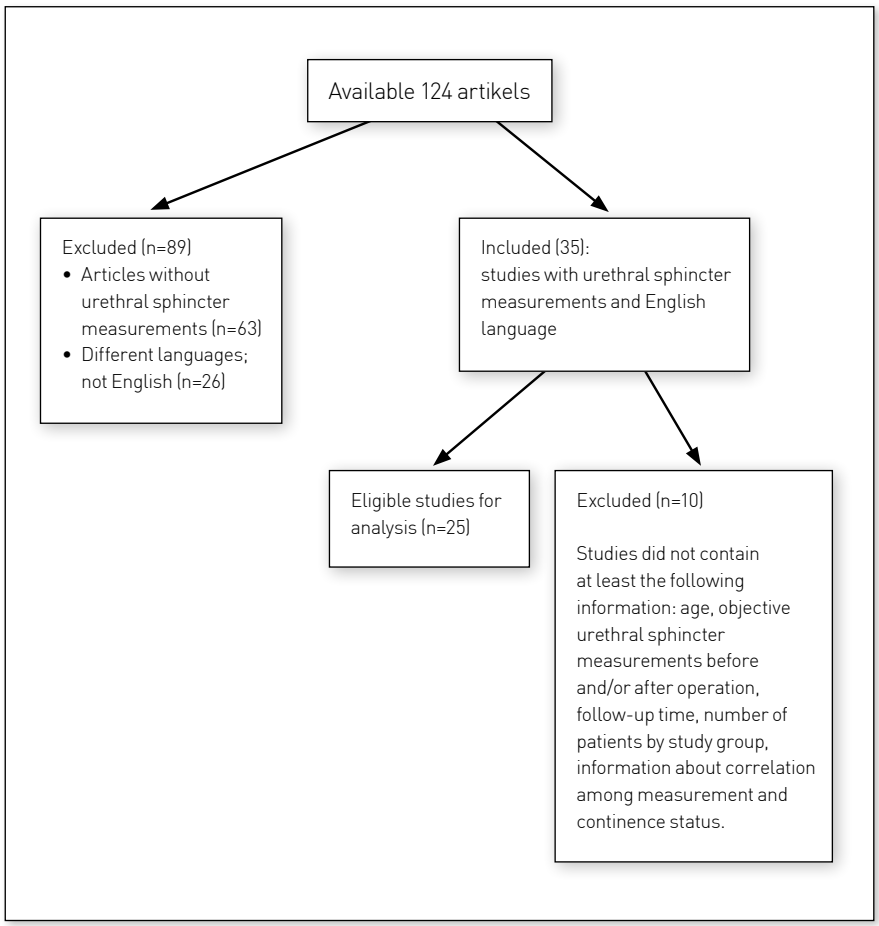
We restricted our review to tests of urethral sphincter function although we recognize that bladder dysfunction may also contribute to post radical prostatectomy incontinence.

Assessment techniques

Sphincter electromyography (2 studies)

Quantitative analysis of interference patterns in a muscle is made of recordings of the EMG activity level in the muscle, by measuring the number of "turns" (spikes in the motor unit) and mean amplitude of the turns. Increased muscle activity will give increased density of the interference pattern in the muscle. Increased fiber density is usually found in muscles with partial nerve lesion with reinnervation by means of

Figure 1. Study profile



polyphasic motor units. [30]

Two studies evaluated the urethral sphincter in patients before and after RRP by sphincter electromyography. [4,5] Aanestad et al [4] assumed that after removal of the proximal urethral sphincter during RRP the interference pattern in the distal urethral sphincter might increase as a compensatory mechanism. Analysis was performed before and after surgery using a Medelec EMG MS 92A EMG machine. Patients were examined in lithotomy position. A concentric needle electrode was

inserted in the striated outer layer of the distal urethral sphincter. Preoperatively, the prostatic apex was used as an anatomical landmark. In the postoperative investigations, the electrode was guided to the correct position in the muscle by listening to the motor unit potentials with the loudspeaker and visually inspecting the sharp EMG signals.

Ten patients were analyzed before and 25-32 months after RRP. Recordings were made in rest and also at attempted maximal "voluntary" activation of the urethral sphincter. They showed a tendency towards post-operative change in the interference pattern (decrease in the mean number of turns during rest and an increased mean amplitude at maximal activation) and an increase in fiber density in the sphincter muscle following RRP, suggesting an iatrogenic partial nerve lesion and reinnervated motor units. The study did not support the hypothesis of increased activity in the distal urethral sphincter as a compensatory mechanism after surgical removal of the proximal sphincter. However, the internal part of the distal urethral sphincter, consisting of smooth muscle fibers unavailable to EMG techniques, may compensate for loss of the proximal sphincter in the bladder neck.

Liu et al [5] performed a study in 20 men to determine whether the cavernous nerves carried fibers to the distal sphincter as well as those supplying the corporal bodies and whether EMG changes occurred after radical lower urinary tract surgery. The sphincter neurophysiological studies were performed using a Medelec Mystro MS 20 system. Three tests were carried out with the patient in supine position: motor unit analysis, sacral reflex latency (equivalent to bulbocavernous reflex) and pudendal somatosensory evoked potential. A concentric needle electrode was inserted transperineally in the midline in an antero-cranial direction towards the apex of the prostate until the typical burst of activity followed repetitive tonically firing units of the urethral sphincter were recorded. Analyses were performed postoperatively after nerve-sparing RRP (n=10) and non-nerve sparing cystoprostatectomy (n=10) and compared to controls. The authors did not find a significant difference between these two patient groups. They concluded that division of the nerves located in the neurovascular bundle in the prostate capsule did not compromise distal urethral sphincter function. The nerve fibres routed through the neurovascular bundles seems to be mainly concerned with innervation of the corporal bodies.

The sensitivity, specificity, the positive and negative predictive value and test –retest reliability were not mentioned for these studies.

Magnetic resonance imaging (6 studies)

Magnetic resonance imaging can be used to analyse the normal anatomy of the male pelvic floor and perineal anatomy. Four studies reported on the role of preoperative and postoperative membranous urethral length (MUL) in the recovery of continence after RP [6-9]. A 1.5-Tesla endorectal MRI was used before and at least 6 months after open RP [6,7] or RALP [8,9]. Both preoperative MUL (the distance from the prostatic apex to the level of the urethra at the penile bulb) and postoperative MUL (the distance from the bladder neck tot the level of the urethra at the penile bulb) and the MUL loss ratio were related to the recovery time and level of urinary continence after RP. A preoperative MUL larger than 12-14 mm was found too be related to a more rapid return of urinary continence after surgery. However, Mendoza et al did not find a significant cutoff value for urethral length.

Recently, von Bodman at al [10] reported on a retrospective study in 600 men undergoing open and laparoscopic radical prostatectomy who underwent preoperative magnetic resonance imaging. They investigated whether pelvic soft tissue and bony dimensions on rectal MRI influence the recovery of continence and whether MRI variables improve the prediction of continence recovery. The authors measured the levator thickness at the height of apical dissection, urethral volume, prostate volume, urethral length, mid pelvic area, outer and inner levator distance. Continence was defined as no pad use. Continence rates at 6 and 12 months were 63% and 76% respectively. Larger membranous urethral length (measured from apex of prostate to base of urethral bulbus), greater urethral volume and an anatomically close relation between the levator muscle and membranous urethra were independent predictors of continence recovery. The addition of these MRI variables to a base model (including: age, comorbidities, clinical stage and grade, PSA and year of surgery) implied a marginal improvement of the predictive accuracy for continence at 12 months. The predictive accuracy remains low which limits their use in clinical practice. Furthermore, this data suggests that it is not the thickness of the levator ani but the close relation to the membranous urethra that has an impact on continence recovery.

The sensitivity, specificity, the positive and negative predictive value and test –retest reliability were not reported for these studies

Endorectal MRI was also used for evaluation of the importance of periurethral fibrosis in the development of PRPI. [6,11] Tuygun et al [11] compared patients with (n=22; (TUR

[6]; TVP [6]; RRP [10]) and without (n=14; (TUR [4]; TVP [4]; RRP [6]) post prostatectomy incontinence (PPI) due to pure sphincter incompetence. Evaluation of the fibrosis was performed postoperatively. Fibrosis was seen in all patients in the study group and in 4 of the control group. Severe periurethral fibrosis was more common for patients with PPI who had undergone RRP, mild to moderate membranous fibrosis was more common for patients after transurethral resection (TUR) or transvesical prostatectomy (TVP). Fibrosis in the 4 patients without PPI was only mild [3] or moderate. [1] The authors claim that fibrosis plays an important role in the development of PPI because it may have a negative effect on external urethral sphincter function. The specificity and the sensitivity of MRI to predict incontinence were 71,4% and 100%, respectively. Others [6] found a tendency towards periurethral fibrosis having a negative effect on the recovery of continence, but statistical significance was not reached.

Urethral pressure profilometry (UPP) (10 studies)

Several studies have shown that sphincter incompetence due to the disruption of the sphincteric innervation, hypoperfusion or direct damage to the sphincteric muscles, is the predominant factor in causing PRPI rather than bladder overactivity. [22,23,31] Both the pre- and postoperative sphincter quality seems to be important in regaining continence after RP. [12] External sphincter function can be studied by UPP. Maximum urethral closure pressure (MUCP; defined by: the maximum difference between urethral pressure and the intravesical pressure) and functional profile length (FPL; defined by: the length of the urethra along which the urethral pressure exceeds intravesical pressure in women) are the two parameters mostly used. [32] Several studies performed UPP before and after RRP (Table 1). Most of the studies show a significant decrease of the functional urethral length after RRP. [13-18] In these studies mean FPL at baseline was 5.0 cm (range 4.3 - 6.1 cm). Postoperatively (range 2 to 10 months after RRP) mean FPL was 2.6 cm (range 1.6 - 3.1 cm). Only one study [19] did not find a difference between the pre- and the postoperative FPL, probably due to the small number of patients. Postoperatively, the FPL for patients who became continent and patients who were still incontinent during follow-up was significantly different in two of five studies, whereas three studies did not show any significant difference between these men. MUCP was significantly decreased after RRP in 6 out of 7 studies. [12,15-17,20,21] Mean MUCP at baseline was 73 cm H_2O (range 49 - 95 cm H_2O). This can probably be explained by the variable methodology

used when performing UPP. Postoperatively mean MUCP was 56 cm H_2O (range 30 - 83 cm H_2O). Recently, we found that for patients who regained continence after RRP the preoperative MUCP was significantly higher compared to patients who remained incontinent after surgery. [16] Postoperatively, the MUCP for patients who became continent and patients who were still incontinent during follow-up was significantly different in five out of seven studies. [12,13,15,16,20] For men who regained continence during follow-up, MUCP was significantly higher compared to those who remained incontinent.

Minervini et al [20] reported on the relation between FPL and MUCP and the severity of incontinence. Postoperative, patients were divided in a continent group (n=14), a moderately incontinent group (n=16) and a severely incontinent group (n=4). FUL was 3.8 cm, 2.6 cm and 1.6 cm, respectively. MUCP was 74 cm H_2O, 41 cm H_2O and 34 cm H_2O, respectively. Statistically significant difference was found between the continent and the incontinent group for the mean functional profile length and the MUCP.

Three studies demonstrated [14, 15, 21] a progressive postoperative (partial) recovery of urethral closing function over time. However, baseline values were not always reached. Some of the investigators concluded that the observed increase in urethral parameter might be related to behavioral training, but this has not been supported by objective measurements. Dubbelman et al [16] showed that more intensive physiotherapy did not have a positive effect on the postoperative urethral sphincter function compared to selftraining by an instruction folder.

The papers did not report on sensitivity, specificity, the positive and negative predictive value and test –retest reliability.

Perfusion sphincterometry. (7 studies)

During perfusion sphincterometry, the perfusion pressure required to move fluid across the lower sphincter is measured.

Leak point pressures

VLPP is defined as the pressure on the bladder by a Valsalva maneuver at which leakage of urine occurs. With these tests the intrinsic sphincter function can be assessed indirectly. However, VLPP is only useful for patients with urinary incontinence, otherwise a leak point pressure is usually not reached. So the test is not useful to assess sphincter function for continent patients before RRP.

Table 1. Overview of clinical studies reporting urethral pressure profile (UPP) parameter values (means) before and after radical retropubic prostatectomy.

Author	Pts with baseline and follow-up UPP [N]	Timing of follow-up UPP in months	Number of continent patients after RRP (%)	Nervesparing technique	MUCP at baseline [cm H_2O] Total Cont. Incont. group	MUCP at follow-up [cm H_2O] Total Cont. Incont. group	FPL at baseline [mm] Total Cont. Incont. group	FPL at follow-up [mm] Total Cont. Incont. group	MUCP Pre vs post total group p-value	FPL Pre vs post total group p-value
John[13]	34	6	28 (82)	NNS=76%; UNS=24%	49	- 42 23 p=0.03	5.0	2.5 2.5 2.5	-	0.01
Rudy[14]	14 / 16	6	2 (13)	-	95	72 93	4.3	1.6	ns	<0.001
Majoros[12]	63	2	43 (68)	NNS=90.5%; UNS=9.5%	64 68.6 67.5 ns	52 56.3 43.9 p<0.0001	-	-	<0.0001	-
Hammerer[15]	82	6	68 (83)	-	89.6	65.2 68.1 53.1 p<0.01	6.1	2.6 2.8 2.1 p<0.02	<0.001	<0.001
Dubbelman[16]	66	6	19 (29)	NNS=43%; UNS=25%; BNS=32%	53.1 66.2 49.7 p=0.001	30.6 41.3 29.2 p=0.01	5.8 5.8 5.8	2.1 2.1 2.0 ns	<0.001	<0.001
Minervini[20]	34	6	14 (41)	-	68	74 41 34 *c m s	4.9	3.8 2.6 1.6 c m s	sig	sig
Kleinhans[17]	44	6	37 (84)	-	78.7	53 50.6 57.0	5.3	3.1 2.25 2.30	0.0012	0.00001
Pfister[18]	20	3	-	-	-	-	5.1	3.0	-	-
Song[21]	72	36	-	-	63.7	53.2	-	-	0.001	-
Constantinou[19]	13	22.9	10 (77)	NNS=31%; UNS=31%; BNS=38%	94	83	3.6	3.2	ns	ns

NNS= nonnerve sparing; UNS= unilateral nervesparing; BNS=bilateral nervesparing

C = Totally dry during normal and strenuous activity

M = Incontinence only during strenuous activity who had to wear a pad

S = Total incontinence

Valsalva's leak point pressure (VLPP) (4 studies)

Most of the studies were performed postoperatively. Only one study performed VLPP measurements before and after RRP. [24] Urodynamic assessment was performed using a 6,7 or 8 F double lumen transurethral catheter and an intrarectal balloon catheter. VLPP was defined as the lowest abdominal pressure induced by cough or Valsalva maneuver causing visible stress incontinence [24] or as total abdominal pressure in the absence of a detrusor contraction causing incontinence as determined by fluoroscopy. [25] Intrinsic sphincter deficiency (ISD) was defined by the demonstration of stress incontinence during Valsalva's maneuver, regardless of the absolute value of leak point pressure.

Preoperatively, none of the patients showed ISD [24]. In all studies, more than half of the patients (range 59 -92%) had ISD at least 6 months after RRP. [24,25] Giannantoni et al [24] found ISD with stress incontinence in 40/54 patients (74%) 8 months after RRP. At 3 years, ISD was present in 19/32 (59%) men compared to 0 men at baseline. Ficazolla et al [25] evaluated 60 men with PRPI at least 6 months after surgery. ISD was present in 90% of the men. Mean VLPP was 93 cm H_2O. VLPP correlated with the degree of stress incontinence, with VLPP being higher in patients with grade 1 stress-incontinence (incontinence with sudden increase in abdominal pressure). The symptom of stress incontinence accurately predicted the finding of intrinsic sphincter deficiency on urodynamic tests (positive predictive value 95%, negative predictive value 100%). Desautel et al [22] reported on a retrospective study in 39 men with PPI. Sphincter damage was the sole cause in 59%. Of all men, 69% had VLPP less than 103 cm H_2O with a transurethral catheter in place. An additional 10 (26%) had VLPP less than 150 upon removal of the catheter. VLPP was an indication of the severity of sphincter damage. However, other studies did not find a correlation between VLPP and incontinence severity (defined by pad usage). [26]

So, although most men with PRPI had ISD, abnormal sphincter function as assessed by VLPP, is not necessarily correlated with clinical severity of incontinence.

Correlations among different perfusion measurements and LPP's. (3 studies)

Unlike LPP measurements, urethral pressure profilometry and perfusion sphincterometry are performed in a simple and standardized way. To see if it is possible to use one simple and standardized measurement several studies analysed the correlation between the different perfusion measurements. Comiter

et al [27], performed a study to assess the correlation among abdominal leak point pressure (ALPP), maximum urethral closure pressure MUCP and retrograde leak point pressure (RLPP) in the evaluation of PRPI. Twenty-four men were evaluated for 6 to 116 months (mean 27) after RRP. A self-administered questionnaire and multichannel video urodynamics were used. The mean ALPP was 49 cm H_2O, the mean MUCP 52 cm H_2O and the mean RLPP 48 cm H_2O. ALPP, RLPP and MUCP were each significantly correlated with pad use. Authors concluded that RLPP and MUCP measurements offer reliable alternatives to ALPP for the evaluation of PRPI.
Kielb et al [28] retrospectively analysed postoperative video-urodynamic outcomes in 146 men with PPI. Stress incontinence (at itself or combined with bladder dysfunction), determined by leakage of contrast through the bladder neck with a Valsalva maneuver, was present in 139 (95%) of the men. Sphincter damage was the sole cause of incontinence in 59% of men. Static UPP measurements in patients with stress incontinence correlated with leak point pressure ($p<0.0001$). Mean MUCPs were lower in men with documented stress urinary incontinence (SUI) compared to those without SUI (46.6 versus 69 cm H_2O, $p=0.001$). This study analysed a select group of patients and only had postoperative outcomes. Pad use correlated both with VLPP and MUCP. However, others did not find such a correlation between maximum urethral closure pressure and ALPP / VLPP. [23]
We can conclude that the correlation between ISD measurements (VLPP and ALPP) and external sphincter measurements (MUCP) as measured during UPP is weak.

Discussion

We reviewed the literature to determine the value of the different measurement techniques used for urethral sphincter function assessment and tried to answer the following questions:" In men having to undergo radical prostatectomy, which measurement techniques that assess preoperative and postoperative urethral sphincter function have predictive value for the postoperative continence status or correlate with the postoperative continence status".
Sphincter electromyography could not show any difference in recorded patterns before and after surgery. Postoperative perfusion sphincterometry, VLPP or ALPP measurements correlated with intrinsic sphincter deficiency in patients with PPI. However, VLPP is poorly correlated with incontinence severity. One limitation

of perfusion sphincterometry is that it only can be performed in patients with urinary incontinence. So, it only can be used after radical prostatectomy. It seems that sphincter electromyography and perfusion sphincterometry play no part in preoperative assessment of urethral sphincter function for patients awaiting radical prostatectomy.

Sphincter length analysed by endorectal MRI seems to have an impact on a patient's continence rate after RRP. It seems that a shorter urethral sphincter length on preoperative endorectal MRI is associated with an increased risk of postoperative urinary incontinence as well as with a longer period of time for the patient to regain continence. However, there is insufficient evidence to propose an exact cut-off value. The use of postoperative pelvic floor exercises as a therapy for incontinence was not described in these studies. Fibrosis of the external urethral sphincter (visible with pelvic MRI) might also have a negative effect on the sphincter function. MRI might be a preoperative diagnostic tool for patients awaiting RRP and postoperative MRI could be useful in the process of analyzing the cause of PPI. Although MRI revealed several beneficial measurements there are some limitations to the interpretation of MRI based measurements: there is no standardized method for measuring MUL by MRI and the reproducibility of measurement of the MUL by MRI is unknown. [2] Furthermore, the sensitivity, specificity, ROC curves and test-retest variability were not documented in any of these studies and in most of the studies MRI was performed preoperatively while the measurements were performed retrospectively.

Just like MRI, UPP might have a role in the preoperative work-up in patients awaiting RRP. Both MUCP and FUL significantly decrease after RRP. Postoperatively, higher MUCP is associated with increased chance of regaining continence. The role of the FPL as preoperative diagnostic tool to distinguish patients who are at risk for persistent urine incontinence is controversial. Limitations of the urethral pressure profile studies were the lack of standardization of UPP measurements, the absence of description of the surgical technique in most of the studies, the use of postoperative therapy for incontinence (Pelvic floor muscle exercises, behavioural training/electrical stimulation of the sphincter, biofeedback reeducation) in some studies. Despite the variable methodology (mostly in type of catheter used for UPP) trends and significant differences between parameter values were comparable in most of the studies. More well-designed studies are needed to obtain sufficient evidence to support MUCP as a preoperative predictor of postoperative risk of urinary incontinence.

Preoperative and postoperative urethral length as measured with MRI and urethral function as measured with UPP seems to be important in the prediction of who regains continence after RRP. With improved surgical techniques there is an opportunity to keep a longer stump of the membranous urethra. However, apart from urethral length many other factors contribute to postoperative incontinence; including neurophysiological deterioration and age related sphincteric atrophy. [33] These factors may partially explain the variability in individual outcomes among patients with a similar membranous urethral length.

Table 2. Evidence summary

Evidence summary	LE
Sphincter electromyography	
• There is no evidence that sphincter electromyography predicts which men will regain continence after RRP.	3
Perfusion sphincterometry	
• Postoperative perfusion sphincterometry, VLPP and ALPP measurements, correlated with intrinsic sphincter deficiency in patients with post prostatectomy incontinence.	2b/3
• Perfusion sphincterometry play no part in preoperative assessment of urethral sphincter function for patients awaiting radical prostatectomy.	2b/3
Urethral pressure profilometry	
• There is some evidence that preoperative determination of UPP parameters MUCP and FPL predicts which men will regain continence after RRP.	2b
• There is insufficient evidence to propose an exact cut-off value	2b
Magnetic resonance imaging	
• There is some evidence that preoperative determination of urethral sphincter length on preoperative endorectal MRI predicts which men will regain continence after RRP	2b
• There is insufficient evidence to propose an exact cut-off value	2b

A combination of preoperative MRI and UPP measurements probably gives the most useful information about the anatomical and functional urethral sphincter length and the chance to regain continence after RRP. Patients should be informed about the possibilities of these diagnostic tests. However, one should also be aware of the costs and the invasive nature of the tests.

Finallly, considering MRI and MUCP measurements, each measurement lacks sensitivity, specificity, positive and negative predictive value in predicting the continence status after RRP. More diagnostic studies are needed to show the exact role of a combination of MRI and UPP in the preoperative management of patients awaiting RRP.

Evidence summary with level of evidence and grade of recommendations of the various assessment techniques are listed in Table 2 and 3.

Table 3. Recommendations

Recommendations	GR
Sphincter electromyography:	
• further well-conducted clinical trials are needed	C
Perfusion sphincterometry:	
• should not be used in preoperative assessment of urethral sphincter function for patients awaiting radical prostatectomy	C
Urethral pressure profilometry	
• further randomized clinical trials are needed	B
• UPP can probably be used in preoperative prediction of who regains continence after radical prosatectomy	B
Magnetic resonance imaging	
• MRI can probably be used in preoperative prediction of who regains continence after radical prostatectomy	B
• Further randiomized clinical trials are needed	B

The most important factor regarding the postoperative continence mechanism probably is the external urethral sphincter although bladder dysfunction is another

contributing factor in PRPI. Unfortunately, the exact impact of the bladder function on the continence status after RRP is still unclear. We recently performed a prospective urodynamic study on detrusor function and pressure-flow parameters before and after RRP. In multivariate analysis, urodynamic parameters predictive of PRPI could not be identified. [34] There is a need to further study the effect of bladder dysfunction and urethral sphincter function on PRPI in prospective diagnostic test accuracy studies with analysis before and after surgery. Diagnostic accuracy can be presented at a specific threshold by using paired results such as sensitivity and specificity, of alternatively positive predictive value and negative predictive value. [35]

Conclusion

Sphincter dysfunction is an important cause of PRPI. A shorter urethral sphincter length and a lower urethral closing pressure are associated with an increased risk of PRPI. Both MRI and UPP, by measuring the sphincter length and the closing pressure, respectively, might play a part in the preoperative work-up for patients awaiting RRP. However, more and larger studies are needed to show the exact role and the reproducibility of MRI and UPP in the preoperative management of patients awaiting for RRP. Furthermore, sensitivity and specificity and predictive value based on the AUC of ROC curves should be determined.

References

[1] Strasser H, Frauscher F, Helweg G, Colleselli K, Reissigl A, Bartsch G. Transurethral ultrasound: evaluation of anatomy and function of the rhabdosphincter of the male urethra. J Urol 1998;159(1):100-105

[2] Myers RP, Cahill DR, Devine RM, King BF, Anatomy of radical prostatectomy as defined by magnetic resonance imaging. J Urol 1998;159(6):2148-58.

[3] Burnett AL, Mostwin JL. In situ anatomical study of the male urethra sphincteric complex: relevance to continence preservation following major pelvic surgery. J urol 1998; 160:1301-6

[4] Aanestad O, Flink R, Haggman M, Norlen BJ. Interference pattern in the urethral sphincter: a quantitative electromyographic study in patients before and after radical retropubic prostatectomy. Scand J Urol Nephrol 1998:32: 378-382

[5] Liu S, Christmas TJ, Nagendran K and Kirby RS. Sphincter electromyography in patients after radical prostatectomy and cystoprostatectomy. Br J of Urol 1992;69:397-403

[6] Paparel P, Akin O, Sandhu JS, Otero JR, Serio AM, Scardino PT et al. Recovery of urinary continence after radical prostatectomy: association with urethral length and urethral fibrosis measured by preoperative and postoperative endorectal magnetic resonance imaging. Eur Urol 2009;55:629-639

[7] Coakley FV, Eberhardt S, Kattan MW, Wei DC, Scardino PT, Hricak H. Urinary continence after radical retropubic prostatectomy: relationship with membranous urethral length on preoperative endorectal magnetic resonance imaging. J Urol 2002;168:1032-5.

[8] Nguyen L, Jhaveri J and Tewari A. Surgical technique to overcome anatomical shortcoming: balancing post-prostatectomy continence outcomes of urethral sphincter lengths on preoperative magnetic resonance imaging. J Urol 2008;179:1907-1911

[9] Mendoza PJ, Stern JM, Li AY, Jaffe w, Kovell R, Nguyen M et al. Pelvic anatomy on preoperative magnetic resonance imaging can predict early continence after robot-assisted radical prostatectomy. J Endourol 2011;25(1):51-55

[10] Von Bodman C, Matsushita K, Savage C, Matikainen MP, Eastham JA, Scardino PT et al. Recovery of urinary function after radical prostatectomy: predictors of urinary function on preoperative prostate magnetic resonance imaging. J of Urol 2012;187:945-950

[11] Tuygun C, Imamoglu A, Keyik B, Alisir I and Yorubulut M. Significance of fibrosis around and/or at external urinary sphincter on pelvic magnetic resonance imaging in patients with postprostatectomy incontinence. Urology 2006;68:1308-1312

[12] Majoros A, Bach D, Keszthelyi A, Hamvas A, Romics I. Urinary incontinence and voiding dysfunction after radical retropubic prostatectomy (prospective urodynamic study) Neurourol Urodyn 2006; 25:2-7

[13] John H, Sullivan MP, Bangerter U, Hauri D and Yalla SV. Effect of radical prostatectomy on sensory threshold and pressure transmission. J Urol 2000;163:1761-1766

[14] Rudy DC, Woodside JR, Crawford ED. Urodynamic evaluation of incontinence in patients undergoing modified Campbell radical retropubic prostatectomy: a prospective study. J Urol 1984; 132(4): 708-12

[15] Hammerer P, Huland H. Urodynamic evaluation of changes in urinary control after radical retropubic prostatectomy. J Urol 1997 ; 157: 233-6

[16] Dubbelman Y, Groen J, Wildhagen M, Rikken B and Bosch R. Urodynamic quantification of decrease in sphincter function after radical prostatectomy: relation to postoperative continence status and the effect of intensive pelvic floor muscle exercises. Neurourol Urodyn 2012;31(5):646-51

[17] Kleinhans B, Gerharz E, Melekos M, Weingartner K, Kalble T and Riedmiller H. Changes of urodynamic findings after radical retropubic prostatectomy. Eur Urol 1999; 35: 217-21

[18] Pfister C, Chappele O, Dunet F, Bugel H and Grise P. Assessment of the intrinsic urethral sphincter component function in postprostatectomy urinary incontinence. Neurourol Urodynamics 2002;21 :194-197

[19] Constantinou CE and Freiha FS. Impact of radical prostatectomy on the characteristics of bladder and urethra. J Urol 1992;148:1215-1220
[20] Minervini R, Felipetto R, Morelli G, Fontana N and Fiorentini L. Urodynamic evaluation of urinary incontinence following radical prostatectomy: our experience. Acta Urologica Belgica 1996;64:5-8
[21] Song C, Lee J, Hong JH, Choo MS, Kim CS, Ahn H. Urodynamic interpretation of changing bladder function and voiding pattern after radical prostatectomy : a long-term follow-up. BJU Int 2010 ;106(5) :681-6
[22] Desautel MG, Kapoor R, Badlani GH. Sphincteric incontinence : the primary cause of post-prostatectomy incontinence in patients with prostate cancer. Neurourol Urodyn 1997;16:153-60.
[23] Gudziak MR, McGuire EJ and Gormley AE. Urodynamic assessment of urethral sphincter function in post-prostatectomy incontinence. J Urol 1996;156:1131-1134
[24] Giannantoni A, Mearini E, Zucchi A, Costantini E, Mearini L, Bini V et al. Bladder and urethral sphincter function after radical retropubic prostatectomy: a prospective long-term study. Eur Urol 2008;54:657-664
[25] Ficazolla MA, Nitti VW. The etiology of post-radical prostatectomy incontinence and correlation of symptoms with urodynamic findings. J Urol 1998;160:1317-1320
[26] Winters JC, Appell RA, Rackley RR. Urodynamic findings in postprostatectomy incontinence. Neurourol Urodyn 1998:17:493-8
[27] Comiter CV, Sullivan MP and Yalla SV. Correlation among maximum urethral closure pressure, retrograde leak point pressure and abdominal leak point pressure in men with postprostatectomy stress incontinence. Urology 2003;62:75-78
[28] Kielb SJ and Clemens JQ. Comprehensive urodynamics evaluation of 146 men with incontinence after radical prostatectomy. Urology 2005;66:392-396.
[29] Lucas MG, Bosch JLHR, Cruz FR, Madden TB, Nambiar A, Neisius A, Pickard RS, de Ridder DJMK, Tubaro A, Turner WH: Guidelines on Urinary incontinence In: European Association of Urology Guidelines 2012 edition. Ed: EAU Guidelines office,
[30] Stalberg E, Antoni L. Computer-aided EMG analysis. Prog Clin Neurophys 1983;10:186-234
[31] Chao R, Maye ME. Incontinence after radical prostatectomy: detrusor or sphincter causes. J Urol 1995; 154:16-18
[32] Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U et al. The standardisation of terminology of lower urinary tract function: Report from the standardisation sub-committee of the international continence society. Neurourology and Urodynamics 2002;21:167-178
[33] Massey A and Abrams P. Urodynamics of the lower urinary tract. Clin Obstet Gynaecol 1985;12:319-41
[34] Dubbelman Y, Groen J, Wildhagen M, Rikken B, Bosch R. Quantification of changes in detrusor function and pressure-flow parameters after radical prostatectomy: relation to postoperative continence status and the impact of intensity of pelvic floor muscle exercises. Neurourol Urodyn 2012;31(5):637-41
[35] Mallett S, Halligan S, Thompson M, Collins GS, Altman DG. Interpreting diagnostic accuracy studies for patient care. BMJ 2012;345:e3999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Part IV

General discussion

Discussion and conclusions

Yvette Dubbelman

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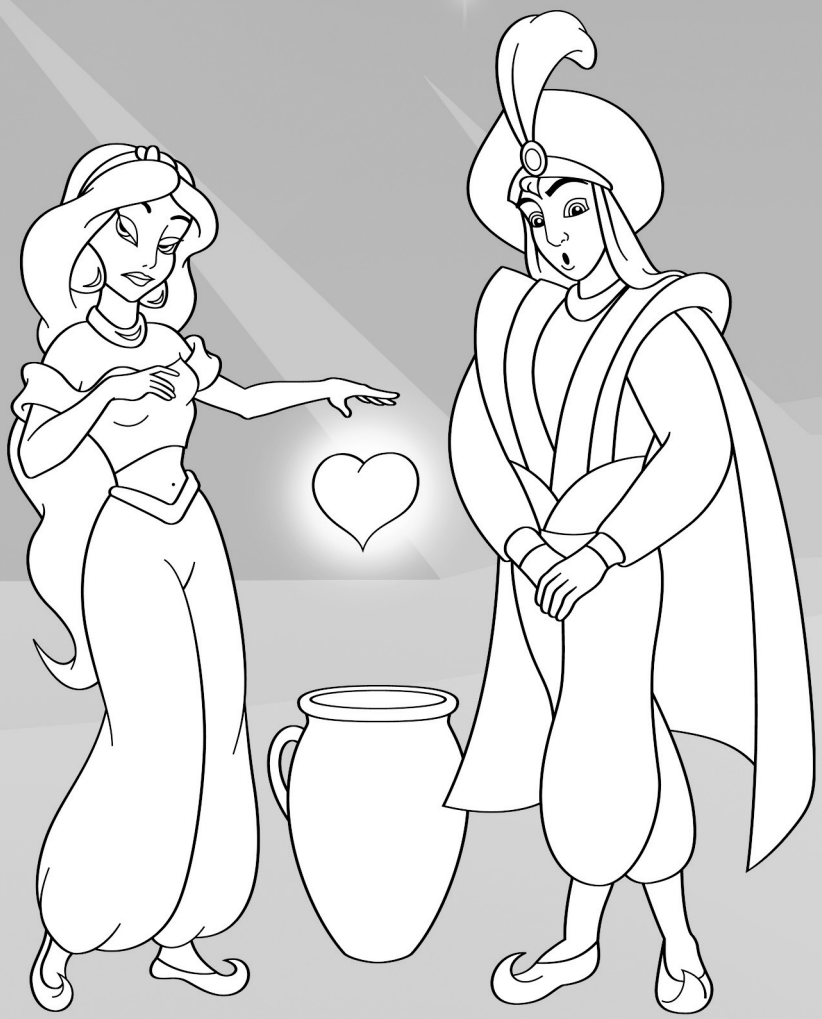

Radical prostatectomy is one of the treatment options for men with organ confined prostate cancer with a life expectancy of more than 10 years. However, this operation can be accompanied by 2 major complications: sexual dysfunction and urinary incontinence.

In the first period after the introduction of the RRP, mean potency rates of 19% (range: 11-40%) were found in a general urological practice irrespective of operation technique. [1,2] With the introduction of the nerve sparing technique in 1982 [3] more favourable outcomes have been reported. We looked for potency rates (at least 12 months after RRP) in literature before 2006. After bilateral and unilateral nerve-sparing radical prostatectomy potency rates of 31% - 86% and 13% - 56% were found respectively. [4,5] In non-nerve sparing radical prostatectomy potency rates of 0% - 17% were reported. Besides nerve-sparing techniques, age was another predictive factor for better outcomes. In men <50 years potency rates vary between 61 and 100%, post-operatively. For men between 50 and 70 years of age the overall potency rate declined to 70-85%. In men, after unilateral and bilateral nerve-sparing procedures potency was found in 47-58% and 44-90%, respectively. Men older than 70 years had low potency rates ranging from 0 and 51%, despite nerve-sparing procedures. The wide range of outcomes is probably affected by the method used to collect the data. The high potency rates were mostly based on interviews or non-validated questionnaires, while the lowest outcomes were based on validated questionnaires (IIEF).

Reported incontinence rates six months after surgery varied between 10-87% [6-8] depending on the method used to report incontinence. Continence rates 12 months after RRP (in the period before 2006) varied between 60 and 93%. [1,4,9]

Recently, Treiyer et al [10] reported on a prospective study of 236 patients who underwent RRP between 2005 and 2007. Postoperatively, recovery of continence and potency (at 6 and 12 months) was achieved in 70 and 75% and in 20 and 26%, respectively. Of all men who underwent bilateral or unilateral nerve-sparing procedure 58% and 43% were potent postoperatively. These outcomes of potency and continence are comparable with outcomes in studies before 2006.

The question is whether potency and continence rates will improve when using newer techniques like (robotic-assisted) laparoscopic prostatectomy?

Minimal invasive treatment

Laparoscopic radical protatectomy

In an effort to further decrease the morbidity of open RP a minimally invasive surgical approach in the treatment of prostate cancer was first described by Schuessler et al in 1997 [11]. These authors performed the first successful laparoscopic RP (LRP). They did not find a significant advantage compared to open RP. In the late 1990s, LRP became more popular because studies reported better outcomes. [12-14] Recently, Ploussard et al [15] reported on LRP performed between 2000 and 2007. A total of 740 patients were included. All patients underwent a nerve-sparing procedure (unilateral or bilateral). Continence (defined as absence or occasional use of a pad) was regained in 94% and 97% of men over 1 and 2 years of follow-up, respectively. There were no significant predictive factors for persistent incontinence. Erections sufficient for intercourse were present in 34.7 % and 64.6% over 1 and 2 years, respectively. This rate reached 67.3 % at 2 years in the matter of bilateral nerve-sparing surgery. Age <60 and bilateral nerve sparing surgery were associated with higher potency rates. However the technical demands of the surgery and the long learning curve have prevented the widespread use of LRP by most urological surgeons. The reduction in the range of motion, two-dimensional vision and counter intuitive hand eye coordination between real and visible movements are the main obstacles associated with a long learning curve. [16]

With the introduction of advanced robotic devices such as the da Vinci Surgical System surgeons hope to reduce operative time and the learning curve for minimally invasive RP. Robotic-assisted laparoscopic prostatectomy (RALP) offers the additional advantages of x10 magnified binocular, three-dimensional visualization, motion scaling with tremor filtration, improved surgical ergonomics and miniature wristed articulating instrument with seven degrees of freedom. [16] The first RALP was performed in Germany in 2000 by Binder and Kramer. [17]

A prospective comparison study between LRP and RALP was performed by Willis et al. [18] Continence (defined as zero pad use) at 6 and 12 mo was 55% and 72% in de LRP group and 66% and 75% in de RALP group (difference not significant). Potency recovery was quicker in the RALP group, but at 12 months outcomes were similar. Sexual bother at 12 months was 71% for both groups. They concluded that

RALP appears to be associated with an earlier return of sexual function compared to LRP. The same conclusion was made by Asimakopoulos et al. [19] They performed a randomized study to compare outcomes between laparoscopic and robot-assisted bilateral nerve-sparing procedure. At 12 months of follow-up no significant differences were observed for continence rate and time span to regain continence. However the capability for intercourse showed a significant advantage for RALP (32% vs 77%). Time span to regain capability for intercourse was also significantly shorter for RALP.

Robotic-assisted laparoscopic prostatectomy

The growth of RALP has been exponential in the last few years and has rapidly overtaken both open and laparoscopic approaches in the USA. It is estimated that 60-70% of all prostatectomies are robotically performed. Reported functional outcomes after RALP showed to be comparable with or tended to be better than open RP and LRP. In a prospective study, Xylinas et al [20] evaluated functional outcomes in 500 men after RALP. Patients completed questionnaires before and 3,6,12,18 and 24 months after surgery. All men were continent and potent before surgery. Incontinence was defined as absence of urinary leakage and no pad requirement. At 12 and 24 months after RALP continence rate was 78% and 88%, respectively. Potency was defined as the ability to achieve an erection sufficient for penetration with or without the use of phosphodiesterase-5 enzyme inhibitor. One and 2 years after RALP 54% and 63% of the men were potent. Two years after RP potency rate reached 68% in case of bilateral nerve sparing surgery. Age< 60 years was significantly associated with potency recovery. Patel et al [21] analyzed outcomes after RALP in 500 cases. Complete continence defined as no use of pads was achieved in 95% and 97% at 6 and 12 months. Of the patients who were potent preoperatively and had had a nervesparing procedure 78% were still potent (with or without the use of oral medications).

A few review articles described the continence and potency rates found in RALP series. Mottrie et al [22] reported continence recovery (defined as no pads) rates ranged between 70–97% at 12 months in the main published RALP series between 2007 and 2010. Patel et al [23] performed a review of pentafecta outcomes after robot-assisted laparoscopic prostatectomy in high-volume centres. Continence and potency rates were part of the review. Weighted means (range) for continence were 87.8 (54-97)% at 6 months and 91.8 (70-97) % at 12 months. Weighted means (range)

for potency in preoperatively potent men at 6, 12 and 18 months were 65 (15-77)%, 74 (43-91.5)% and 95 (63-100)%, respectively. Coelho et al [16] reported in a review continence (defined as no pad or one pad for security) rates of 13-38%, 23-82%, 47-93% and 70-97% after RALP at 1, 3, 6 and 12 months of follow-up. Weighted mean continence rates were 53%, 78%, 86% and 91%, respectively. Overall potency rates after nervesparig procedures ranged from 14,7% to 77% and from 43% to 78% at 6 and 12 months postoperatively. Weighted mean potency rate was 61% and 71% at 6 and 12 months, respectively. Potency rates according to the NS technique were 47-80% for unilateral NS and 63-100% for bilateral NS procedure with a follow-up of more than 18 months.

Overall, continence rates at 6 and 12 months after RALP ranged between 47% - 97% and 70% -97%, respectively. Potency rates at 6, 12 and 18 months ranged between 15-77%, 43-91.5% and 63-100%, respectively. The high scores were found in high volume centers after bilateral nerve sparing approach. These outcomes are comparable with outcomes found after RRP an LRP.

Comparison of RRP, LRP and RALP

No randomized controlled trials comparing RRP, RALP and LRP were identified. There are not many review articles available.

Few data are available concerning RRP and minimally invasive RP. Perioperative outcomes (mean blood loss, catheterization time and hospital stay) appear to favour minimally invasive approaches. Data about potency and continence were similar for open RP and minimally invasive RP. [24]

Some studies found RALP to be superior to RRP and LRP. In a non-randomized study, Kim et al [25] compare functional outcomes after RALP and RRP in 528 and 235 patients respectively. Continence was defined as being completely pad free. Potency was defined as having an erection sufficient for intercourse with or without a PDE-5 inhibitor. Continence showed similar recovery for the RRP and the RALP group. However during the learning curve continence recovery was in favour of RALP. Factors independently predictive of continence recovery were younger age and longer membranous urethral length on preoperative MRI. Recovery of potency was more rapidly in the RALP group. At 6 months, 1 and 2 years potency rates were 33%, 57%, 83% and 6,7%, 28%, 45% for the RALP group and the RRP group, respectively. Median time to potency was 9,8 and 24.7 mo in the RALP and the RRP group, respectively.

Younger age, surgical method (RALP vs RRP) and higher preoperative serum testosteron were independent prognostic factors for potency recovery. In this study patients after RALP demonstrated superior functional recovery. However, due to lack of randomization baseline characteristics were not comparable for both groups. Patients in the RRP group were significantly older and the approach to surgery was predominantly a non-nerve-sparing one. Differences between potency outcomes can probably be explained by these biases.

Tewari et al showed an earlier recovery of urinary continence and return of erections in patients treated with RALP than in those treated with RRP. Time needed to reach continence and return of erections was 160 and 440 days after RRP vs 44 and 180 days after RALP. [26]

Coelho et al [27] reviewed the literature perioperative outcomes, postoperative surgical margin (PSM) rates and functional outcomes of several large series (N>250) of RRP, LRP and RALP. They found that all of the mentioned approaches were safe options for treament of patients with localized prostate cancer, presenting similar overall complication rates. Minimal invasive treatment was associated with decreased operative bloodloss and risk of transfusion when compared with RRP. Weighted mean PSM rates were lower and continence and potency rates higher after RALP, compared with RRP and LRP. Outcomes of potency and continence rates were similar after RRP and LRP. At 6 mo and 12 months after surgery continence rates ranged from 39% to 78% and 61% to 94%, 70% to 95% and 82% to 95%, 62% to 97% and 82% to 97% for RRP, LRP and RALP, respectively. Weighted mean continence rates at 12 months of follow-up for RRP, LRP, RALP were 79%, 84.4% and 92% respectively. Weighted potency rates after bilateral nerve sparing, at 12 mo follow-up were 60.6% (range: 40-76), 54% (range: 43-76) and 93.5% (range: 80-100) after RRP, LRP and RALP, respectively. Overall potency rates at 12 months were 17-39%, 52-78% and 62-78%, for RRP, LRP and RALP, respectively. There is a trend towards better functional outcomes after RALP compared to RRP and LRP. However some problems arise while comparing the different surgery approaches. There are no randomized studies, there is a lack of longterm follow-up studies, definitions used to describe continence and sexual function are not standardized and there is a lack of the use of validated questionnaires. The use of pharmacological therapy may have further confounded the results. Therefore definitive conclusions cannot be drawn yet.

Meta-analysis and other systematic reviews could also not prove the advantage of any

surgical approach in terms of functional and oncological outcomes. [28,29] Ficarra et al [29] found that in a cumulative analysis of comparative studies continence rates after LRP and RRP were overlapping, with 12 months continence rates ranging from 60% to 93% after RRP and from 66% to 95% after LRP. Comparitive and noncomparitive studies showed no significant advantage for LRP and RRP in terms of erectile function recovery. Potency rates ranged from 10 % to 93% after RRP and from 42% to 76% after LRP. Data from RALP studies suggested an advantage in terms of urinary continence and erectile function, specifically indicating a quicker recovery of continence and potency for RALP compared to RRP. However, data from referral centers showed continence rates ranging form 84% to 97% and potency rates from 70% to 80% similar to the best series of RRP and LRP. Ficarra et al [29] concluded that the available data were not sufficient to prove the superiority of any surgical approach in terms of functional and oncological outcomes. In terms of costs RRP is cheaper than LRP and RALP, with 4437, 5687 and 6752 US dollars, respectively.

Other domains of sexual function

Furthermore we analysed patients who were operated by RRP before 2006. We focused on different domains of sexual function and continence. We found a decrease in sexual activity, spontaneous erections and orgasmic function of 67.3%, 29.4% and 66.8% after operation. However sexual interest was still present in almost all men. After bilateral nerve-sparing procedure orgasmic function was preserved in 73.4% of men. Prognostic factors for decrease in sexual activity and spontaneous erections were age and surgical approach. Orgasmic function was significantly affected by age $\geq$ 60 years, non-nerve sparing procedure and severe incontinence (more than two pads a day). We did not ask for orgasmic associated incontinence (climacturia) but in literatuur climaturia after RRP was present in 20-45%. In our study orgasm was the only sexual function that significantly improved over years. In almost half of the men orgasm recovered to normal five years after surgery. A likely explanation for the return of orgasmic function may be nerve regeneration and the confident feeling of being cured of prostate cancer. We found a trend towards a better recovery of orgasm in patients with bilateral nerve sparing surgery over the years. In studies analysing potency after nerve-sparing procedures, orgasm was present in 66-80% of patients postoperatively, regardless of normal or absent potency.

In literature, the impact of RP on sexual life (not only focusing on erectile function) has become more and more important in recent studies. Beside erectile dysfuntion, we know now that patients also suffer from orgasm disorders and other sexual dysfunction. It becomes clear that patients suffer in many different domains of sexual function. Messaoudi et al [30] studied the impact of RALP on a patient's sexual health and satisfaction according to sexual motivation. They analysed 63 men who were sexually active and potent preoperatively. After RP 50%, 80% and 78% of men reported decrease in sexual desire, intercourse frequency and anorgasmia / less satisfying orgasm, respectively. Climacturia was reported in 25% being bothersome in 56%. Comprised sexual function had a strong psychological and emotional impact on the patients. Two-thirds of the men experienced at least one of the following: loss of masculine identity, loss of self-esteem, and anxiety of performance. The more sexually motivated patients experienced greater distress and were less satisfied. Tewari et al [31] analysed postoperative potency and orgasmic outcomes in 408 men after RALP, who were potent and able to achieve orgasm preoperatively. After BNS RP 90.7% of the men were able to achieve orgasm postoperatively, compared with 82% and 60.8% after UNS and NNS RP, respectively. Younger age and nerve-sparing technique had a positive influence on the recovery of orgasm.

Significant incontinence during sexual activity may occur in the absence of stress urinary incontinence during non-sexual activities. Mitchell et al reported on incontinence during sexual activity after RP. The percentage of patients who had any bother of incontinence during sexual activity was 44.4% at 3 months, which decreased to 36% at 24 months, respectively. More than 10% of men with no stress incontinence problem during daily activity reported major bother from incontinence during sexual activity. [32] Comparable outcomes were reported by Nilsson et al. [33] They found climacturia after RP (RRP and RALP) to be present in any form in 39% of the sexually active men. Among men who experienced orgasm-associated incontinence 86% were daytime continent. Yet, in men who were daytime incontinent 28% never experienced climacturia. Men who had a transurethral resection of the prostate before the radical prostatectomy, men who reported loss of penile length or reported sexual dysfunction showed an increased risk of developing climacturia. Climacturia showed to have a negative effect on sexual mental health. These recent data on orgasm and climacturia after RP are comparable with literature before 2006

and with our results, despite modified operation techniques.

Sexual bother

Sexual bother after RRP is present in 2-72 % of men. Analysing predicting factors and treatment options becomes more important. Potential predictors of sexual bother were analysed by Steinsvik et al. [34] They studied whether sexual bother after RP (RRP and RALP) can be predicted preoperatively. Sexual bother and sexual function were analysed both before and after RP. The prevalence of SB and sexual dysfunction was 18 % and 33% at baseline and increased to 66% and 84% at 1 year after RP, respectively. Predicting factors for sexual bother were: preoperative sexual bother, sexual activity and nervousness.

Some treatment options were mentioned. Anti-incontinence surgery can have a beneficial effect on bother due to urinary incontinence during sexual activity. Sexual quality of life can be improved. [35] Treiyer et al [10] showed that participation in a postoperative rehabilitation program had a positive influence on the outcome with regard to health related quality of life, postoperative potency and urinary continence.

Aetiology of erectile dysfunction and urinary incontinence

Erectile dysfunction can be classified as psychogenic, organic (neurogenic, hormonal, arterial, cavernosal, or drug-induced) or mixed psychogenic and organic (Table 1). [36] The aetiology of erectile dysfunction following radical prostatectomy is multifactorial, but neurogenic factors seem to play a major role. Vascular factors may be of importance in selective cases.

Arterial insufficiency and veno-occlusive dysfunction can be found in 32-59% and 26-52% of the patients after operation, respectively. The prognosis for the return of erectile function seems to be worst when venous leakage is present. Some investigators found that preservation of the accessory pudendal arteries may favourably influence the recovery of sexual function and decrease the time to recovery of spontaneous erections after radical prostatectomy. They found significant hemodynamic changes after sacrificing the accessory pudendal artery. However, others could not confirm these observations. [37] Colour Doppler ultrasound (CDU)

appears to be the most reliable, non-invasive diagnostic test for erectile dysfunction after radical prostatectomy in patients who do not respond to pharmacotherapy. We demonstrated that most of the postoperative abnormal values found with CDU are already present before the operation in men who reported to have a normal sexual potency preoperatively. Care must be taken when interpreting outcomes of studies performed only after the operation. More prospective studies on vascular involvement are required for a full understanding of its role in post-radical prostatectomy sexual dysfunction, including an analysis of the vascular status before the procedure.

Studies on post-prostatectomy ED pathophysiology showed that prolonged penile ischemia could cause penile structural changes (such as fibrosis), which in turn may cause venous leakage. The loss of smooth muscle fibers after denervation is another explanation for this phenomenon. Such structural changes represent a continuous process, which might not be detectable three months after surgery. The fact that there was no significant change in hemodynamic indices at 3 months after surgery in our haemodynamic study suggests that observal structural changes have not taken place at that point. This has implications for research on rehabilitation therapy.

Neurogenic factors appeared to be the most common explanation of sexual dysfunction after RRP. There is a clear relation between the number of spared neurovascular bundles and the recovery of potency. Also, a strong correlation between the number of preserved neurovascular bundles and age and the recovery of sexual potency was found. Younger patients in general might need fewer preserved bundles to remain potent compared to older patients.

Urethral sphincter incompetence and bladder dysfunction are mentioned as the most important causes of post-prostatectomy incontinence. Several studies have shown that sphincter incompetence, due to the disruption of the sphincteric innervation, hypoperfusion or direct damage to the sphincteric muscles are predominant factor causing PRPI. Surgical damage to the detrusor muscle, trigone, bladder neck, posterior urethra and external sphincter probably also has a negative impact on lower urinary tract function probably causing detrusor overactivity, reduced bladder capacity and reduced bladder compliance. Apart from surgical damage, pre-existing bladder dysfunction in the aging male may also have a negative impact on continence after RRP. Decreased bladder perfusion due to longstanding elevation of voiding detrusor pressure as a result of bladder outlet obstruction, can initiate a reduction in bladder compliance.

In our studies sphincter incompetence was the most important cause for persistent PRPI. Both the pre- and postoperative sphincter quality seem to be important in regaining continence after RRP.

For further improvement of functional outcomes after RP it seems important to minimize the loss of the urethral sphincter and to preserve nerves not only on the posterolateral side but also on the anterior and anterolateral side of the prostate and the urethral sphincter.

Table 1. Classification and common causes of erectile dysfunction [36]

Category of erectile dysfunction	Common disorders	Pathophysiology
Psychogenic	Performance anxiety Relationship problems Psychological stress depression	Loss of libido, overinhibition, or impaired nitric oxide release
Neurogenic	Stroke or Alzheimer's disease Spinal cord injury Radical pelvic surgery Diabetic neuropathy Pelvic injury	Failure to initiate nerve impulse or interrupted neural transmission
Hormonal	Hypogonadism hyperprolactinemia	Loss of libido and inadequate nitric oxide released
Vasculogenic (arterial and cavernosal)	Atherosclerosis Hypertension Diabetes mellitus Trauma Peyronie's disease	Inadequate arterial flow or impaired veno-occlusion
Drug-induced	Antihypertensive and antidepressant drugs Antiandrogens Alcohol abuse Cigarette smoking	Central suppression Decreased libido Alcoholic neuropathy Vascular insufficiency
Caused by other systemic disease and aging	Old age Diabetes mellitus Chronic renal failure Coronary heart disease	Usually multifactorial, resulting in neural and vascular dysfunction

Prognostic factors

In the years before 2006, the most important prognostic factors for recovery of sexual potency were the number of spared neurovascular bundles, age and sexual activity before the operation. Risk factors for post-radical prostatectomy incontinence as defined by the 4th International Consultation on Incontinence included: age, radiation, functional sphincteric length, membranous urethral length, surgical technique, preoperative incontinence and certain medical comorbidities. [23] Nowadays studies are still performed to analyse prognostic factors for better functional outcomes after RP concerning sexual function and continence.

Age

A young age age seems to be a prognostic factor for an earlier return of continence and potency. Mendiola et al [38] presented an age-stratified prospective assessment of urinary and sexual function of 300 patients after RALP. Urine continence at 3 months postoperative was 76% for men aged <50; 55% for men aged 50-59 and 43%for men aged 60 or older (p=0.06). However, at 12 months continence levels were equal for the three groups; 90-93%. Potency rate at 3 months after nerve sparing procedure (bilateral and unilateral) was 67% for men aged <50; 56% for men aged 50-59 and 40% for men aged 60 or older (p=0.04). Potency rate at 12 months was 87%, 76% and 62% respectively. Younger men continue to report superior potency outcomes compared to older men over the first postoperative year after RALP. Patel et al found no statistically significant difference for time to regain continence and continence rates between age groups (≤55; 56-65 and >65 years) after RALP. However, younger men had higher potency rates and shorter time to recovery of sexual function when compared to older men. [39]

Nervesparing technique

Most studies showed a beneficial effect on the recovery of potency after RP. [10,15] However, the importance of surgical technique during dissection of the NVBs for preservation of potency after RALP is not clear, studies still show conflicting results. [26, 40 vs 41]

Transperitoneal vs extraperitoneal approach

Chung et al [42] analysed the effect of transperitoneal (TP) versus extraperitoneal (EP) RALP on functional outcomes. Continence (defined as no pad use) rates at 6 and 12 months were equal for the EP and the TP group (94.6% vs 96.7% at 6 months and 96.6 % vs 98.6% at 12 months). However the continence rates immediately after surgery, at 2 weeks and at 1 month were higher in the EP group than in the TP group. Potency rates were 51.8% in the TP group and 54.8% in the EP group, 12 months after bilateral nerve sparing surgery. The EP approach seems to have better functional outcomes in the first months after surgery. Similar outcomes are reached at a follow-up of 1 year.

Hyperlipidemia

Hyperlipidemia was found to be a significant negative predictive factor of postoperative erectile function recovery within 1 year following RALP. [43] We should take into consideration controlling hyperlipidemia in patients who has vasculogenic erectile dysfunction.

Surgical method and preoperative serum testosteron

Surgical method (RALP vs RRP) and higher preoperative serum testosterone were found to be independent prognostic factors for recovery of sexual function. [25]

Preoperative sexual activity and bladder neck sparing approach

In a multicenter study, Gacci et al [44] reported on predicting factors for continence recovery one month after RP. Of 1972 patients only 32.7% were completely continent one month after RP. There were no significant differences in continence status between various surgical approaches (open, robotic or laparoscopic RP). Preoperative normal sexual activity and bladder neck sparing approach were predictors for continence recovery in one month. Age and nervesparing approach had no significant impact on continence recovery. Authors explained this finding by a good vascularisation of the penis. The internal pudendal artery supplies both the penis and the membranous urethra. Fibers form the pudendal nerve, contained in the neurovascular bundles, provide somatic control for both the external urethral sphincter and the corpora cavernosa. Therefore, satisfactory preoperative erectile function is suggestive of good vascularization and innervation of the urethral sphincter, in addition to the penis,

which can be determinant for continence recovery.
Preoperative erectile function (measured by the IIEF) was also a independent predictor of urinary continence recovery in a study by Gandaglia et al. [45]

BMI, membranous urethral length, IIEF-5 score and age

Another predicting factor for continence after RALP is: longer membranous urethral length on preoperative MRI. [25] Lower IIEF-5 score, increased BMI (cutoff value 30 kg/m^2), and older age were associated with a decreased continence rate. Nervesparing procedure did not significantly affect continence. [46] Several technical modifications were proposed to promote an earlier return of continence after RP. Anterior and posterior reconstruction of the rhabdosphincter tended to have better outcomes for return of continence [47-49], however, other studies did not confirm such a beneficial effect. [50, 51]

The amount of urine loss 1 week after catheter removal

We showed in univariate and multivariate logistic regression analysis that the amount of urine loss 1 week after catheter removal, as a continuous variable, was a significant prognostic factor for the persistence of incontinence six months after RRP. Others found comparable outcomes. [52,53]

Maximum urethral closure pressure

We found that pre- as well as post-prostatectomy MUCP was significantly lower in persistently incontinent men compared to the men who regained continence. Non-nerve sparing approach and bladder neck sparing approach were prognostic factors for a higher relative decrease of the MUCP after RRP.
John et al [54] and Majoros et al [55] also demonstrated a significantly lower postoperative MUCP in incontinent men compared to men who regained continence.

Pelvic floor muscle exercises

From chapter 5 it is clear that the exact role of postoperative pelvic floor muscle exercises (PFME) is still not clear. Whereas some studies showed a beneficial effect on the recovery of continence after RP, we and others could not conform this. In our study of 66 men, we could not find a beneficial effect of post-operative intensive physiotherapist guided PFME over an instruction folder-guided approach neither in

continence rates nor in time to regain continence.
The benefit of starting PFME before surgery was studied in a randomized prospective study by Centemero et al. [56] They compared one group of patients who started PFME preoperatively and continued postoperatively to another group of patients who started PFME postoperatively. After 1 and 3 months continence was achieved in 44% and 59% of the men in the first group versus 20% and 37% of the men in the second group. Authors concluded that preoperative PFME might improve early continence and QoL outcomes after RRP. Others found comparable outcomes. [57] Further studies are needed to show the exact role of preoperative PFME in patients with organ confined prostate cancer.

Conclusions

From the results combined in this thesis the following conclusions can be drawn and practical implications can be given:

- Urinary continence and sexual potency rates have not changed over the last 10 years. Outcomes of potency and continence rates were similar after RRP and LRP. There are conflicting data from RALP studies on a possible advantage of open RP and LRP in terms of urinary continence and erectile function. Specifically, an earlier recovery of continence and potency for RALP compared to open RP and LRP is not found in all studies. There are some problems with comparing the different surgical approaches, there are no randomized controlled studies, there is a lack of long term follow-up, definitions used to describe continence and sexual function are not standardized and there is a lack of the use of validated questionnaires. Available data are not sufficient to prove the superiority of any surgical approach in terms of functional and oncological outcomes. Therefore definitive conclusions can still not be made.
- It is clear that RP has a negative impact on erectile function. In the last few years there has been an increasing attention to other areas of the sexual function outside the erectile function, in particular orgasmic function. A patient's sexual health becomes more important. Pre-operative sexual counselling seems to be important and should address the possible changes in the quality of the orgasm, the absence of orgasm and the occurrence of climacturia after RRP. However, the ability to reach an orgasm even with a flaccid penis, without emission and

ejaculation should also be mentionend just like the possibility of recovery of the orgasm over years particularly for patients who have had a bilateral nervesparing procedure. Prognostic factors for orgasmic dysfunction are comparable with the most important prognostic factors for erectile function after RRP in literature.

- Although many studies have confirmed the importance of both neurogenic and vascular factors in the aetiology of sexual dysfunction after RRP, our prospective study suggests that vascular factors are less important in the aetiology of ED after RRP. No structural vascular changes had taken place in a time period of three months after surgery compared to preoperative findings. The fact that there was no significant change in hemodynamic indices at three months after surgery could be important, because it suggests that observal structural changes have not taken place by that point. This has implications for research on rehabilitation therapy. Neurogenic factors seem to play a major role in the aetiology of sexual dysfunction after RRP. A non-nerve sparing radical prostatecomy is a serious risk factor for regaining sexual dysfunction after surgery.
- Sphincter dysfunction seems to be the most important cause of PRPI. Both maximum urethral closure pressure (MUCP) and functional profile length (FPL) analysed by UPP, decrease significantly after RRP. Low preoperative MUCP and short FPL seem to be associated with an increased risk of postoperative urinary incontinence. A good preoperative sphincter muscle mass and function seem to protect against PRPI. However, a 100% continence rate after RRP will probably not be achievable as there will always be some men with a low preoperative MUCP that will end up with an insufficient sphincter mass in spite of meticulous and expert operative technique.
- On the basis of our results, case series after RALP that report a near 100% continence rate are likely to have used flawed methodology for the reporting of the continence rates.
- Due to RP bladder function seems to change. There is an increase of the maximum flow rate of the urine (Q_{max}) increase and a decrease of the bladder pressure required for this flow ($p_{detQmax}$) and the urethral resistance factor (URA). Pre-operatieve detrusor overactivity might have a negative impact on regaining continence after RP. However, statistical significance was not reached in multivariate analysis.
- The amount of urine loss one week after catheter removal can help in counseling

the patient during the postoperative period about the possibility of regaining continence.

- Intensive physiotherapist-guided PFME seem to have no beneficial effect on the recovery of continence within the first six months after RRP. PFME can have benefit in selected patients, especially men who have difficulty in understanding the instructions described in the folder. Our results at least show that more intensive PFME do not result in improved involuntary sphincter function.
- More intensive PFME might have a lowering effect on bladder outflow resistance after RRP, and may decrease the chance of de novo DOA 6 months after the RRP. Pelvic floor muscle exercises might have a role in the preoperative period to strengthen the pelvic floor muscles before RP.
- Both MRI and urethral pressure profilometry might play a part in the preoperative work-up in patients waiting for RRP. More and larger studies are needed to show the exact role of MRI and UPP in the preoperative management of patients waiting for RRP. However, in patients for whom postoperative incontinence is a big concern at this moment, measuring the urethral sphincter function by MRI and/or urethral pressure profilometry might help in counseling the patient about the possibility of PRPI.

Limitations of this thesis:

- Chapter 4: first, we could not find structural vascular changes in a time period of three months after surgery compared to preoperative findings. Prolonged penile ischemia could cause penile structural changes (such as fibrosis), which in turn may cause venous leakage. Such structural changes represent a continuous process, which might not be detectable three months after surgery. Secondly, the small cohort can be a reason for the lack of a statistically significant difference between pre- and postoperative erectile function and prognostic factors.
- Chapter 5: first, we collected data from a long period (1977-2007) in which operations were performed by different surgeons: this could possibly give some form of bias. Secondly, we did not use a self-administered questionnaire, but different physicians were the interviewers of the standardized non-validated questionnaires. This could possibly give some overestimation of the outcomes. Thirdly, the lack of available follow-up information.
- Chapter 6: the number of patients recruited fell short of the target determined

by the sample size calculation. Therefore, results should be regarded with caution because of the fact that the study was underpowered. Subsequently, one must take into account a high risk of finding no difference where in fact this might very well exist (Type II error).

Who is the most ideal candidate for undergoing a radical prostatectomy?

A healthy man who is younger than 60 years of age with good pre-operative sexual function, an excellent urethral sphincter function (high MUCP and good FPL) and an organ confined prostate cancer with a bilateral nerve sparing approach being a likely surgical option. Unfortunately, most men are older than 60 when the indication for a radical prostatectomy is made. Therefore, this profile is rare when it comes to radical prostatectomy candidates.

References

[1] Stanford JL, Feng Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer the prostate cancer outcomes study. JAMA 2000;283:354-60
[2] Davidson PJT, Van Den Ouden D and Schroeder FH. Radical prostatectomy: prospective assessment of mortality and morbidity. Eur Urol 1996;29:168-173.
[3] Walsh PC and Donker PJ. Impotence following radical prostatectomy: insight into aetiology and prevention. J Urol 1982;128:492-497.
[4] Walsh PC, Marschke P, Ricker D, Burnett AL. Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. Urology 2000;55:58-61.
[5] Geary ES, Dendinger TE, Freiha FS and Stamey TA. Nerve sparing radical prostatectomy: a different view. J Urol 1995;154: 145-149.
[6] Minervini R, Felipetto R, Morelli G et al. Urodynamic evaluation of urinary incontinence following radical prostatectomy: our experience. Acta Urol Belg 1996;64:5-8.
[7] Lepor H, Kaci L.The impact of open radical retropubic prostatectomy on continence and lower urinary tract symptoms: a prospective assessment using validated self-administered outcome instruments. J Urol 2004;171;1216-1219.
[8] Rudy DC, Woodside JR, Crawford ED. Urodynamic evaluation of incontinence in patients undergoing modified Campbell radical retropubic prostatectomy: a prospective study. J Urol 1984;132(4):708-12.
[9] Bianco Jr Fj, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta") Urology 2005;66(Suppl 5):83-94
[10] Treiyer A, Anheuser P, Butow Z and Steffens J. A single center prospective study: prediction of postoperative general quality of life, potency and continence after radical retropubic prostatectomy. J Urol. 2011 May;185(5):1681-5.
[11] Schuessler WW, Schulam PG, Clayman RV, Kavoussi LR. Laparoscopic radical prostatectomy: initial short-term experience. Urology 1997;50:854-7
[12] Guillonneau B, Vallancien G. Laparoscopic radical prostatectomy: the Montsouris experience. J Urol 2000;163:418-22
[13] Rassweiler J, Sentker L, Seemann O et al. Laparoscopic radical prostatectomy with the Heilbronn technique. An analysis of the first 180 cases J Urol 2001;166:2101-8
[14] Eden CG, Cahill D, Vass JA et al. Laparoscopic radical prostatectomy: the initial UK series. BJU Int 2002;90:876-82
[15] Ploussard G, Taille de la A, Xylinas E, Allory Y, Vordos D, Hoznek A. Prospective evaluation of combined oncological and functional outcomes after laparoscopic radical prostatectomy: trifecta rate of achieving continence, potency and cancer control at 2 years. BJU Int. 2011 Jan;107(2):274-9.
[16] Coelho RF, Chauhan S, Palmer KJ, Rocco B, Patel MB and Patel VR. Robotic-assisted radical prostatectomy: a review of current outcomes. BJU Int. 2009 Nov;104(10):1428-35.
[17] Binder J, Kramer W. Robotically-assisted laparoscopic radical prostatectomy. BJU Int 2001:87:408-10
[18] Willis DL, Gonzalgo ML, Brotzman M, Feng Z, Trock B, Su L. Comparison of outcomes between pure laparoscopic radical prostatectomy: a study of comparitive effectiveness based upon validated quality of life outcomes. BJU Int 2012;109:898-905
[19] Asimakopoulos AD, Pereira Fraga CT, Annino F, Pasqualetti P, Calado AA, Mugnier C. Randomized comparison between laparoscopic and robot-assisted nerve-sparing radical prostatectomy. J Sex Med 2011;8:1503-1512.
[20] Xylinas E, Durand X, Ploussard G, Campeggi A, Allory Y, Vordos D, et al. Evaluation of combined oncologic and functional outcomes after robotic-assisted laparoscopic extraperitoneal radical prostatectomy: trifecta

rate of achieving continence, potency and cancer control. Urol Oncol. 2011 Jun 28. [Epub ahead of print]
[21] Patel VR, Thaly R, Shah K. Robotic radical prostatectomy: outcome of 500 cases. BJU Int 2007;99:1109-1112.
[22] Mottrie A, Gallina A, de Wil P, Thuer D, Novara G, Ficarra V. Balancing continence function and oncological outcomes during robot-assisted radical prostatectomy (RARP). BJU Int 2011;108:999-1006
[23] Patel VR, Abdul-Muhsin HM, Schatloff O, Coelho RF, Valero R, Ko YH et al. Critical review of 'pentafecta' outcomes after robot-assisted laparoscopic prostatectomy in high-volume centres. BJU Int 2011;108:1007-1017
[24] Cathcart P, Murphy DG, Moon D, Costello AJ, Frydenberg M. Perioperative, functional and oncological outcomes after open and minimally invasive prostate cancer survey: experience from Australasia. BJU Int. 2011 Apr;107 Suppl 3:11-9.
[25] Kim SC, Song C, Kim W, Kang T, Park J, Jeong IG, Lee S et al. Factors determining functional outcomes after radical prostatectomy: robot-assisted versus retropubic. Eur Urol. 2011 Sep;60(3):413-9.
[26] Tewari A, Srivasatava A, Menon M; Members of the VIP Team. A prospective comparison of radical retropubic and robot-assisted prostatectomy: experience in one institution. BJU Int 2003;92:205-10
[27] Coelho RF, Rocco B, Patel MB, Orvieto MA, Chauhan S, Ficarra V et al. Retropubic, laparoscopic and robot-assisted radical prostatectomy: a critical review of outcomes reported by high-volume centers. J Endourol 2010;24:2003-2015.
[28] Parsons JK, Bennettt JL. Outcomes of retropubic, laparoscopic and robotic-assisted prostatectomy. Urology 2008;72:412-416.
[29] Ficarra V, Novara G, Artibani W et al. Retropubic, laparoscopic and robotic-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. Eur Urol 2009;55:1037-1063.
[30] Messaoudi R, Menard J, Ripert T, Parquet H, Staerman F. Erectile dysfunction and sexual health after radical prostatectomy: impact of sexual motivation. Int J Impot Res. 2011 Mar-Apr;23(2):81-6
[31] Tewari A, Grover S, Sooriakumaran, Srivastava A, Rao S, Gupta A, Gray R, Leung R, Paduch DA. Nerve sparing can preserve orgasmic function in most men after robotic-assisted laparoscopic radical prostatectomy. BJU Int. 2012;109:596-602
[32] Mitchell SA, Jain RK, Laze J, Lepor H. Post-prostatectomy incontinence during sexual activity: a single center prevalence study. J Urol 2011;186:982-5
[33] Nilsson AE, Carlsson S, Johansson E, Jonsson MN, Adding C, Nyberg T, Steineck G and Wiklund NP. Orgasm-associated urinary incontinence and sexual life after radical prostatectomy. J Sex Med 2011;8:2632-2639.
[34] Steinsvik EAS, Axcrona K, Dahl AA, Eri LM, Stensvold A, Fossa SD. Can sexual bother after radical prostatectomy be predicted preoperatively? Findings from a prospective national study of the relation between sexual function, activity and bother. BJU Int. 2012;109:1366-74
[35] Jain R, Mitchell S, Laze J, Lepor H. The effect of surgical intervention for stress urinary incontinence (UI) on post-prostatectomy UI during sexual activity. BJU Int. 2012;109:1208-12
[36] Lue TF. Erectile dysfunction. N Engl J Med, 2000 Jun 15;342(24) 1802-1813
[37] Blander DS, Broderick GA, Malkowicz SB, Van Arsdalen KN and Wein AJ. Retrospective review of flow patterns following retropubic prostatectomy. Int J Impot Res 1999;11:309-314.
[38] Mendiola FP, Zorn KC, Mikhail AA, Lin S, Orvieto MA, Zagaja GP et al. Urinary and sexual function outcomes among different age groups after robot-assisted laparoscopic prostatectomy. J of endourol 2008 ;22:519-524
[39] Patel VR, Coelho RF, Chauhan S, Orvieto MA, Palmer KJ, Rocco B et al. Continence, potency and oncological outcomes after robotic-assisted radical prostatectomy: early trifecta results of a high-volume surgeon. BJU Int 2010;106: 696-702
[40] Coughlin G, Pankaj D, Palmer KJ, Samavedi S, Patel V. Athermal early retrograde release of the neurovascular bundle during nerve-sparing robotic –assisted laparoscopic radical prostatectomy. J Robot Surg 2009;1:13-7

[41] Krambeck AE, DiMarco DS, Rangel L J et al Radical prostatectomy for prostatic adenocarcinoma: a matched comparison of open retropubic and robot-assisted techniques BJU Int 2008;103:448-53
[42] Chung JS, Kim WT, Ham WS, Yu HS, Chae Y, Chung SH. Comparison of oncological results , functional outcomes, and complications for transperitoneal versus extraperitoneal robot-assisted radical prostatectomy: a single surgeons experience. J Endourol. 2011 May;25(5):787-92.
[43] Ko WJ, Truesdale MD, Hruby GW, Landman J and Badani KK. Impacting factors for recovery of erectile function within 1 year following robotic-assisted laparoscopic radical prostatectomy. J Sex Med 2011;8:1805-1812.
[44] Gacci M, Carini M, Simonato A, Imbimbo C, Gontero P, Briganti A, De Cobelli O, et al. Factors predicting continence recovery 1 month after radical prostatectomy: results of a multicenter survey. Int J Urol. 2011 Oct;18(10):700-8
[45] Gandaglia G, Suardi N, Gallina A, Capitanio U, Abdollah F, Salonia A, Nava L, et al. Preoperative erectile function represents a significant predictor of postoperative urinary continence recovery in patients treated with bilateral nerve sparing racidal prostatectomy. 2012 J Urol;187(2):569-74
[46] Pick DL, Osann K, Skarecky D, Narula N, Finley DS, Ahlering TE. The impact of cavernosal nerve preservation on continence after robotic radical prostatectomy. BJU Int 2011; 108:1492-1496
[47] Rocco F, Carmignani L, Acquati et al . Restoration of posterior aspect of rhabdosphincter shortens continence time after radical retropubic prostatectomy. J Urol 2006;175:2201-6
[48] Patel VR, Coelho RF, Palmer KJ, Rocco B. Periurethral suspension stitch during robotic-assisted laparoscopic radical prostatectomy. Description of the technique and continence outcomes. Eur Urol 2009;56:472-8
[49] Tewari A, Jhaveri J, Rao S et al . Total reconstruction of the vesico-urethral junction. BJU In4t 2008;101:871-7
[50] Menon M, Muhletaler F, Campos M, Peabody JO. Assessment of early continence after reconstruction of the periprostatic tissues in patients undergoing computer assisted (robotic) prostatectomy: results of a 2 group parallel randomized controlled trial. J Urol 2008;180:1018-23
[51] Joshi N, de Blok W, van Muilekom E, van der Poel H. Impact of posterior musculofascial reconstruction on early continence after robot-assisted laparoscopic radical prostatectomy: results of a prospective parallel group trial. Eur Urol 2012;58(1):84-9
[52] van Kampen M, Geraerts I, de Weerdt W, Van Poppel H. An easy prediction of urinary incontinence duration after retropubic radical prostatectomy based on urine loss the first day after catheter withdrawal. J Urol 2009;181:264-6
[53] Ates M, Teber D, Gozen AS, Tefekli A, Hruza M, Sugiono M, Erdogan S, Rassweiler L. A new postoperative predictor of time to urinary continence after laparoscopic radical prostatectomy: the urine loss ratio. Eur Urol 2007;52:178-85
[54] John H, Sullivan MP, Bangerter U, Hauri D and Yalla SV. Effect of radical prostatectomy on sensory threshold and pressure transmission. J Urol 2000; 163(6): 1761-6
[55] Majoros A, Bach D, Keszthelyi A, Hamvas A, Romics I. Urinary incontinence and voiding dysfunction after radical retropubic prostatectomy (prospective urodynamic study) Neurourol Urodyn 2006; 25:2-7
[56] Centemero A, Rigatti L, Giraudo D, Lazzeri M, Lughezzani G, Zugna D, Montorsi F, Rigatti P,et al. Preoperative pelvic floor muscle exercise for early continence after radical prostatectomy: a randomized controlled study. Eur Urol 2010: 57;1039-1044
[57] Burgio KL, Goode PS, Urban DA, Umlauf MG, Locher JL. Preoperative biofeedback assisted behavioral training to decrease post-prostatectomy incontinence: a randomized controlled trial. J Urol 2006;175:196-201.

Summary

One of the curative treatment options of prostate cancer in men with a life expectancy of more than 10 years is radical retropubic prostatectomy. Under general anesthesia, a midline incision is made in the lower part of the abdomen. The prostate together with the seminal vesicles will be removed. The urethra is re-attached to the bladder by sutures. This procedure has some unwanted side effects / complications. The two main complications include impotence (the loss of erections) and urinary incontinence (leakage). These complications can have major consequences for the quality of life of the patient. This thesis aims to analyse the aetiology and prognostic factors for the complications of RRP mentioned above **(Chapter 1)**. It also aims to analyze the impact of a RRP on other domains of sexual function (including orgasm), on the bladder function and the urethral sphincter function. Furthermore, this thesis looks at the usefulness of pelvic floor muscle exercises in the recovery of continence and examines methods for measuring the urethral sphincter function that can be used as a preoperative diagnostic tool in predicting the probability of PRPI. **Chapter 2** describes the anatomy, nerve supply and vascularisation of the various components of the urethra and describes the male sexual response cycle. This chapter was written for a better understanding of the next chapters. **Chapter 3** shows the sexual function after radical prostatectomy and focuses on factors that can ensure a successful outcome. It shows the potency rates after radical prostatectomy found in the literature. Studies that described outcomes before and after surgery were compared. There was a major difference between the outcome in selected centers and a general hospital. In centers where many operations were performed results were better. In literature there is a wide range of potency rates. After a bilateral nerve sparing operation potency rates vary between 31% and 86%. After unilateral nerve-sparing procedure potency rates vary between 13% and 56%. Age of the patient, sparing of the neurovascular bundle, and sexual function before the operation were factors that potentially affect a positive outcome after surgery. However, despite these prognostic factors, a certain proportion of patients is still impotent after surgery. Both neurogenic and vascular factors seem to play a role in the development of impotence after radical prostatectomy.

Chapter 4 analyzed penile hemodynamic changes after RRP in 48 patients. Colour

Doppler ultrasound was performed to evaluate the vascularisation of the penis before and 3 months after surgery. Besides visual erotic stimulation of the penis, an intracavernous injection with papaverine / phentolamine, an agent which can induce an erection was given. Furthermore, psychosexual changes due to the operation were analyzed by questionnaires. The questionnaires were completed by the patients before, 3 months and 5 years after surgery. There were no structural vascular changes observed after surgery. Due to these findings the idea that vascular changes are an important part in the onset of impotence following RRP is less likely. The outcome of the questionnaires showed that after surgery there is a significant decrease in the erectile function, coitus satisfaction, orgasmic function and sexual desire. However over the years (according to the 5 years follow-up) an improvement in the orgasm function was seen, particularly in patients who had had a bilateral nervesparing procedure.

Chapter 5 continues the discussion on sexual function after radical prostatectomy, with the focus on orgasmic function. In the literature, little is known about the orgasmic function after RRP, while other data indicate that orgasm is an important part of sexual function. A database analysis was performed collecting data from 1021 patients. Patients were interviewed before and after RRP for two years. The questions were related to sexual interest, sexual activity, the occurrence of spontaneous erections and orgasmic function. In addition, factors potentially influencing orgasmic function, such as patient age, type of operation, pathological stage and continence status were analysed for their predictive value.

Interestingly, after the RRP sexual interest in almost all patients remained intact. In contrast, the number of men who were sexually active decreased from 82% to 67%. Spontaneous erections were present in 30% of men (before surgery this perentage was 90%). The number of men who have a normal orgasm decreased from 90% to 67%. Men who had had a non-nerve sparing procedure, who were older than 60 years, or who suffered from severe incontinence were at greatest risk of losing orgasmic function. So it is striking that despite the loss of erections in most patients, the orgasm function in the majority of men continue to exist. This is an important positive finding to make clear to the patient when discussing the complications of RRP.

The second part of the thesis dealt with the complication that has probably the greatest impact on quality of life: incontinence. **Chapter 6** shows the results of a prospective study analysing the impact of intensive physiotherapy in the resolution of urinary

incontinence after RRP. In addition, potential prognostic factors were analyzed. Patients were randomized into 2 groups. The first group of patients (n = 36) received an instruction folder with pelvic floor muscle exercises. The second group of patients (n = 34) received the same folder as the first group and were also supported by a specialist pelvic floor physiotherapist (intensive pelvic floor physiotherapy). Intensive pelvic floor muscle exercises showed no additional effect on the continence status 6 months after RRP. It should be noted that the sample size was not reached. Subsequent studies from other institutions have confirmed our findings. In the multivariate analysis, the amount of urine 1 week after removing the bladder catheter was a prognostic factor for the persistence of incontinence. The cause of the incontinence is likely to be found in bladder or sphincter. The contribution of sphincter-related factors in the development of urinary incontinence after RRP seems to be greatest.

Chapter 7 describes the changes in bladder function after RRP. This study is part of the aforementioned prospective study. Therefore it was also possible to analyse the effect of intensive pelvic floor muscle exercises on bladder function. Urodynamic investigation was used to analyse bladder function. The maximum flow rate of the urine (Q_{max}) increased significantly, the bladder pressure required for this flow ($p_{detQmax}$) and the urethral resistance factor (URA) decreased significantly after RRP within the total group of patients. Men who were incontinent 6 months after RRP had significantly more detrusor overactivity before surgery. Postoperative Q_{max} was significantly higher and the URA significantly lower in patients receiving physiotherapist guided PFME. Intensive PFME might reduce bladder outflow resistance.

Although in the univariate analysis, preoperative detrusor overactivity was a factor with an increased risk of persistence of incontinence, in multivariate analysis no prognostic factor for persistence of incontinence was found. Therefore, standard preoperative urodynamic studies seem to play no role as a preoperative predictor of post-radical prostatectomy incontinence in patients with localized prostate cancer.

Chapter 8 focuses on the urethral sphincter function, another possible cause of post radical prostatectomy incontinence. Urethral pressure profilometry was used to analyse sphincter function. The functional profile length of the sphincter and the maximum urethral closing pressure can be calculated here. In addition, the effect of intensive physiotherapy on the urethral sphincter function was analyzed. Data from 66 patients were available. After surgery, the sphincter length decreased by 64% and the maximum urethral closing pressure (MUCP) by 41%. Men who were

continent after 6 months tended to have a significantly higher value of MUCP before surgery. A low preoperative MUCP value seems to be a major factor in persistence of urinary incontinence after RRP. A non-nerve sparing procedure was a prognostic factor for a greater relative decrease in MUCP, which in turn has a negative effect on the sphincter function. Intensive physiotherapy had no additional effect on urethral sphincter function. The urethral sphincter function seems to be the most important factor of post-radical prostatectomy incontinence. There are several different ways to analyse the urethral sphincter function. **Chapter 9** summarizes the various methods used to study the urethral sphincter function. All available methods were examined whether they could serve as a preoperative diagnostic tool in predicting the risk of PRPI. The methods for the assessment of urethral sphincter function were sphincter electromyography, magnetic resonance imaging, perfusion sphincterometry and urethral pressure profilometry (UPP). MRI and urethral pressure profilometry seems to be valuable preoperative diagnostic tools in patients waiting for RRP. However, more and larger prospective studies are needed to show the exact role of MRI and UPP in the preoperative management of patients waiting for RRP and for whom postoperative incontinence is a big concern.

In the last part of the thesis **(Chapter 10)**, the previous chapters are discussed and a comparison with the results from the contemporary practice based on newer techniques is made. Furthermore, practical implications based on the conclusions of the thesis are given.

Despite new techniques like the laparoscopic radical prostatectomy (LRP) and the robot assisted radical prostatectomy (RALP) functional outcomes after a follow-up of 1 year seems to be similar for all techniques. Some studies suggest that patients who are operated on by RALP have a quicker recovery of continence and potency compared to patients who are operated with the other techniques. However, meta-analyses show that the available data were insufficient to prove superiority of any surgical approach. Just like potency outcomes, results of other sexual domains (eg orgasm) do not changed over the years. In the contemporary literature, there is an increasing attention for the sexual function in a broader sense and for the psychological effects of sexual dysfunction.

The aetiology of sexual dysfunction and incontinence after RRP seems to be mainly neurogenic. Furthermore, the urethral sphincter function plays an important role in the onset of incontinence. Age, the length of the membranous urethra, the maximum

urethral closure pressure and surgical technique (sparing the neurovascular bundle) seem to be the main factors that affect the functional outcomes. The amount of urine loss after removing of the catheter seems to be a measure of the severity of incontinence in the postoperative phase. Both the endorectal MRI and the urethra pressure profile measurement can have a role in the pre-operative counseling of the patient. This can make the patient better informed about expected developments in continence recovery. As regards the impotence there seems to be a role for postoperative rehabilitation programs to improve the quality of life.

Samenvatting in het Nederlands

Een van de curatieve behandelingen van prostaatkanker voor mannen met een levensverwachting van tenminste 10 jaar is de radicale retropubische prostatectomie. Hierbij wordt onder algehele narcose een snede in de onderbuik gemaakt en de prostaat samen met de zaadblaasjes verwijderd. De urethra (plasbuis) wordt vervolgens middels hechtingen weer aan de blaas vastgemaakt. Door deze ingreep kunnen een aantal ongewenste neven effecten / complicaties optreden. De twee belangrijkste complicaties zijn impotentie (het wegvallen van de erecties) en urine incontinentie (urineverlies). Deze complicaties kunnen grote gevolgen hebben voor de kwaliteit van leven van de patiënt. Dit proefschrift heeft tot doel oorzaken en prognostische factoren voor de bovengenoemde complicaties van een RRP te onderzoeken **(Hoofdstuk 1)**. Een ander doel is analyseren van de impact van een RRP op andere domeinen van de seksuele functie (waaronder het orgasme), op de blaasfunctie en op de urethrale sfincter functie. Verder richt dit proefschrift zich op het nut van bekkenfysiotherapie bij het herstel van de continentie en onderzoekt het of er meetmethoden zijn voor de urethrale sfincter functie die gebruikt kunnen worden als een preoperatief diagnostisch hulpmiddel in het voorspellen van de kans op post radicale prostatectomie incontinentie (PRPI). **Hoofdstuk 2** beschrijft de anatomie, zenuwvoorziening en vascularisatie van de urethra en gaat in op de seksuele respons cyclus van de man. Dit hoofdstuk werd geschreven voor een beter begrip van de hierop volgende hoofdstukken.

Hoofdstuk 3 beschrijft de seksuele functie voor en na open radicale prostatectomie waarbij het focus ligt op het vinden van factoren die kunnen zorgen voor een succesvolle uitkomst. Het toont de potentie cijfers na radicale prostatectomie die in de literatuur gevonden worden. Studies die zowel voor als na de operatie potentie cijfers konden weergeven werden met elkaar vergeleken. Er was een duidelijk verschil zichtbaar tussen de grote centra en de kleinere algemene klinieken. In centra waar veel operaties werden verricht waren de uitkomsten beter. In de literatuur tot 2006 wordt een brede spreiding van uitkomsten van potentie percentage gezien. Na bilaterale zenuwsparende operatie ligt het percentage mannen dat potent is tussen 31% en 86%. Na unilaterale zenuwsparende benadering ligt dit percentage tussen 13% en 56%. Leeftijd van de patiënt, sparen van de neurovasculaire bundel, en

seksuele functie voor de operatie waren factoren die de potentie uitkomsten na de operatie positief beïnvloeden. Echter ondanks deze prognostische factoren zal een deel van de patiënten toch impotent worden na de operatie. Zowel neurogene als vasculaire factoren lijken een rol te spelen in het ontstaan van de potentie stoornissen na radicale prostatectomie. In **hoofdstuk 4** worden hemodynamische veranderingen in de penis tgv de RRP bestudeerd bij 48 patiënten. Door middel van Colour Doppler echografie werd de vascularisatie van de penis voor en 3 maanden na operatie onderzocht. Naast visuele erotische stimulatie werd de penis ook geïnjecteerd met papaverine/phentolamine, een middel wat een erectie kan opwekken. Verder werd aan de hand van vragenlijsten gekeken naar de psycho-seksuele veranderingen door de operatie. De vragenlijsten werden preoperatief, 3 maanden na en 5 jaar na operatie door de patiënten ingevuld. Er werden geen structurele vasculaire veranderingen waargenomen na operatie. Hiermee wordt het idee dat vasculaire veranderingen een belangrijk deel vormen in het ontstaan van impotentie na RRP minder waarschijnlijk. Uit de vragenlijsten kwam naar voren dat er na de operatie een significante afname was van de erectiele functie, coïtus tevredenheid, orgasme functie en seksueel verlangen. Echter in de loop van de jaren, aan de hand van de 5 jaars follow-up, was wel een verbetering te zien van met name de orgasme functie, in het bijzonder bij patiënten die bilateraal zenuwsparend waren geopereerd.

Hoofdstuk 5 gaat verder in op de seksuele functie na radicale prostatectomie, waarbij het focus ligt bij de orgasme functie. In de literatuur is weinig bekend over de orgasme functie na RRP, terwijl uit andere gegevens blijkt dat orgasme functie toch een belangrijk onderdeel is van de seksuele functie. Er werd een database analyse verricht waarbij gegevens van 1021 patiënten werden verzameld. Patiënten werden voor en na RRP geïnterviewd gedurende twee jaar. De vragen hadden betrekking op de seksuele interesse, seksuele activiteit, het voorkomen van spontane erecties en de orgasme functie. Daarnaast werd gekeken naar factoren die mogelijk invloed konden hebben op de uitkomsten als: leeftijd van patiënt, operatie techniek, pathologisch stadium van de tumor en continentie status. Opvallend was dat na de RRP de seksuele interesse bij bijna alle patiënten intact bleef. Daarentegen was het aantal mannen dat nog daadwerkelijk seksueel actief was gedaald van 82% naar 67%. Spontane erecties kwamen nog voor bij 30% van de mannen (dit was voor de operatie nog aanwezig bij 90% van de mannen). Het aantal mannen dat nog een normaal orgasme kon krijgen daalde van 90% naar 67%. Mannen die niet zenuwsparend werden geopereerd, die

ouder waren dan 60 jaar of die last hadden van ernstige incontinentie liepen het grootste risico om de orgasme functie te verliezen. Opvallend is dus wel dat ondanks het wegvallen van de erecties in de meeste patiënten, de orgasme functie in het merendeel van de mannen blijft bestaan. Dit is een belangrijke positieve bevinding om kenbaar te maken aan de patiënt bij het bespreken van de complicaties van een RRP.

Het tweede deel van het boekje behandeld de complicatie die waarschijnlijk de grootste impact heeft op de kwaliteit van leven, namelijk urine incontinentie. In **hoofdstuk 6** wordt in een prospectieve studie gekeken naar het effect van intensieve fysiotherapie bij het herstel van urine incontinentie na RRP. Daarnaast werden potentiële prognostische factoren onderzocht. Patiënten werden volgens het principe van randomisatie ondergebracht in 2 groepen. De eerste groep patiënten (n=36) ontvingen een folder waarin bekkenbodem spieroefeningen stonden beschreven. De tweede groep patiënten (n=34) ontvingen ook de folder maar werden daarnaast ondersteund door een gespecialiseerde bekkenfysiotherapeut (intensieve bekkenfysiotherapie). Intensieve bekkenfysiotherapie bleek geen extra effect te hebben op het verkrijgen van continentie 6 maanden na RRP. Er dient vermeld te worden dat het benodigd aantal patiënten niet werd gehaald. Studies van andere instelling hebben onze bevindingen bevestigd. Bij de multivariate analyse bleek de hoeveelheid urineverlies 1 week na verwijderen van de blaas katheter een prognostische factor voor het persisteren van de incontinentie. De oorzaak van het urineverlies is waarschijnlijk te vinden op blaas of sfincter nivo. Sfincter gerelateerde factoren lijken de grootste bijdrage leveren aan het ontstaan van urine-incontinentie na RRP. **Hoofdstuk 7** beschrijft de veranderingen van de blaasfunctie na RRP. Deze studie vormt een onderdeel van de hierboven genoemde prospectieve studie. Daardoor was het ook mogelijk het effect van intensieve bekkenfysiotherapie op de blaasfunctie te bestuderen. Voor de analyse van de blaasfunctie werd een urodynamisch onderzoek verricht. De maximale straal van de urine (Q_{max}) nam significant toe, de blaasdruk nodig voor deze straal ($p_{detQmax}$) en de urethrale weerstand factor (URA) namen significant af na RRP binnen de totale groep patiënten. Mannen die incontinent bleven 6 maanden na RRP hadden significant meer overactiviteit van de blaas voorafgaande aan de operatie. Postoperatief was de Q_{max} significant hoger en de URA significant lager bij de patiënten die in de groep zaten met de intensieve FT behandeling. Meer intensieve bekkenbodem spieroefeningen zouden de blaas uitgang weerstand mogelijk kunnen

verminderen. Hoewel in de univariate analyse, preoperatieve overactiviteit van de blaas een factor was met een verhoogd risico op het persisteren van de incontinentie, werd in de multivariate analyse geen prognostische factor voor het persisteren van incontinentie na RRP gevonden. Standaard preoperatief urodynamisch onderzoek lijkt geen rol te spelen als preoperatieve voorspeller van post radicale prostatectomie incontinentie in patiënten met gelokaliseerd prostaatkanker.

In **hoofdstuk 8** wordt een andere mogelijke veroorzaker van de urine incontinentie belicht, namelijk de urethrale sfincter functie. Het urethra drukprofiel werd gebruikt bij de analyse van de sfincter functie. De sfincter lengte en de maximale sluitings druk kan hierbij worden berekend. Daarnaast werd ook het effect van intensieve fysiotherapie op de urethrale sfincter functie nader bekeken. Gegevens van 66 patiënten waren beschikbaar voor analyse. Na de operatie was de sfincter lengte met 64% en de maximale urethrale sluitdruk (MUCP) met 41% afgenomen. Mannen die na 6 maanden continent waren hadden een significant hogere MUCP waarde voorafgaande aan de operatie. Een lage preoperatieve MUCP waarde lijkt een belangrijke factor voor het persisteren van de incontinentie na RRP. Een niet-zenuw sparende operatie was een prognostische factor voor een grotere relatieve afname van de MUCP, wat weer een negatief effect heeft op de sfincter functie. Intensieve fysiotherapie had geen aanvullend effect op de urethrale sfincter functie. De urethrale sfincter functie lijkt de meest belangrijke factor van post radicale prostatectomie incontinentie te zijn.

Het analyseren van de urethrale sfincter functie kan op vele manieren. **Hoofdstuk 9** geeft een overzicht van de verschillende meetmethoden die gebruikt zijn om de urethrale sfincter functie te bestuderen. Van al deze meetmethoden is vervolgens bekeken of zij kunnen dienen als een preoperatief diagnostisch hulpmiddel in het voorspellen van de kans op PRPI. Optionele metingen voor urethrale sluitspier functie waren sluitspier elektromyografie, magnetische resonantie beeldvorming (MRI), perfusie sfincterometrie en urethrale druk profilometrie (UPP). MRI en urethrale druk profilometrie lijken waardevolle preoperatieve diagnostische hulpmiddelen te zijn bij patiënten die wachten op RRP. Echter meer en grotere studies zijn nodig om inzicht te krijgen in de exacte rol van MRI en UPP als diagnostisch hulpmiddel in de therapiekeuze bij patiënten die in afwachting zijn van een RRP en voor wie postoperatieve incontinentie een groot probleem is. In het laatste deel van het proefschrift **(hoofdstuk 10)** worden de voorgaande hoofdstukken bediscussieerd en wordt een vergelijking getrokken met de resultaten uit de hedendaagse praktijk

gebaseerd op nieuwere technieken. Tevens komen praktische implicaties gebaseerd op de conclusies van het proefschrift aan de orde. Ondanks nieuwe technieken als de laparoscopische radicale prostatectomie (LRP) en de robot –geassisteerde radicale prostatectomie (RALP) lijken de functionele uitkomsten na een follow-up van 1 jaar voor alle technieken vergelijkbaar. Enkele RALP studies suggereren dat patiënten die geopereerd worden met de RALP een sneller herstel hebben van hun continentie en potentie ten opzichte van patiënten die door middel van de andere technieken worden geopereerd. Echter uit meta-analyses komt naar voren dat de beschikbare data onvoldoende van kwaliteit zijn om superioriteit van een van de chirurgische aanpakken te bewijzen. Net als de potentie uitkomsten zijn ook de uitkomsten van andere seksuele domeinen (bv het orgasme) in de loop van de jaren niet veranderd. Wel is zichtbaar in de literatuur dat hedendaags steeds meer aandacht komt voor de seksuele functie in bredere zin en voor de psychische effecten van seksuele disfunctie. De oorzaak voor het ontstaan van seksuele stoornissen en incontinentie lijkt met name neurogeen. Daarnaast speelt de urethrale sphincter functie een belangrijke rol bij het incontinentie probleem. Leeftijd, de lengte van de mebraneuze urethra, de maximale urethrale sluitings druk en operatie techniek (sparen van de neurovasculaire bundel) lijken de belangrijkste factoren die invloed hebben op de functionele uitkomsten. De hoeveelheid urine verlies na verwijderen van de katheter lijkt een maat voor de ernst van de incontinentie in de postoperatieve fase. Zowel de endorectale MRI als het urethradruk profiel kunnen een rol hebben in de preoperatieve counseling van de patiënt. Aan de hand hiervan kan de patiënt beter worden voorgelicht over het verwachte beloop van het continentie herstel. Wat betreft de impotentie lijkt er een rol weggelegd voor postoperatieve rehabilitatie programma's om zo de kwaliteit van leven te verbeteren.

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De manuscriptcommissie werd aangevuld met Prof.dr. H. van Poppel en Prof.dr. A.A.B. Lycklama à Nijeholt. Heel hartelijk dank voor het zitting nemen in de commissie.

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Curriculum vitae

Yvette Dubbelman is op 9 november 1971 te Dordrecht geboren. In juli 1991 behaalt zij haar VWO diploma aan de Guillaume Farel te Ridderkerk. Aansluitend volgt zij de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. Tijdens haar doctoraalfase wordt de interesse voor wetenschappelijk onderzoek gewekt. Een jaar lang doet zij onderzoek naar "de lange termijn gevolgen van totale lichaamsbestraling bij rhesusapen" op de afdeling hematologie aan de Erasmus Universiteit te Rotterdam. Daarnaast verricht zij onderzoek naar "de ervaringen van de hartklep bioprothesen" op de afdeling Thoraxchirurgie van het Academisch Ziekenhuis Rotterdam-Dijkzigt. De doctoraalfase van de studie geneeskunde wordt afgerond in maart 1995. In september 1997 behaalt zij cum laude haar artsdiploma. In datzelfde jaar ontvangt zij van het "Bataafsch Genootschap der Proefondervindelijke Wijsbegeerte" een studieprijs voor "beste medisch student 1997".

Hierna wordt zij arts-assistent geneeskunde niet in opleiding (AGNIO) op de afdeling urologie van het Academisch ziekenhuis Dijkzigt en start zij haar promotieonderzoek naar"Functionele complicaties na radicale prostatectomie", hetgeen uiteindelijk resulteert in dit proefschrift. In januari 2001 wordt zij aangenomen voor de opleiding urologie in Rotterdam. Deze opleiding begint voor haar in het Ikazia ziekenhuis te Rotterdam met de 2-jarige vooropleiding heelkunde.

De opleiding tot uroloog wordt vervolgd op de afdeling urologie van het toenmalig Academisch Ziekenhuis Rotterdam-Dijkzigt (opleiders: Prof.dr. J.L.H.R. Bosch en dr. G.R. Dohle) en daarna in het Sint Franciscus Gasthuis te Rotterdam (opleider: dr. J.H.M. Blom). Sinds maart 2007 is zij als lid van de maatschap urologie verbonden aan het Sint Elisabeth Ziekenhuis te Tilburg en het Tweesteden Ziekenhuis te Waalwijk.

Sinds mei 2003 is zij getrouwd met Michiel van den Haak. In augustus 2005 krijgen zij samen hun dochter Indy.

List of Publications

Neelis KJ, Dubbelman YD, Wognum AW, Thomas GR, Eaton DL, Egeland T, Wagemaker G. Lack of efficacy of thrombopoietin and granulocyte colony-stimulating factor after high dose total-body irradiation and autologous stem cell or bone marrow transplantation in rhesus monkeys. Exp Hematol 1997 Sep;25(10):1094-103.

Neelis KJ, Dubbelman YD, Qingliang L, Thomas GR, Eaton DL, Wagemaker G. Simultaneous administration of TPO and G-CSF after cytoreductive treatment of rhesus monkeys prevents thrombocytopenia, alleviates neutropenia, and promotes the recovery of immature bone marrow cells. Exp Hematol 1997 Sep;25(10):1084-93.

RB Hokken, LA van Herwerden, AJJC Bogers, N Verbaan, Y Dubbelman, TP Willems, E Bos. Twenty-five years aortic valve replacement in Rotterdam; choice of valve prostheses in a changing population. Cardiologie 1997;9:305-12.

YD Dubbelman, M Heeringa en FH Thung. Ernstige tardieve dyskinesieën tijdens behandeling met risperidon en fluoxetine. Ned Tijdschr Geneeskd 1998;26:1508-1511.

YD Dubbelman, RB Hokken, LA van Herwerden, N Verbaan, AJJC Bogers, EW Steyerberg en E Bos. "Aortaklepvervanging met bioprothesen: risicofactoren voor late mortaliteit en reoperatie". Cardiologie 1999;6:549-555.

Yvette D Dubbelman, Ries Kranse, Willeke Bolle, Annet Verkerk and Gerald H Mickisch. Results of radical prostatectomy for prostate cancer; a personal series. Hoofdstuk in het boek: Carcinoma of the prostate. (Schattauer, Stuttgart-New York)

Yvette D. Dubbelman, Gert R. Dohle, Frits H. Schröder. Sexual function before and after radical retropubic prostatectomy: A systematic review of prognostic indicators for a successful outcome. Eur Urol. 2006 Oct;50(4):711-8; discussion 718-20.

Yvette D. Dubbelman, Mark F. Wildhagen and Gert R. Dohle. Penile vascular evaluation and sexual function before and after radical retropubic prostatectomy: 5 year follow-up.
Int J Androl. 2007 Jul 25;

Dubbelman Y, Groen J, Wildhagen M, Rikken B, Bosch R. The recovery of urinary continence after radical retropubic prostatectomy: a randomized trial comparing the effect of physiotherapist-guided pelvic floor muscle exercises with guidance by an instruction folder only. BJU Int. 2010 Aug;106(4):515-22.

Dubbelman Y, Wildhagen M, Schröder F, Bangma C, Dohle G. Orgasmic dysfunction after open radical prostatectomy: clinical correlates and prognostic factors.
J Sex Med. 2010 Mar;7(3):1216-23.

Dubbelman YD, Groen J, Wildhagen MF, Rikken B, Bosch JL. Urodynamic quantification of decrease in sphincter function after radical prostatectomy: relation to postoperative continence status and the effect of intensive pelvic floor muscle exercises.
Neurourol Urodyn. 2012 Jun;31(5):646-51.

Dubbelman Y, Groen J, Wildhagen M, Rikken B, Bosch R. Quantification of changes in detrusor function and pressure-flow parameters after radical prostatectomy: relation to postoperative continence status and the impact of intensity of pelvic floor muscle exercises.
Neurourol Urodyn. 2012 Jun;31(5):637-41.

Dubbelman Y and Bosch R. Urethral sphincter function before and after radical prostatectomy; systematic review of the prognostic value of various assessment techniques. Accepted by Neurourol Urodyn 2012 Oct.