

**SEXUAL FUNCTIONING OF MALE PATIENTS IN
RADIOTHERAPY AND UROLOGY**

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SEXUAL FUNCTIONING OF MALE PATIENTS IN RADIOTHERAPY AND UROLOGY

HET SEKSUEEL FUNCTIONEREN VAN MANNELIJKE
PATIËNTEN IN RADIOTHERAPIE EN UROLOGIE

PROEFSCHRIFT

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In Memoriam

Dino Incrocci

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Chapter 1

Introduction

Introduction

In the differential diagnosis of men with erectile dysfunction (ED) it is important to know whether or not the male patient is potentially sexually potent, i.e. whether or not a (semi) rigid erection, presumably sufficient for intercourse, can occur (e.g.1). Preferably such information is gathered by a thorough history taking, and, if necessary, followed by non-invasive investigations. Penile erection is the result of a neurovascular response to a complex set of visual, tactile and psychogenic stimuli (2). It is thought to result from increased arterial flow through the cavernous vessels with subsequent sinusoidal engorgement and decreased venous return. Anatomic innervation is derived from both sympathetic and parasympathetic chains at the posterolateral surface of the prostate (2).

Several years ago, long before the introduction of sildenafil (Viagra®), we started to use visual sexual stimulation (VSS) and vibrotactile stimulation (VIB) (see Appendix), to be followed, at a later stage by intracavernosal injection (ICI) in routinely screening men with ED (3). It was thought to be necessary to differentiate between somatic and psychogenic ED; moreover, it was believed that the physiological responses had some therapeutic properties in itself (4). Nowadays we find it sufficient to take a good sexual history, preferably using a validated structured questionnaire. To that end we have developed a 15-item questionnaire regarding various aspects of sexual functioning over the past four weeks, adapted at the circumstances of different patient's categories. This questionnaire gives detailed information about patient's sexual (dys)functioning.

Loosing a testicle can result in a change of body image and difficulties in sexual functioning (e.g. 5,6,7). Patients should be counseled in sexual and intimate matters and the possibility to receive a testicular prosthesis should be offered. Cosmetic appearance after implantation is satisfactory, although not perfect. Unfortunately it seems that the possibility of having a testicular implant is not always routinely discussed with the patient, e.g. some time before the moment of castration for testicular cancer. We thought it worthwhile to study sexual functioning in a group of patients who had received a testis prosthesis.

External beam radiotherapy (ERT) for benign diseases is gaining its popularity in spite of the fear of secondary malignancies, but it still has its place in specific diseases. Peyronie's disease (PD) has been claimed to be successfully treated with ERT (8,9), but sexual functioning in patients with PD following ERT has never been thoroughly assessed.

We have undertaken such a study in 106 PD-patients treated with ERT in our hospital over the last 15 years.

Quality of Life in cancer patients has recently become very important (10,11). Current trials pay in general more attention to matters related to well-being and life expectations after cancer treatment (12). Unfortunately, sexual functioning is not always well investigated. There still seems to be difficulties in facing the subject of "sex" in cancer patients. Doctors are reluctant to discuss sexual matters and they are usually focussed on long survival. Patients are nowadays more aware of such matters and they are more keen to make their own choices among the various treatment modalities (13). Sexual dysfunction after radiation for prostate cancer is becoming a concern, even more so because of the increasing number of screening programs and prostate specific antigen testing, which results in a higher incidence of younger patients diagnosed with prostate cancer. It is still debatable whether early detection and treatment of prostate cancer by either radical surgery or radiation therapy will result in longer overall survival (14). It remains for a fact, however, that patients undergoing radical surgery are usually younger and with less comorbidity than patients undergoing ERT (15), therefore sexual functioning in patients undergoing surgery is often better than in patients receiving ERT.

The impact of the treatment (either surgery or radiotherapy) on potency can only be determined if a baseline, pretreatment assessment of erectile function is included (16). It has been suggested that high percentages (up to 60%) of the patients may be impotent already before radiation treatment (17). Therefore, there is a need of baseline, pretreatment data. This prompted us to study sexuality in a group of prostate cancer patients awaiting treatment.

Many papers have been published dealing with ED after radiation for prostate cancer, with an enormous variety in the methodology used for ED evaluation. Different definitions of potency/impotence have been used; moreover, time of ED evaluation since treatment is often not indicated. Because of these differences and the great variability in the literature there is a need of an up to-date overview to critically analyze the -sometimes contrasting- findings in the literature regarding sexual functioning after radiation therapy for prostate cancer. Thus, in the final chapter of this thesis a review of the existing literature on sexuality following radiation therapy for prostate cancer is presented.

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Chapter 2

Visual erotic and vibrotactile stimulation and intracavernous injection in screening men with erectile dysfunction: a 3 year experience with 406 cases

L. Incrocci, W.C.J. Hop and A.K. Slob

Int J Impotence Res 1996;8:227-232

Visual erotic and vibrotactile stimulation and intracavernous injection in screening men with erectile dysfunction: a 3 year experience with 406 cases

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To establish the number of patients with erectile dysfunction (ED) who appear to be sexually potent when exposed to visual erotic (VES) and vibrotactile stimulation (VIB) and to investigate whether or not older patients are less responsive to VES/VIB than young patients.

Retrospective analysis of data on 406 consecutive patients screened for ED with VES, VES + VIB, VES + Intracavernous injection (ICI).

Partial or full erection was obtained in 34% of patients with VES, 52% with VES + VIB, 82% with VES + ICI. Men < 40 y (n = 86) responded better than men > 40; between 40 and 80 no differences in penile responses were found. 50% of patients who reported no morning/night erections appeared to have good, rigid nocturnal penile tumescence (NPT).

The use of VES, VES + VIB, VES + ICI is strongly recommended in the screening of men with ED of all ages; up to 80% will respond with a good erection. Only a positive penile response has diagnostic significance. The positive results reduce the necessity for further invasive investigations.

Keywords: erectile dysfunction; visual erotic stimulation; vibrotactile penile stimulation; intracavernous injection; impotence

Introduction

In screening patients with erectile dysfunction (ED) it is important to know whether or not the man is potentially sexually potent. Preferably such information is gathered through a thorough history taking followed by non-invasive investigations. Since 1988 we have routinely exposed our patients with ED to visual erotic stimulation (VES) while penile circumference and rigidity were measured with an erectometer.¹ The latter device was also used for nocturnal penile tumescence (NPT) measurements when patients were asked to sleep with an erectometer around the base of the penis for four consecutive nights.¹ Over the years we optimized our VES methodology with concomitant vibrotactile stimulation (VIB) to the underside of the top of the penis.²⁻⁴ When poor or no penile response was obtained following VES and VES + VIB, an intracavernous injection (ICI) with a vaso-active drug was given,⁵ followed by VES.⁶⁻⁸ It should be kept in mind that only a positive penile response to VES or VES + VIB has diagnostic and possibly therapeutic significance.^{1,9}

We thought it worthwhile to retrospectively study the data on all patients who visited our psychophysiology laboratory in the years 1991-1993; we reported earlier on patients in the preceding years 1988-1990.^{9,10} One of the main questions in the present study was how many of these men with ED were sexually responsive in the laboratory. In other words, is it worthwhile to carry out this rather time consuming investigation in differential diagnosis of men with ED? To what extent is age a significant factor in the sexual response? The latter question was posed because Buvat and co-workers¹¹ had indicated that VES seemed useless over the age of 50, even when it was combined with a low dose ICI with a vasoactive agent. In the late eighties the ICI with a vasoactive substance became popular in the process of differential diagnosis of ED.¹²⁻¹⁴ Quite recently the combinations of VES and ICI was advocated.^{6,15} A final question dealt with the

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proportion of psychogenic vs somatogenic origin of the ED in our patients.

Materials and methods

This paper reports retrospectively on filed data of 406 consecutive patients with ED who visited our outpatient urology clinic and psychophysiological laboratory in the years 1991 through 1993, for differential diagnosis of their problems. Erectile dysfunction can be defined as 'inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance'.¹⁶ All patients were routinely evaluated for relevant hormones and underwent a physical examination by the urologist; in these years echocolor/doppler studies were not routinely carried out. Subjects were orally interviewed regarding their personal, medical and sexual history, as well as their sexual functioning and problems. They were also asked to fill out a number of forms soliciting detailed information on current sexual functioning. Questionnaires had been used earlier and had appeared to give satisfactory information.¹

When past history revealed that patients did not experience morning/night erections they were asked to sleep for four consecutive nights with an erectometer: two nights with a yellow (requires approximately 250 gr expansion force), two nights with a green erectometer (requires about 450 gr expansion force). It should be emphasized that the erectometer measures increase in *penile circumference* as well as *rigidity*.¹ Patients were instructed how to use the erectometers and how to register the increments. A pre-paid envelope was used to mail erectometers and data to the investigators. The use of the erectometer is not a standard practice internationally, although in our clinic and some other Dutch clinics it has been used for many years.

In the psychophysiology laboratory virtually all patients were exposed to an erotic video (VES; duration approximately 10 min), while penile response (that is mm increase in circumference) was measured with a yellow erectometer. Subjective sexual and genital arousal was filled out on a questionnaire after the VES. Depending on the sexual orientation of the patient heterosexual or homosexual erotic videos were used.

Our VES methodology was improved by administering concomitant Vibrotactile stimulation (VIB) to the underside of the tip of the penis.^{7,27} The minivibrator, attached to a yellow erectometer, weighing approximately 20 g, generates vertical and lateral displacement. The output frequency is adjustable from 10–60 Hz and the surface area of stimulation is approximately 270 mm.^{2,3} When the use of VIB became a routine procedure, this meant that patients were exposed to VES twice (two

different videos), once without and once with VIB. This was done because patients virtually never responded with a full, rigid erection with VES alone.

In our patients, when no response occurred, VES (a third erotic video) was combined with an ICI of papaverine sulfate (other vasoactive substances were not used in those years). The median dose administered was 50 mg (mean 52.2 ± 18.7 s.d.). A lower dose (between 15 and 50 mg) was given when the patient had earlier responded positively to papaverine in the outpatient clinic, and higher doses (between 50 and 100 mg) when the patient had not responded earlier.

Because the data were not normally distributed, and no suitable transformation of data approximated a normal distribution, non-parametric statistics were applied, namely Kruskal-Wallis test or Mann-Whitney test for comparisons between groups and Wilcoxon's test for comparisons within groups. Correlation coefficients given are Spearman's (r_s). The level of significance was set at $P = 0.05$ (2 tailed).

Results

Social, medical and other parameters

Mean age of the 406 patients was 50.6 ± 12.5 s.d. (median 52; range 19–81). Ethnic background was 64% ($n = 258$) Dutch white, 11% from Surinam roots ($n = 43$), 22% from Turkish, Moroccan and other nationalities ($n = 91$), 3% unknown. The vast majority of men indicated a heterosexual orientation (96%, $n = 389$), 3% were homo or bisexual ($n = 12$). About one-third of the patients ($n = 135$) were on medication known to possibly affect sexual functioning, namely antihypertensives, antidepressants and major tranquillizers. Only 15% ($n = 61$) had undergone some surgery that could be associated with erectile difficulties, namely prostatectomy and heart or major vascular surgery. Approximately one-third ($n = 141$; 35%) had a chronic disease assumed to be associated with erectile dysfunction. The most prevalent diseases were diabetes mellitus ($n = 57$, including those with hypertension), and hypertension only ($n = 38$). There were 129 (32%) men who smoked an average of 13 cigarettes per day (range 1–50 day), 160 (39%) did not smoke, and of 117 it was unknown. A total of 264 men consumed alcoholic beverages, with a mean of 1.3 glasses/day (range 0.5–10 day), 87 (21.4%) abstained from alcohol, while for 55 (13.5%) it remained unknown.

Sexual activities

In Table 1 mean frequencies per month of various sexual activities are depicted: morning/night erec-

Table 1 Sexual activities (frequencies per month; mean \pm s.d.) and sexual difficulties (7 point semantic scale 1 = always, 4 = about 50% of the time, 7 = never; only extremes 1 and 2; 6 and 7 are presented) as reported by the 406 patients

Sexual activities	N	Median	Mean \pm s.d.	Sexual difficulties	Often (1 \pm 2)	Seldom (6 \pm 7)
Morning/night erections	350	2	7.7 \pm 10.5	Problems with achieving an erection	49% (n = 153)	24% (n = 76)
Spontaneous daytime erections	338	0	1.9 \pm 5.6	Problems with maintaining erections	78% (n = 245)	7% (n = 23)
Sexual activity with partner	351	2	3.9 \pm 4.9	Premature ejaculation	32% (n = 99)	58% (n = 178)
Masturbation	363	0	2.2 \pm 5.4	Inability to ejaculate	11% (n = 31)	55% (n = 166)
Erotic dream	333	0	0.5 \pm 1.4	Fear of failure	47% (n = 144)	35% (n = 106)

Table 2 Patients with erectile difficulties. Age and objective penile response (mm increase in circumference) following visual erotic stimulation (VES), VES combined with vibrotactile stimulation (VIB), and following VES combined with intracavernous injection (ICI) with the vasoactive drug papaverine. Values are means \pm s.d. and medians

Age (yrs)	VES			VES + VIB			VES + ICI		
	n	Mean \pm s.d.	Median	n	Mean \pm s.d.	Median	n	Mean \pm s.d.	Median
≤ 40	86	12.8 \pm 12.1	9.5	31	15.5 \pm 14.0	12.0	7	24.1 \pm 11.9	31.0
41–60	226	7.0 \pm 8.7	4.0	96	7.6 \pm 9.1	4.0	44	19.7 \pm 8.1	22.0
61 \geq	77	7.2 \pm 9.2	4.0	38	7.4 \pm 8.8	2.5	15	20.5 \pm 11.1	21.0
Total	389*	8.4 \pm 9.9	4.0	165	9.0 \pm 10.6	4.0	66	20.3 \pm 9.2	21.5

* From 17 patients (406–389) thorough history taking revealed adequate penile responses, which made further psychophysiological investigation not necessary.

tions (median 2, range 0–60), spontaneous daytime erections (median 0, range 0–60), sexual activity with a partner (median 2, range 0–28), masturbation (median 0, range 0–60) and erotic dreams (median 0, range 0–8).

Sexual difficulties can also be seen in Table 1. About half of the patients had severe problems with achieving an erection sufficient for intercourse, and almost 80% reported severe difficulties in maintaining their erection. About one-third of all patients suffered (also) from 'premature ejaculation' (PE), and approximately 10% of patients reported severe difficulties or inability to ejaculate. It should be noted that many of the patients with ED also experience PE, not the classical form where they lack control, but they intentionally come relatively fast because otherwise they fear to lose their erection before orgasm/ejaculation. About half of the patients experienced fear of failure with sexual activity.

Age

Patients were grouped according to age into three categories: young (under 40 y of age), middle (between 40 and 60), and older (61 and older) (see Table 2). The penile response data (mm increase in circumference) subjected to Kruskal–Wallis test revealed an overall significant difference between age groups for VES ($P=0.001$) and VES + VIB ($P=0.026$), but not for VES + ICI ($P=0.56$). Subsequent pairwise analyses with the Whitney test revealed that penile response data of the middle

and older men never differed significantly, whereas the younger men differed from both other groups with VES ($P < 0.01$) and with VES + VIB ($P < 0.025$).

VES combined with VIB or ICI

The mean penile response was highest with VES + ICI (20.3 mm increase in circumference), followed by VES + VIB (9.0 mm) and VES alone (8.4 mm). The 160 patients who were exposed both to VES and VES + VIB showed a significantly greater penile response (Wilcoxon, $P < 0.001$) to VES + VIB (9.1 mm \pm 10.7 s.d.) than to VES alone (5.5 mm \pm 7.6 s.d.) and VES + ICI (20.6 mm \pm 9.3 s.d.; Wilcoxon $P < 0.001$). Of the 12 patients who were exposed to all three conditions it appeared that VES + ICI was most effective (21.8 mm \pm 10.2 s.d.) in causing a penile response than VES (4.7 mm \pm 4.5 s.d.) or VES + VIB (4.8 mm \pm 5.2 s.d.).

Subjective sexual responses

Subjective sexual responses to VES, VES with VIB and VES with ICI, are presented in Table 3. For sexual arousal it is obvious that the number of male patients that respond strongly increases from 46% with VES, to 61% with VES + VIB and 73% with VES + ICI. Similar results, somewhat more outspoken, were found for the strongest subjective penile response: 34% with VES, 52% with VES + VIB, and 82% with VES + ICI. For both parameters a reciprocal picture emerges for the percentages of patients

Table 3 Patients with erectile difficulties (number and percentages). Sexual arousal, subjective penile response (1 and 2: no response; 5, 6, 7: partial-full erection/ejac), and patient's estimated degree of erection (0–100%) following visual erotic stimulation (VES), VES combined with vibrotactile stimulation (VIB), and following VES combined with intracavernous injection (ICI) with papaverine

Item	Ves			VES + VIB			VES + ICI		
	No response	Strong response	Total	No response	Strong response	Total	No response	Strong response	Total
Sexual arousal (1–7)	63 (17%)	168 (46%)	(362)	20 (13%)	96 (61%)	(156)	3 (5%)	45 (73%)	(62)
Penile response (1–7)	128 (31%)	138 (34%)	(380)	30 (19%)	84 (52%)	(163)	4 (7%)	54 (82%)	(65)
Penile response (0–100%)	Mean: 30.7 ± 28.6 Median: 24.0 n = 295			Mean: 41.9 ± 30.9 Median 35.0 n = 144			Mean: 67.2 ± 26.4 Median 68.0 n = 61		

Table 4 Nocturnal penile tumescence (NPT) data of patients who do not report morning/night erections and patients who do experience morning/night erections. NPT-data are means of 2 consecutive nights (mm increase in peniscircumference) with yellow (250 gr expansion force), and 2 consecutive nights with green (450 gr expansion force) erectometer

Morning/night erections	n	Yellow	Median Mean ± s.d.	Green Mean ± s.d.	Median
Never	78	13.3 ± 10.4	10.5	10.4 ± 10.6	7.5
Occasionally/frequent (1 × per month or more)	94	17.8 ± 8.7	18.5	15.0 ± 9.4	15.0
	172	16.0 ± 10.1	15	13.0 ± 10.2	12.5

that do not respond (31%, 19% and 7% respectively). The patients' estimated mean degrees of erection (0–100 mm analog scale) were about 30% with VES, 42% with VES + VIB, and 67% with VES + ICI.

When correlations were calculated between subjective sexual arousal (semantic scale 1–7) and subjective penile response [semantic scale: 1 (no feelings), 6 (full erection), 7 (ejaculation/orgasm)] on the one hand and objective penile response (mm increase in circumference) on the other hand the following results were obtained. With VES, both sexual arousal and subjective penile response were correlated significantly with objective penile response, that is mm increase in circumference ($r_s = 0.39$, $n = 360$, $P < 0.001$ and $r_s = 0.62$, $n = 378$, $P < 0.001$ respectively). With VES + VIB similar results emerged: sexual arousal was correlated with objective penile response ($r_s = 0.40$, $n = 156$, $P < 0.001$). With VES following ICI correlations were different between objective penile response and sexual arousal ($r_s = 0.23$, $n = 52$, $P < 0.07$), and subjective penile response ($r_s = 0.16$, $n = 65$, ns).

Morning/night erections

As can be seen from Table 4 many patients who did not report morning/night erections, did display these, however, when measured with erectometers. With the yellow erectometer 15 of 78 (19%) had a very low response (0–4 mm), 20 (26%) scored between 5 and 10, whereas 43 (55%) had a good

score of 10 mm or more. With the green erectometer these figures were 39%, 18% and 43% respectively. Furthermore, patients who reported morning/night erections responded significantly better than patients who 'never' experienced morning/night erections (with yellow erectometer 17.8 vs 13.3 mm, $P < 0.001$; with green erectometer 15.0 vs 10.4 mm $P < 0.001$).

Discussion

In contrast to what has been suggested by Buvat and coworkers¹² it is clear from this present investigation that many older as well as younger men with ED showed a good penile response to VES. Men under 40 y of age responded significantly better than men over 40; between ages 40 and 80 y men did not differ in the penile response to VES. The addition of VIB to the VES significantly increased penile response in men of all ages. ICI combined with VES caused a very substantial increase in penile response in virtually all patients of all ages. In recent years, from 1994 onward, we combine ICI with VES + VIB which gives even better results.

In somewhat more detail this means that VES caused no response in roughly one-third (31%) of the patients ($n = 128$) and a strong response (partial/full erection) also in one-third (34%). The combination of VES + VIB administered to 163 patients, caused no response in 19% of the patients but a strong response in about half of them (52%). Finally, VES + ICI caused no response in only 7% of the

patients tested this way ($n=66$) and a strong response in 82%.

From the present study it seems worthwhile to invite patients who do not experience morning/night erections to sleep with the erectometers for four consecutive nights. More than 50% of such men appear to have good, rigid erections (it should be remembered that the erectometers also indicate rigidity). This corroborates earlier results from our laboratory.¹ Although the Rigiscan[®] undoubtedly provides more detailed information about nocturnal penile tumescence,^{16,19} the use of the Rigiscan[®] could be restricted to 'difficult' cases when past history and erectometers gave no or poor results.²⁰ Although the use of both erectometers has been suggested¹ we no longer believe this to be useful. From the present study it appeared that there was a high positive correlation between measurements of the yellow and the green erectometer ($r=0.75$, $P<0.001$). Therefore, we believe one could decide to use only the green erectometer, which requires about 450 gr expansion force, for two consecutive nights.

It is of interest to note that there were no significant correlations between NPT measurements and penile responses to VES, VES+VIB, or VES+ICI (all r between 0.09 and 0.30). This is in line with earlier assumptions that nocturnal penile erections might be different from daytime erections elicited by visual erotic stimuli.²¹⁻²³

A positive penile response to VES or to VES+VIB should be positively reinforced by the doctor to the patient: it shows that nothing serious is wrong, that the genital apparatus is basically capable of responding sexually. When no response occurs, one should be keen to reassure the patient and explain that such a response has *no diagnostic significance*.¹ Failure to respond may result from lack of interest, dislike of the film, anxiety, fear to lose control, etc.^{9,11} Although some urologists dislike the fact that a negative response has no diagnostic significance, we believe that the test nevertheless is very worthwhile because so many patients with ED show a positive response, which has diagnostic relevance.

Recently, Bancroft and Malone²⁴ reported that 'because of the high proportion of false negative results, ICI monitoring is of very limited diagnostic value' (p 123). We have earlier advocated^{9,25} that ICI should be given in a sexually positive atmosphere, (that is a quiet private room, provided with sexually stimulating materials: video or magazines), to reduce the occurrence of false-negative results. Other investigators⁹ also reported that audiovisual sexual stimulation improved the response to ICI of pharmacologic agents. We suppose that the high proportion of false negative results in the Bancroft and Malone study²⁴ could be the result of the presumably rather 'cold', asexual clinical setting in which the ICIs were administered and the penile

response was monitored. The results of the present study, 82% with a very strong penile response to ICI+VES, supports our supposition. Furthermore, in 1994, 70 men with ED received ICI plus VES+VIB and showed a mean increase in penile circumference of approximately 26 mm (at the tip of the penis, behind the phallus), and a mean subjective penile erection of 82% (24% experienced an orgasm/ejaculation).

When all results are taken into account, VES exposure and NPT information, we reach the following preliminary diagnoses: (primarily) psychogenic 84% ($n=330$), mixed organic and psychogenic 14% ($n=54$) and purely organic 2% ($n=8$). Although the number of patients with a psychogenic or primarily psychogenic diagnosis may appear to be high, this finding supports earlier reports from our outpatient clinic in which we found sexual potency in 71% of men with ED.¹ There could be some bias in the patients who were referred to our psychophysiology laboratory: maybe some patients with very obvious organic problems were not always referred by the urologists. However, recent data of 100 consecutive patients with ED of a urology outpatient clinic investigated with similar methodology as in the present paper revealed a 50% purely psychogenic and 23% primarily psychogenic diagnosis.⁴ In the latter study 3% were pure organic, 12% primarily organic, 7% mixed, and 5% of uncertain etiology.

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Chapter 3

Diagnosis and treatment of erectile dysfunction in retrospect

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Diagnosis and treatment of erectile dysfunction in retrospect

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Background We sought to establish relationships between current sexual functioning, the findings of initial psychophysiological screening (PPS) and the treatment undergone in patients with erectile dysfunction (ED).

Methods A follow-up study (1–4 years later; mean time period 1.9) was carried out among 406 patients with ED, of which a representative sample of 237 responded. An extensive questionnaire was used including items dealing with the original medical examination, including PPS, treatment, subjective experience of the treatment and psychosexual functioning over the 3 months prior to the questionnaire study. Questionnaire data were linked with originally collected PPS data, including the sexual-history data.

Results Present sexual satisfaction was positively correlated with original numbers of spontaneous daytime and morning/night erections, but was not correlated with the degree of genital and sexual arousal elicited

by visual sexual stimulation (VSS). Treatment results were not satisfactory in 55% of patients. Autoinjection therapy (AIT) and psychotherapy yielded higher satisfaction scores than other treatments. In general men < 40 years appeared to be more sexually active and satisfied, and to experience fewer sexual problems than the older patients.

Conclusions The occurrence of spontaneous daytime erections and morning/night erections, obtained by history taking, indicates a psychogenic cause of the ED, and has clear predictive significance for later sexual functioning. While a positive outcome of PPS suffices to make the diagnosis of non-organic ED, it does not, contrary to what we had expected, predict later sexual functioning.

Keywords: erotic video, follow-up investigation, impotence, penile erection, psychophysiological screening.

Introduction

Psychophysiological screening (PPS) has been advocated as a useful adjunct in the procedures employed in the differential diagnosis of erectile dysfunction (ED).^{1–5} PPS comprises the measurement of penile responses to explicit erotic stimuli, i.e. erotic videos with concomitant vibrotactile penile stimulation and, in more recent years, combined with intracavernous injection (ICI) of vasoactive substances like papaverine, phentolamine or prostaglandine PGE₁.^{6–8} Through visual sexual stimulation (VSS), attempts were made to produce a penile erection, proving that the neurovascular erection mechanisms are intact. It should be borne in mind that the absence of a partial or full erection during PPS has no conclusive diagnostic significance.^{3,9}

We have earlier suggested that a positive PPS response (the occurrence of an erection) could have a predictive value with respect to treatment outcome and could also have a therapeutic effect.¹⁰ These suggestions could not be confirmed by Vrugink.¹¹ Both of these studies comprised relatively small groups of patients (43 and 37 patients respectively) who were contacted by questionnaire or telephone interview, between 1 and 4 years after the consultation for ED during which PPS was carried out.

One reason for carrying out the present follow-up study, in a much larger group of patients with ED, was to shed light on this apparent discrepancy in the possible predictive value of PPS. A second aim was to ascertain the current sexual functioning of these patients and to relate the follow-up data with those obtained during the original medical examination for ED, between 1 and 4 years earlier.

Methods

During the years 1991 through to 1993 a total of 457 patients with ED were referred to the psychophysiology laboratory, of which 406 (see ref. 4) underwent complete PPS. One to 4 years later (end of 1994) 436 patients for whom the address was available were sent a questionnaire. Questionnaires were returned by 237 patients (54%), 203 of whom had undergone complete PPS. There were 199 non-responders.

Nearly all referred patients had undergone a physical examination by the urologist and a routine blood analysis. Complete PPS comprised an initial oral interview about personal, medical and sexual history, including sexual functioning and problems. Patients were also asked to fill out a number of forms soliciting detailed information on current sexual functioning.¹ Subsequently, patients were exposed to an erotic video (VSS) while changes in penile circumference and rigidity were measured with an erectionmeter[®] (which requires approximately 250-g expansion force¹). Then VSS was repeated with another video, and with concomitant vibrotactile stimulation (VIB) to the underside of the tip of the penis (for details see ref. 9). If no response occurred, VSS with a third erotic video was combined with an intracavernous injection (ICI) of papaverine sulfate (other vasoactive substances were not used in those years). After each VSS subjective and genital arousal were filled out on a questionnaire. It should be mentioned that we had not completely standardized our methodology in that the sequence of the erotic stimuli varied from one patient to another.

On the basis of the PPS findings the patient's sexual dysfunction was tentatively classified as (mainly) psychological or (mainly) somatic.¹⁻⁴

In the present follow-up investigation an extensive questionnaire was used with items dealing with the original medical examination, including PPS and treatment, the subjective experience of the treatment (if undergone), and the psychosexual (dys)functioning over the past three months.

Non-parametric statistics were applied: Kruskal-Wallis test or Mann-Whitney *U*-test for comparisons between groups, and Wilcoxon's test for comparisons within groups. Correlation coefficients are Spearman's (r_s). $P = 0.05$ (two-tailed) was considered the limit of significance.

This study was approved by the Medical Ethical Committee of Dijkzigt Academic Hospital/Erasmus University, Rotterdam, The Netherlands.

Results

General data

The age of the 237 responders varied from 21 to 82 years (mean 52.5; median 54). The time between the original medical examination and the present follow-up investigation varied from 1 to 4 years (mean 1.9). According to the recent, not always completed, questionnaire the patients reported that they originally suffered from erectile dysfunction alone ($n = 187$; 79%), or combined with premature ejaculation ($n = 12$; 5%), anorgasmia ($n = 6$; 2.5%), low libido ($n = 6$; 2.5%), anatomical defect ($n = 10$; 4%) painful erection ($n = 6$; 2.5%) and prostatism ($n = 3$; 1%). Patients reported that they had originally undergone one or more of the following investigations: echocolor/doppler of the penis ($n = 49$; 21%), ICI ($n = 149$; 63%), VSS/VIB ($n = 203$; 86%), nocturnal penile tumescence (NPT) with erectionmeters ($n = 115$; 49%).

Comparison of responders and non-responders

The two groups were compared on the following relevant items: age, genital arousal during VSS/VIB (mm increase in penile circumference), NPT, frequency of morning/night erections, and frequency of spontaneous daytime erections. None of these parameters differed significantly between the two groups ($P \geq 0.23$). We therefore conclude that the sample of responders adequately represents the whole patient population.

Treatment undergone

Many patients declined to receive treatment after the initial screening. Some form of treatment was reported to have been received by 54% ($n = 128$) of the patients. In many instances ($n = 79$) patients learned autoinjection therapy (AIT) with a vasoactive substance (papaverine or papaverine/phenolamine), or the use of a vacuum pump device ($n = 30$). Psychological treatment such as sex, relationship or psychotherapy was undergone by 19 patients, while 14 men received drug treatment (Yohimbine, Clomipramine or other). Surgery was applied to five men with a prosthesis, and three men underwent vascular reconstruction. Comparisons of the efficacy of the various treatments will be discussed below.

Only 35% ($n = 45$) reported to be (reasonably) satisfied with the results of the treatment, 55%

($n = 70$) were (very) unsatisfied, 6% ($n = 8$) were neutral, while 4% ($n = 5$) failed to report. In comparison with 109 patients who had *not* undergone treatment the satisfaction with current sexual functioning did not differ significantly ($P = 0.48$). Within the group of patients that received treatment there was an overall difference in the degree of satisfaction varying with the nature of the treatment ($P = 0.017$), with highest satisfaction scores for ICI ($n = 51$; 3.4 ± 1.8 SD) and psychotherapy ($n = 12$; 3.2 ± 2.1 SD) and lowest scores for vacuum pump therapy ($n = 12$; 1.8 ± 1.1 SD).

Current treatment

At the time of the present investigation 68 patients were still using some form of medical treatment: 37 men were using autoinjection therapy, six a vacuum pump device, four an elastic band, nine oral medication, and seven 'another'. Again, the injection group had the highest satisfaction scores.

Comparison with original complaint

More than half of the patients reported no change in their original complaint ($n = 129$; 54%), about one quarter of the patients ($n = 57$; 24%) reported an improvement, and 49 patients (21%) indicated a further deterioration of their sexual functioning. There appeared to be an effect of age in a comparison between patients < 40, patients between 41 and 60, and patients > 60 years of age ($P < 0.001$). The youngest group reported an improvement significantly more often than the two older groups; the latter two did not differ significantly.

Comparisons with original PPS findings

Correlations were assessed between present satisfaction scores and various items measured with the original psychophysiological screening. The genital arousal (millimetre increase in penile circumference) and sexual arousal (seven-point subjective scale) in response to erotic video exposure (which correlated highly significantly ($r_s = 0.67$; $P = 0.001$) with each other), were not significantly correlated with the present sexual satisfaction score. Objective nocturnal penile tumescence (NPT) data as measured with the erectimeters, likewise failed to correlate with satisfaction scores.

Significant correlations were obtained between present sexual satisfaction scores and the original occurrence of spontaneous daytime erections ($n = 191$, $r_s = 0.17$;

$P = 0.02$), and the original frequency of morning/night erections ($n = 191$, $r_s = 0.26$; $P = 0.001$). Morning/night erections and present sexual satisfaction were significantly correlated for patients over 40 years ($n = 154$, $r_s = 0.26$, $P = 0.001$), but not for the younger age group ($n = 37$).

Age and various current sexually relevant items

In Table 1 various sociosexual parameters and sexual problems are enumerated for three different age groups. In general the youngest age group appeared to be more sexually active and satisfied, and to experience fewer sexual problems than the oldest age group. On all parameters, with the exception of masturbation frequency, an overall comparison between the three age groups yielded highly significant differences.

Discussion

The present study comprises a 54% sample of a population of 457 patients with erectile dysfunction who had been referred to the psychophysiology laboratory over a 3-year period. The sample appeared to be representative of the total group by all relevant parameters. Many of the details obtained during the original medical examination, including psychophysiological screening (PPS), have been published before.⁴ In that publication we concluded that 84% of the cases were primarily of psychogenic origin, 2% were considered purely organic, while the remainder (14%) were of mixed organic and psychogenic origin. The percentage of purely organic cases is likely to be biased by the fact that patients with very obvious organic causes were usually not referred to the psychophysiology laboratory. In the present paper we are concerned with the results of a follow-up investigation through an extensive questionnaire 1 to 4 years after the original examination.

Correlations were determined between present satisfaction with sexual functioning and various data obtained during the original psychophysiological screening. Present sexual satisfaction was positively correlated with the original occurrence of spontaneous daytime erections, and with the original frequency of morning/night erections. Present sexual satisfaction was not significantly correlated with the degree of genital and sexual arousal during the original visual sexual stimulation. Thus VSS/VIB responses did not have a predictive value for later sexual functioning. This may be partially caused by the variations, introduced during the original screening, in the sequence in which the stimuli were

Table 1 Patients with erectile dysfunction: sociosexual parameters and sexual problems observed over the last 3 months prior to the recent questionnaire follow up. Note the importance of age for virtually all items presented. Values are the means \pm SEM

Sociosexual parameters	Age			Statistics (Kruskal-Wallis)	Total n (all ages)				
	n \leq 39 yr	n = 40-60 yr	n \geq 61 yr						
Relationship duration (yr)	31	6.2 \pm 1.0	91	20.6 \pm 1.2	45	29.7 \pm 2.2	<i>P</i> = 0.001	167	20.4 \pm 1.1
Relationship quality (1 = very unhappy; 7 = very happy)	32	6.2 \pm 0.1	102	5.2 \pm 0.2	49	5.3 \pm 0.2	<i>P</i> = 0.008	183	5.4 \pm 0.1
Coitus with orgasm (freq./month)	34	5.6 \pm 0.8	103	4.3 \pm 0.5	39	2.3 \pm 0.5	<i>P</i> = 0.004	176	4.1 \pm 0.4
Morning erections (freq./month)	33	11.4 \pm 1.4	91	9.1 \pm 1.0	43	6.1 \pm 1.1	<i>P</i> = 0.007	167	8.8 \pm 0.7
Masturbation (freq./month)	26	5.8 \pm 0.8	66	4.7 \pm 0.8	27	3.2 \pm 1.0	<i>P</i> = 0.002	119	4.6 \pm 0.5
Quality of sex life (1 = very bad; 7 = excellent)	39	3.8 \pm 0.2	129	3.1 \pm 0.1	60	2.9 \pm 0.2	<i>P</i> = 0.017	228	3.2 \pm 0.1
Satisfaction with sexual functioning (1 = very low; 7 = very high)	40	4.1 \pm 0.3	132	3.0 \pm 0.2	62	2.7 \pm 0.2	<i>P</i> = 0.002	234	3.1 \pm 0.1
Sexual problems	Age			Statistics (Kruskal-Wallis)	Total n (all ages)				
	n \leq 39 yr	n = 40-60 yr	n \geq 61 yr						
No sexual desire	38	5.3 \pm 0.3	116	4.4 \pm 0.2	58	4.4 \pm 0.2	<i>P</i> = 0.02	212	4.6 \pm 0.1
Sexual problems with:									
getting an erection	38	5.0 \pm 0.3	121	3.5 \pm 0.2	59	2.9 \pm 0.2	<i>P</i> = 0.001	218	3.6 \pm 0.1
sustaining an erection	38	4.5 \pm 0.3	120	3.0 \pm 0.2	59	2.6 \pm 0.2	<i>P</i> = 0.001	217	3.2 \pm 0.1
Coitus impossible because of insufficient erection	36	5.0 \pm 0.3	114	3.2 \pm 0.2	55	2.6 \pm 0.2	<i>P</i> = 0.001	205	3.4 \pm 0.2
Premature ejaculation	36	4.4 \pm 0.4	114	4.1 \pm 0.2	53	5.2 \pm 0.3	<i>P</i> = 0.01	203	4.4 \pm 0.2
Laborious orgasm/ejaculation	36	5.9 \pm 0.3	113	4.8 \pm 0.2	54	4.4 \pm 0.3	<i>P</i> = 0.001	203	4.9 \pm 0.1
Fear of failure	36	5.2 \pm 0.3	116	3.9 \pm 0.2	51	3.8 \pm 0.3	<i>P</i> = 0.007	203	4.1 \pm 0.2
Partner not interested in sex	35	5.3 \pm 0.3	107	5.2 \pm 0.2	49	4.4 \pm 0.3	<i>P</i> = 0.02	191	5.0 \pm 0.1

offered (VSS, VIB, VSS + VIB). A predictive value of the response during PPS may arise following the introduction of a complete standardized PPS methodology (see below).

About half of the patients (54%) had undergone some form of treatment; approximately one-third of these was satisfied with the results of the treatment, while 55% were dissatisfied. Autoinjection therapy (AIT; 79 patients), and psychotherapy (19 patients) yielded higher satisfaction scores than other forms of treatment.

With regard to the original dysfunction, 24% of the patients reported an improvement, 21% a deterioration, while 54% experienced no change.

These rather disappointing results (shared by other long-term follow-up studies.¹²⁻¹⁴) indicate the need for a more appropriate therapeutic approach to patients with erectile difficulties. Ideally, the doctor should be able to choose from a broad spectrum of therapeutic possibilities relevant for the individual patient and his partner. Unfortunately, this was usually not possible for the patients reported in this study. In recent years we have optimized our PPS methodology in the following manner: each patient first undergoes VSS, then VSS + VIB, and subsequently ICI if the penile response

is unsatisfactory.³⁻⁹ Data obtained so far with this new procedure applied to our 1994/1995 patients (*n* = 384) showed that an ICI of a small dose of prostaglandine (5-10 μ g) or papaverine/phentolamine (0.5-1 ml) resulted in a full erection in nearly all patients who had not achieved one with VSS and VSS + VIB.¹⁵ Prolonged erection (lasting 4-6 h) occurred in 6% of cases. These latter data confirm our earlier suggestion in which we advocated the combined use of an erotic positive atmosphere with ICI.⁶ In addition to the improvement of our PPS methodology, we have added the availability of psychosexual counselling in combination with somatic treatments such as AIT, vacuum pump and drug medication. Continued evaluation, short term as well as long term, of these procedures remains obligatory to ensure optimal diagnosis and treatment of men with erectile dysfunction.

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Chapter 4

Testicular prostheses: body image and sexual functioning

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Testicular prostheses: body image and sexual functioning

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Objectives To evaluate retrospectively the body image and sexual functioning in patients who have a testicular prosthesis (TP).

Patients and methods The medical charts were evaluated for 30 adult patients who received 32 TPs between 1985 and 1997. A questionnaire was mailed to each patient, asking about body image, satisfaction with the implant and with sexual functioning.

Results Of the 30 patients, 22 (73%) replied; their mean (range) age was 30 (18–47) years. Most of the patients had a silicone gel-filled TP. No complications were reported in 25 (83%) patients and 80% reported no sexual problems: 20% felt uncomfortable in intimate contacts. 65% found their body image improved after

having a TP, 58% were satisfied with their current sexual life, 90% had no erectile dysfunction and 45% reported premature ejaculation.

Conclusions Patients who have lost a testis for any reason should be informed about the availability of a TP. Prostheses were well accepted and no systemic disease was reported. Almost all patients reported an improvement in their body image. Sexual life and performance were apparently not compromised by having a TP. New surgical procedures are recommended to improve the cosmetic appearance of a TP in the scrotum.

Keywords Testicular prosthesis, body image, sexual function

Introduction

'To have balls' is a popular expression in Southern European countries (and elsewhere), indicating that a man is courageous and strong [1]. Surgical castration, trauma or agenesis of a testicle may produce psychosexual dysfunction, especially in young men. Testicular prostheses (TPs) have been used since 1941; the first (made of vitallium) was implanted in a 27-year-old patient who lost a testicle after trauma and subsequently became depressed [2]; the depression resolved after the implantation. There are relatively few studies reporting on the outcome of implanting a TP and in only two papers were the patients' perceptions assessed [3,4]. In no reports have the sexual aspects of having an implant been evaluated. Thus the present study was conducted to evaluate retrospectively the body image and sexual functioning in patients with a TP.

Patients and methods

The medical charts were evaluated for 30 men who had had a TP implanted at our hospital during 1985–97; the reasons for insertion, the side and size of the implants and possible complications were retrieved from these

charts. A questionnaire was mailed to each patient, and they were invited to visit the outpatient clinic for an interview and a cosmetic evaluation. The questionnaire consisted of two parts; the first nine questions dealt with body image and satisfaction after insertion, and the second part consisted of 24 questions concerned with sexual functioning (possible problems with erections, premature ejaculation, frequency of sexual activity) and satisfaction about sexual life. Some patients did not answer all the questions.

Results

The questionnaire was returned by 22 patients (73%); 18 patients (60%) attended the hospital for an interview and a cosmetic evaluation of the implant. The mean (range) age of these patients was 30 (18–47) years. Of the eight patients who did not reply, four were lost to follow-up and four refused to participate in the evaluation. The reasons for and the side of insertion are shown in Table 1. In three patients the TP had been re-implanted, in one because the TP inserted in another hospital had ruptured, and in two because they needed a larger TP. One patient had undergone a vasectomy and 11 patients had undergone previous inguinal surgery because of orchidopexy or inguinal hernia. In the 26 men who had undergone orchidectomy, the mean

Table 1 Reasons for, side of insertion, type and size of the testicular implant in 30 patients, and in parentheses for the 22 who returned the questionnaire

Variable	Number
<i>Reasons</i>	
Undescended	11 (8)
Cancer	7 (5)
Agenesis	5 (3)
Torsion	6 (5)
Pain	1 (1)
<i>Side</i>	
Right	12 (7)
Left	16 (13)
Both	2 (2)
<i>Type</i>	
Gel-filled	22 (15)
Unknown gel-filled or solid	10 (9)
<i>Size</i>	
Medium	6 (5)
Large	21 (15)
Unknown	5 (4)

(median, range) interval between orchidectomy and insertion of a TP was 51 (20, 0–228) months. The type and size of TP is shown in Table 1.

At our hospital, the TP is inserted via an inguinal incision; a scrotal pouch is created bluntly and the TP is subsequently fixed with one suture to the lowest point in the hemiscrotum. Patients received prophylactic antibiotics on the day of surgery. In 25 patients (83%) no complications were reported. One patient (3%) complained of postoperative pain and two (7%) had a scrotal haematoma which needed no treatment. Three patients, among whom was the one who had a haematoma, reported a cranial migration of the implant. Two of these patients were re-operated to reposition the TP. There were no infections.

Three of 21 patients (14%) reported that the implant had the same appearance and consistency as the remaining testis; 12 (57%) considered it slightly different and six (29%) judged it completely different. Sixteen of 20 men reported no sexual problems and four felt uncomfortable in intimate contacts with their partner. Eleven of 21 patients (52%) reported no problems in being naked with other men, while eight (38%) did not undress in the presence of other people because they were embarrassed. There were no significant correlations between the appearance of the TP and the occurrence of problems in intimate contacts with their partner, being naked with other men or undressing in the presence of others.

Nine of 22 men (41%) considered their body appearance greatly improved after receiving a TP; six (27%)

reported a slight improvement, in six (27%) there was no change and one (5%) reported it to be worse. There were no systematic differences between patients with or without cancer (as a cause of testicular loss) in any of the variables assessed. Twenty-one of the 22 (95%) men would undergo surgery again if necessary.

Eleven of 19 men were satisfied with their sexual life: 16 reported spontaneous erections at night or during the day (mean frequency 12/month, range 0–28). The mean (range) masturbation frequency was 6 (0–28)/month and sexual activity with partner 9 (0–12)/month. Seventeen of the 19 patients reported being always able to obtain or maintain an erection sufficient for sexual intercourse, while two had problems. Eight of 18 men reported premature ejaculation and one of 15 indicated fear of failure in sexual matters.

The cosmetic evaluation showed a tight implant in all patients, which caused an asymmetric scrotal appearance, also described by each man as 'different' from the normal anatomy. No systemic disease was reported in any of the patients.

Discussion

There are only two studies reporting on patients' perceptions of a TP [3,4] but assessments of the sexual aspects of having a TP are lacking; the present questionnaire study tried to address this issue. Of the present patients, 68% reported an improvement in their body appearance after insertion of a TP. These results corroborate with the findings of Lynch and Pryor [4] and Gritz *et al.* [5]. It is possible that losing a testicle through hemicastration causes more concern about masculinity and body image than growing up with one testis because of maldescent of the second. In the present 30 patients, 14 had undergone (hemi)castration and 11 had one undescended testis. There were no differences in the improvement in body image after having a TP between patients with an undescended testis and patients who were (hemi)castrated.

Sexual dysfunction has been reported in patients castrated because of testicular cancer [5,6], but not after receiving a TP. Of the present patients, 11% reported having problems with erections and 45% complained of premature ejaculation; 58% were satisfied with their sexual life. These data are similar to those reported for a group of young men treated for testicular cancer (orchidectomy with or without a subsequent TP) [5]. Although not specifically assessed in the present study, the low frequency of sexual problems could be related to the positive body image and the high satisfaction rate of these patients after insertion of a TP.

No complications were reported in 83% of the patients, a result in accordance with other reports [7]. None of

the present patients had a ruptured TP: although such rupture has been reported, it seems to have no medical consequences [8]. Patients who have undergone previous scrotal surgery have a greater complication rate than men undergoing insertion at the time of orchidectomy [9]. In the present study, there was only one patient with previous scrotal surgery (a vasectomy) and this was also the only patient reporting pain after insertion of a TP.

There was no systemic disease in these patients possibly related to a silicone TP. Particle shedding and migration from silicone genitourinary prosthetic devices has been reported, but with no clinical implications [10,11]. Cosmetically, the currently used implants are far from ideal. The TP in all the present patients was judged to be too high and too tight in the scrotum. New surgical procedures are required to improve the cosmetic appearance, e.g. not suturing the TP to the scrotum. Patients with sutured TPs should be taught to massage the implant to avoid capsular tissue, which makes the implant too firm: this could also help to give a more natural feeling.

In conclusion, the implantation of a TP is simple, has a very low complication rate and a high satisfaction rate in patients. The body image is greatly improved after receiving a TP and sexual dysfunction is minimized. No systemic disease related to the silicone TP was reported. Men of any age (and their partners) benefit from the restoration of normal social and sexual functioning. Suturing the TP to the scrotum is not recommended, as it causes an unnatural appearance.

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Chapter 5

Low-dose radiotherapy in 179 patients with Peyronie's disease: treatment outcome and current sexual functioning

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LOW-DOSE RADIOTHERAPY IN 179 PATIENTS WITH PEYRONIE'S DISEASE: TREATMENT OUTCOME AND CURRENT SEXUAL FUNCTIONING

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Purpose: To analyse retrospectively treatment outcome in patients irradiated for Peyronie's disease.

Methods and Materials: The records of 179 patients, median age 52 years, that received radiotherapy (RT) between 1982 and 1997 were reviewed. 78% presented with painful erections and 89% with penile deformity. The symptoms were present for a median duration of 6 months (range, 1–72 months). The RT schedule consisted of 13.5 Gy (9 × 1.5 Gy, 3 fractions per week) using orthovoltage X-rays in 123 patients or 12 Gy (6 × 2 Gy, daily fractions) using electrons in 56 patients. A questionnaire regarding current sexual functioning was mailed to 130 patients whose addresses could be traced; 106 (82%) responded.

Results: At mean follow-up period of 3 months, 83% reported that pain was diminished or had disappeared after RT. Twenty-three percent of patients reported a decrease in penile deformity. Following RT, surgical correction of penile curvature was performed in 29% of patients. No RT-related complications occurred except transient dysuria in 1 patient. Questionnaire data: 72% of patients were currently sexually active, 48% had erectile dysfunction, and 49% expressed dissatisfaction with their current sexual functioning.

Conclusion: Low-dose external RT (12–13.5 Gy) results in relief of pain in the majority of patients with Peyronie's disease. Improvement in penile deformity was observed, avoiding surgery in a number of patients. No significant RT-associated morbidity was encountered. It is disappointing that almost 50% of patients complain of sexual functioning, but this is presumably not related to radiotherapy. © 2000 Elsevier Science Inc.

Peyronie's disease, Radiotherapy, Fibrosis, Sexual functioning.

INTRODUCTION

Peyronie's disease was named for François Gigot de la Peyronie, a French surgeon who in 1743 described a fibrous cavernositis due to nodes in the corpora cavernosa, accompanied by penile curvature and discomfort with erection (1). The curvature is the result of a plaque of scar tissue in the tunica albuginea of the penis, limiting expansion during tumescence. The etiology and pathogenesis of Peyronie's disease is not yet completely understood. A proposed model is that Peyronie's disease is initiated by a trauma, i.e., mechanical stress during sexual intercourse (2). This leads to rupture of microvasculature in subjects with genetic predisposition for fibrosis, together with loss of tissue elasticity as a normal aging process. Vessel damage causes deposition of fibrin in tissue space consequently promoting ingrowth of inflammatory cells, macrophages, and fibroblasts resulting in pathological penile fibrosis with plaque formation and even ossification in advanced disease (2).

Unsatisfactory medical treatment options for Peyronie's disease include oral Vitamin E, potassium amino-benzoate

(Potaba), colchicine, tamoxifen, or intralesional injections with verapamil, corticosteroids, or collagenase. Surgery remains an option for nonresponders and in case of severe penile deformity. Radiotherapy has been previously reported as a successful treatment modality. Treatment outcome ($n = 139$) and current sexual functioning ($n = 106$) of a total of 179 patients irradiated for Peyronie's disease at our clinic are the subject of this paper.

METHODS AND MATERIALS

The radiotherapy records of 179 patients treated for Peyronie's disease in the period, 1982–1997, were reviewed. Median age at treatment was 52 years (range, 25–76 years). One-hundred-thirty-nine patients (78%) presented with painful erections and 159 patients (89%) with penile curvature; 34 patients (19%) reported erectile dysfunction. Symptoms were present for a median duration of 6 months (range, 1–72 months); 30 men (17%) had received prior oral therapy (Vitamin E, corticosteroids), surgery, or other treat-

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Table 1. Patient demographics ($n = 179$)

Median (range) age (years)	52 (25–76)
Median duration (range) of symptoms (months)	6 (1–72)
	n (%)
Dupuytren's contractures	30 (17)
Diabetes mellitus	12 (7)
Hypertension	4 (2)
Penile trauma	20 (11)
Plaque location	
Dorsal	169 (94)
Ventral	6 (3)
Both	1 (1)
Unknown	3 (2)
Number of plaques	
One	158 (88)
Two	11 (6)
Unknown	10 (6)
Median plaque surface (range) (cm ²)	3.3 (0.5–18)

ments unsuccessfully. Thirty patients (17%) reported Dupuytren's contractures, 10 patients (5.5%) reported a penile trauma during sexual activity, and 10 more patients a penile trauma without erection. Patients' demographics are summarized in Table 1.

At the time of this retrospective analysis (July 1998) a 15-item questionnaire regarding sexual desire, sexual activity, quality of erections, and satisfaction with sexual life was mailed to the 130 patients who could be contacted by phone or by mail (14 patients had died, 35 were not traceable). One-hundred-six men (82%) responded; 12 men did not want to answer the questions, 12 more men did not return the questionnaire, even after a second mailing.

Radiotherapy

Two treatment regimens have been used following the years. Orthovoltage radiotherapy with a median of 250 kV photons (range, 120–250 kV) was used in 123 patients (69%); they received a total dose of 13.5 Gy, in 3 fractions of 1.5 Gy per week, followed by a second and third course after 3–4 weeks interval. Fifty-six patients (31%) received a total dose of 12 Gy in 6 fractions of 2 Gy daily, using electron beams, median 10 MeV (range, 4–14 MeV) and bolus material. Target volume was the plaque area with generous margins, mostly the entire length of the penis, excluding the glans (median surface 48 cm², range, 12–120 cm²). A single portal was used; a 5-mm lead shield was

always used to protect testicles, scrotum, and suprapubic region.

Statistical methods

Percentages were compared using the χ^2 or the Fisher exact test. The Mann-Whitney test was used to compare graded outcomes and continuous data between groups. $p = 0.05$ (two-sided) was considered the limit of significance.

RESULTS

One-hundred-thirty-nine patients (78%) attended follow-up after a mean period of 3 months (range, 0–13 months). Eighty-three percent of patients reported that pain with erect penis was diminished or had disappeared completely after radiotherapy; penile curvature was diminished or had disappeared in 29 patients (23%), and erectile function was improved in only 3 men (8%) after radiation. At physical examination, fibrotic plaques were smaller in 44 patients (32%) and had disappeared in 10 patients (7%). Symptoms prior to radiotherapy and treatment outcome of the 139 patients who attended follow-up is summarized in Table 2. Response to radiotherapy treatment was mostly achieved within 3 months (72% of men). A single patient (0.6%) reported transient dysuria during radiation. At follow-up, 33% of patients had further been treated with surgery (41 men), Vitamin E (1 man), oral corticosteroids (3 men), and ultrasound (1 man). Patients who had been operated had all penile curvature. There was no association between pain and penile curvature and plaque surface at presentation. Smaller plaques and longer follow-up seemed to correlate with better treatment results, although this was not statistically significant. Younger age at treatment was correlated with better pain decrease ($p = 0.05$), but not with improved decrease in penile curvature ($p = 0.63$). Regarding decrease in penile curvature there was a trend that orthovoltage gave better results than electron beams (respectively 28% and 11%, $p = 0.06$); in patients treated with electron beams the best results were obtained with bolus material, 18% vs. 8% without ($p = 0.57$).

Sexual functioning questionnaire

The median age of patients who responded to the questionnaire was 59 years (range, 35–84 years). Not all patients answered all the questions. Sixty-eight patients (72%) were

Table 2. Symptoms prior to radiotherapy and treatment outcome of 139 patients at follow-up

Symptoms	Incidence n (%)	Response				
		No change n (%)	Diminished n (%)	Disappeared n (%)	Worsened n (%)	Unknown n (%)
Penile pain	119 (86)	17 (14)	45 (38)	53 (45)	4 (3)	0 (0)
Penile curvature	130 (94)	85 (65)	24 (19)	5 (4)	11 (8)	5 (4)
Erectile dysfunction	36 (26)	19 (53)	3 (8)	0 (0)	1 (3)	13 (36)
Fibrous plaque(s)	139 (100)	72 (52)	44 (32)	10 (7)	6 (4)	7 (5)

sexually active; of these, 34 (51%) and 41 (61%) of 67 had problems sometimes or always in, respectively, getting or maintaining an erection sufficient for sexual activity. Only one-third of the patients sought therapy for their erectile dysfunction. Overall 49% of patients (45/92) expressed dissatisfaction with their current sexual life.

DISCUSSION

The origin of Peyronie's disease or induratio penis plastica, typically occurring in middle-aged men, is not yet completely understood. Trauma of the penis with subsequently deposition of fibrin and formation of a fibrotic plaque is the most likely pathophysiologic mechanism (2-4). Epidemiologic studies have shown a threefold increase of Peyronie's disease among patients with previous genital or perineal traumatism (5). The relationship between Peyronie's and Dupuytren's disease, a progressive contracture of fingers leading to distorted hand functioning, has been previously reported (2, 6, 7), in a percentage similar to our group of patients (17%). In Dupuytren's contractures, the presence of fibrin in the hand nodules has been confirmed (8). Because of the hypothesis of an inflammatory etiology, empirical treatments have been tried with unsatisfactory results. Vitamin E, because of its antioxidant effect preventing fibrosis, was already used in 1948 by Scott and Scardino (9). They reported a 91% decrease of the plaque size and 78% of penile curvature (9). Wagenknecht summarized data from 2752 patients treated with Potaba reporting a subjective improvement in 60% of patients (range, 10-82%) (10). Akkus *et al.*, in 1994, reported on 24 patients treated with oral colchicine; 11% noted a slight decrease and 26% a marked decrease of curvature, 78% had reduction of pain (11). Intralesional therapy with collagenase has been used by Gelbard *et al.* with curvature decrease in 65% of patients; only men with less than 30° curvature and less of 2-cm plaque size noted actually substantial improvement (12, 13). Intralesional verapamil, a calcium-channel blocker, modifies fibroblast phenotype reducing synthesis and secretion of collagen and increasing collagenase activity (14). Levine treated 38 patients with intralesional verapamil and noted a rapid reduction of pain in 97% and of curvature in 76%, after a follow-up of 24 months (15). Several surgical approaches have been used, from plaque excision with dermal grafting to correction of penile deformity without tissue excision (16). Surgery may result in penile shortening or diminished penile sensitivity, which is unpleasant for the patient; and results are not more successful than noninvasive approaches (17). Only severe angulations making intercourse impossible should undergo surgery; in most patients with Peyronie's disease pain is the only symptom they seek therapy for. Radiotherapy for Peyronie's disease has been used since 1939 (6, 7, 18-29). Carson *et al.* reported on 40 patients treated with orthovoltage radiotherapy in doses between 6 and 16 Gy (average, 9 Gy); 78% had a decrease of pain and 6% of curvature; no improvement of erectile function was noted (18). Viljoen *et al.* treated 42

patients with an average total dose of 23 Gy and 47 patients with 25 Gy, with 250 kV orthovoltage radiotherapy (7). A questionnaire to assess long-term results at 33 months average was mailed to all patients, 47 were returned and adequately completed. Pain was reduced in 84%, angulation in 38%, and 7% had an improvement of erectile function (7). Rodrigues *et al.* treated 38 patients with 200-250 kV orthovoltage radiotherapy to a total dose of 9 Gy (3 × 3 Gy, 5 alternating days); 16 patients had still complaints after this schedule and were irradiated again with the same technique up to a total dose of 18 Gy (6). The overall results were a decrease of penile pain in 76% and of curvature in 48%, 60% had improvement of sexual life. No complications of radiation were reported (6). In our group of patients, pain was decreased or had disappeared in 83% and curvature, in 23%. These results are similar to figures reported in the literature (6, 7, 18). There are reports stating that Peyronie's disease is self-limiting in 50% of untreated patients and improves spontaneously within 12-18 months (30, 31). However, 72% of our patients experienced pain relief within 3 months, following radiotherapy which is considerably shorter than the possible normal evolution of the disease (30, 31). It is understandable that men who desire sexual activity and experience erectile discomfort do not want to wait too long to find a solution for their problem. Patients were referred to us by the urologist, to be treated immediately, when no spontaneous improvements occurred after a 6-month (median) observation period. Erectile function improved in a low percentage of patients after radiotherapy treatment (8% in our group), demonstrating that the etiology of this dysfunction is much more complex than only a plaque. Seventy-two percent of patients who responded to our questionnaire were sexually active, but also experienced problems getting (51%) or maintaining (61%) an erection. This could be explained as due to the aging process; patients did not consider their erectile or sexual dysfunction as a consequence of their radiation treatment. No radiation-induced malignancy has been reported in our patients or in the literature with such doses. We currently use a daily fractionation dose of 2 Gy to a 12 Gy total dose, with electron beams, 8-10 MeV, and bolus material, confined to the plaque plus generous margins, with shielding of scrotum and suprapubic region. With this modality, no complications have been reported. We understand that a group of control patients would have been ideal for a thorough comparison with our radiation treatment results. Unfortunately, this was not possible, because patients with Peyronie's disease, after a short period of observation, were referred to our hospital for radiation therapy, because of persisting pain. In our opinion, it would be difficult to initiate a randomized, prospective study comparing radiation and no treatment, because of the small number of patients referred for radiotherapy (5 patients per year in our center and 40 in the whole of The Netherlands in 1997). We are aware of the limitations of a retrospective analysis. However, an ongoing prospective study at our hospital with evaluation of complaints prior to radiation treatment and of outcome 3

and 6 months after radiotherapy, using questionnaires, show similar results. In both studies most of the patients are satisfied with the results of radiotherapy and do not need surgery afterwards. The small percentage of patients in the retrospective analysis who had surgery following radiation all had severe penile curvature with no possibility of sexual intercourse. It is disappointing that almost 50% of our patients express dissatisfaction with their current sexual life, and 51% has difficulty getting an erection. Although a control group for comparison is lacking, we have no reason to believe that sexual complaints are related to radiation. Nevertheless, these data indicate that sexual counseling in patients with Peyronie's disease before and after radiotherapy is highly recommended.

CONCLUSION

Low-dose (12–13.5 Gy) external radiotherapy seems to be effective in patients with Peyronie's disease who complain of painful erections that do not disappear after a wait-and-see period. Improvement in penile deformity is also observed, reducing the need of surgical correction. Surgery remains a good option in cases with severe curvature when sexual activity is impaired and when pain has not disappeared spontaneously or after radiation treatment. Radiotherapy is a noninvasive, not expensive, outpatient procedure with a high satisfaction rate and with no morbidity at such doses. Randomized, controlled studies are lacking.

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Chapter 6

Current sexual functioning in 106 patients with Peyronie's disease treated with radiotherapy 9 years earlier

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CURRENT SEXUAL FUNCTIONING IN 106 PATIENTS WITH PEYRONIE'S DISEASE TREATED WITH RADIOTHERAPY 9 YEARS EARLIER

LUCA INCROCCI, WIM C. J. HOP, AND A. KOOS SLOB

ABSTRACT

Objectives. To analyze retrospectively the sexual functioning and treatment outcome in patients after radiotherapy (RT) for Peyronie's disease.

Methods. During 1982 to 1997, 179 patients with Peyronie's disease were treated at our radiation oncology department. One hundred thirty patients whose address could be traced were sent a questionnaire about their symptoms before RT, treatment outcome, and current sexual functioning (the past 4 weeks). One hundred six patients, mean age 59 years, responded.

Results. Before RT, 44% reported painful erections, 97% penile curvature, and 18% erectile dysfunction. Sixty-nine percent reported that after RT, penile pain was diminished and 29% that penile curvature was decreased; 13% reported improved erections. With respect to their current sex life, 51% reported sometimes or always having problems getting an erection and 61% in maintaining an erection; 36% never experienced spontaneous erections. Fifty-four percent reported not having erections rigid enough for sexual activity. Since RT (mean 9 years), there had been a moderate or severe decrease in sexual interest (17%), sexual activity (41%), and sexual pleasure (32%). Overall, 49% of patients were dissatisfied with their current sexual functioning.

Conclusions. Low-dose external RT resulted in relief of pain in two thirds of patients with Peyronie's disease. An improvement in penile curvature was reported in one third of patients. One half of men reported problems in getting an erection. The rigidity of erections was satisfactory in only 54%. There was a moderate to severe decrease in sexual interest, activity, and pleasure after RT; however, this was associated with age, although comorbidity or medications cannot be excluded. UROLOGY 56: 1030-1034, 2000. © 2000, Elsevier Science Inc.

Peyronie's disease (PD) is a benign condition in which a plaque of scar tissue in the tunica albuginea of the penis produces penile curvature and possibly discomfort with erections. The etiology and pathogenesis are not completely understood. A prevalent hypothesis is that trauma to the penis during sexual activity leads to rupture of vessels, with subsequent deposition of fibrin, resulting in pathologic penile fibrosis and plaque formation.¹

Many treatment options (eg, vitamin E, corticosteroids, intralesional verapamil, and collagenase) have been used, with varying satisfactory outcomes.² It is also possible to refrain from treatment, since PD can be self-limiting in many patients. However, if penile discomfort is severe, therapy is necessary. In the latter case, radiotherapy (RT) can be an effective treatment modality. Obviously, in cases of severe penile curvature, surgery remains the therapy of first choice. The sexual function in patients with PD after RT is a much neglected area; it has not been studied in any detailed manner. Therefore, the present study was undertaken to determine the current sexual functioning of patients and treatment outcome in retrospect. The study population consisted of 106 patients with PD treated with RT in our radiation oncology department.

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TABLE I. Sexual desire in the past 4 weeks and significance of sex

	Not at All	A Little	Some	Much	Very Much
Did you have sexual desire? (n = 92)	9 (10)	20 (22)	45 (49)	14 (15)	4 (4)
How significant is sex for you? (n = 91)	5 (5)	30 (33)	0 (0)	48 (53)	8 (9)

Numbers in parentheses are percentages.

TABLE II. Frequency of spontaneous erections in the past 4 weeks

	Never	1/wk	2-6/wk	1/day	≥2/day
Did you have a spontaneous erection? (n = 91)	33 (36)	25 (27)	19 (21)	10 (11)	4 (5)

Numbers in parentheses are percentages.

MATERIAL AND METHODS

During 1982 to 1997, 179 patients with PD were treated with RT. The treatment modality was taken from the medical charts. We could trace 130 patients. They were sent a questionnaire on treatment outcome and current (ie, the past 4 weeks) sexual function. Questions regarded the presence of penile pain and curvature before RT, the duration of symptoms, the response to treatment, and possible side effects. The sexual function questions concerned sexual desire, significance of sex, frequency and rigidity of spontaneous erections, difficulty in getting or maintaining an erection, rigidity of erections during sexual activity, and overall satisfaction with current sexual life. Patients were also asked whether a decrease of sexual interest, activity, and pleasure had occurred since RT. The sexual questionnaire was adapted from a standard questionnaire used during the past 10 years in screening men with erectile dysfunction (ED).^{3,4}

RADIOTHERAPY

Sixty-four patients (60%) were treated using orthovoltage x-rays (9×1.5 Gy, three fractions weekly, median energy 250 kV, range 120 to 250) and 42 patients (40%) with electrons (6×2 Gy, daily fractions, median energy 10 MeV, range 4 to 14). The penile plaque plus the margins was the target volume (median surface 48 cm², range 12 to 120). The suprapubic region, scrotum, and testes were always shielded with 5-mm lead sheets.

STATISTICAL ANALYSIS

Percentages were compared between groups using the chi-square or the Fisher exact test; within-group comparisons were made using McNemar's test. The Mann-Whitney *U* test was used to compare graded outcomes and continuous data between groups. The correlation coefficients (*r*) given are Spearman's. *P* = 0.05 (two-sided) was considered the limit of significance.

RESULTS

Of the 130 patients sent questionnaires, 106 (82%) responded (mean age 59 years, range 35 to 84); 12 men did not want to answer the questions because of privacy reasons and another 12 did not return the questionnaire, even after a second mailing.

From the questionnaire data, it appeared that at the first consultation, 44% reported painful erections, 97% penile curvature, and 21% ED. Symp-

toms had been present for a median duration of 6 months (mean 11, range 1 to 72). Trauma to the penis was reported by 19% of the patients, and 36% had Dupuytren's disease. Twenty-two percent of the patients had previously been treated unsuccessfully (5 patients with vitamin E, 10 with corticosteroids, 1 with verapamil, and 6 had undergone surgical correction of the penile deformity). At the time of RT, about one third of patients reported using concomitant medication known to possibly affect sexual functioning (eg, antihypertensive or antidepressant agents); 40% smoked an average of 15 cigarettes daily (range 3 to 25).

Of the patients with pain before RT, 69% reported that it had diminished; 29% also experienced a decrease in penile curvature. Of the patients with ED before RT, 13% reported that their erections had improved after RT; 40% had a response within 6 weeks, 32% within 3 months, and 28% after 3 months. Eleven percent reported discomfort during RT (mostly dysuria). Finally, 24% had undergone surgery because of persisting severe penile curvature after RT. At the time of the questionnaire (July 1998), 53% used medication (known to possibly affect sexual functioning), almost twice as high as the percentage before RT (29%; *P* < 0.0001). Thirty-one percent of patients smoked (mean 15 cigarettes daily, range 3 to 30), significantly less than before RT (40%; *P* = 0.006).

SEXUAL FUNCTION

Patients' sexual desire and the significance of sex during the past 4 weeks is reported in Table I. The frequency of spontaneous erections and difficulty in getting and maintaining an erection are reported in Tables II and III, respectively. The rigidity of the erections is summarized in Table IV. All these variables were correlated with age: the older the patient, the lower the sexual desire (*r* = -0.28, *P* < 0.01), the less significance attributed to sex (*r* = -0.18, *P* = 0.08), the lower the frequency of spontaneous erections (*r* = -0.41, *P* < 0.001),

TABLE III. Difficulty in getting and maintaining an erection in the past 4 weeks

	No	Sometimes	Always
Did you have difficulty in getting an erection? (n = 67)	33 (49)	21 (31)	13 (20)
Did you have difficulty in maintaining an erection? (n = 67)	26 (39)	26 (39)	15 (22)

Numbers in parentheses are percentages.

the less satisfaction with sexual life ($r = -0.21$, $P < 0.05$), and the more difficult it was to achieve ($r = +0.37$, $P < 0.01$) and maintain ($r = +0.35$, $P < 0.01$) an erection. Ninety-two percent of patients before and 72% after RT were sexually active ($P = 0.002$). After RT, 26 patients were not sexually active because of various reasons: lack of erections ($n = 12$), absence of sexual desire ($n = 9$), absence of sexual partner ($n = 1$), absence of sexual desire in the partner ($n = 2$), or other reasons ($n = 7$). After RT treatment, no decrease in sexual interest, activity, or pleasure occurred in 62%, 33%, and 51% of patients, respectively. A decrease in sexual interest, activity, and pleasure also correlated strongly with increasing age. Overall, 49% of patients reported not being satisfied with their current sexual life, 25% were somewhat satisfied, and 26% were (very) much satisfied.

At the time of the questionnaire (before Viagra was introduced in The Netherlands), only 13 patients were receiving ED treatment: 5 received intracavernosal injections, 3 used a vacuum device, and in 5 patients the treatment was not specified.

COMMENT

PD remains a mysterious disease. Epidemiologic studies have shown a threefold increase in PD among patients with previous genital and perineal trauma.⁵ Also, the association with Dupuytren's contractures has been reported,^{1,5} although at a percentage lower than in our patients (about 20% versus our 36%). RT has been used previously with good results.⁶⁻⁸ The sexual function in patients irradiated for PD has never been thoroughly studied. Usually only one question was asked immediately after treatment: has there been an improvement in sexual activity or in erectile function?^{6,7} Sexual dysfunction in patients with PD may be due to severe angulation, pain, or ED. The latter is attributed to veno-occlusive impairment.^{9,10} Before RT, 21% of our patients reported ED; a similar percentage has been reported by patients undergoing surgery.⁹ In our patients, erectile function improved in only 13% after RT, but penile pain di-

minished in two thirds of patients and penile curvature decreased in about 30%. Some reports have stated that PD is self-limiting in 50% of untreated patients and symptoms disappear spontaneously within 18 months.^{11,12} It is understandable that men who desire sexual activity and experience penile discomfort do not want to wait such a long period. For those men, RT is a serious treatment option, since 69% of our patients experienced pain relief within 3 months after RT, considerably shorter than the possible normal evolution of the disease.^{11,12}

We understand that a group of control patients who did not undergo RT would have been helpful for comparison. A control group was not possible in our study, since all patients were referred to us for immediate treatment, when no spontaneous improvements had occurred after a 6-month observation period. We do not have data on the sexual function of our patients immediately after RT treatment. We mailed our questionnaire at an average of 9 years after RT; patients were also 9 years older. Sixty-eight percent of patients expressed sexual desire and for 62%, sex was (very) much significant. Sexual activity before RT was higher, but this was almost 10 years earlier. Thirty-six percent of patients never had spontaneous erections; 51% sometimes or always had difficulty in getting an erection, and 61% had difficulty in maintaining an erection. Rigidity was enough for sexual activity in only 46% of patients who were sexually active. Although of older age (ie, 59 years old), 72% of patients were sexually active, comparable with the data from the Massachusetts Male Aging Study.¹³ The decrease in sexual interest, activity, and pleasure after RT treatment (compared with before RT) may be explained by the increased age. Other risk factors (eg, medication and disease) could also play a role; unfortunately, detailed information was lacking.

When patients were divided into three age groups (younger than 49, 50 to 69, and older than 69 years), all aspects of sexuality correlated strongly with age. In the older group, incidence of problems in getting and maintaining erections and less sexual desire, satisfaction, frequency, and rigidity of spontaneous erections and erections during sexual activity was significantly higher. Patients indicated a high satisfaction rate after RT regarding penile pain, but almost 50% were dissatisfied with their current sexual life. It is of interest that our patients, although they were irradiated for PD some 9 years earlier, reported the same problems concerning sexual function as patients of the same age without earlier treatment for PD.¹³ About 50% of patients reported problems in getting or maintaining an erection, but two thirds did not use any treatment modality.

TABLE IV. Rigidity of spontaneous erections and erections during sexual activity in the past 4 weeks

	Not at All	Somewhat	Half	Rigid	Very Rigid
How rigid were spontaneous erections? (n = 59)	1 (2)	5 (8)	26 (44)	20 (34)	7 (12)
How rigid were erections during sexual activity? (n = 68)	3 (4)	0 (0)	34 (50)	18 (27)	13 (19)

Numbers in parentheses are percentages.

CONCLUSIONS

The results of our study demonstrate that the principal advantage of RT in patients with PD is a decrease in pain and discomfort. RT is less effective in improving erectile function. Problems with sexual functioning seem to be related to patient age rather than PD.

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EDITORIAL COMMENT

The authors report a series of patients who underwent RT for PD. Although studies in the 1980s suggested some value to RT for the pain associated with PD, its beneficial effects on penile angulation and plaque have been reported only rarely.¹ Similarly, studies by Gelbard et al.² investigating the natural

history of PD demonstrate convincingly that penile pain resolves spontaneously in most patients with stable PD.

A report by Hall et al.³ in 1995 carefully examined the results of RT on the corpus cavernosum smooth muscle tissue after 1200 cGy of external beam RT. This small dose produced significant abnormalities and radiation change in the corpus cavernosum tissue. Clinical changes included woody induration, an abnormal nocturnal penile tumescence monitoring study, and a pharmacocavernosometry study demonstrating probable new onset of diffuse corporeal veno-occlusive dysfunction. Attempted treatment with pharmacologic injection therapy was unsuccessful, and penile prosthesis implantation, although successful, was quite difficult. Careful histologic analysis of the excised corpus cavernosum smooth muscle tissue revealed extensive fibrosis in arterial vasculopathy. There was a significant loss of trabecular smooth muscle, with desmin immunohistochemical staining revealing extensive fibrosis.

Since studies of the natural history of PD have documented resolution of pain in the vast majority of patients without invasive therapy and because RT provides little therapeutic benefit for patients complaining of penile curvature, plaque, and induration, RT must be carefully considered before suggesting it as an alternative for the treatment of PD. More importantly, external beam RT appears to produce significant corpus cavernosum smooth muscle fibrosis, which results in aggravation of the ED frequently associated with PD and, perhaps, a new onset of severe veno-occlusive ED, and substantial arteriopathy. With newer, less invasive, alternatives such as verapamil plaque injection and anti-inflammatory agents, RT should be used only rarely and with careful counseling of the patient before treatment to inform him of the possibility of inadequate treatment of penile pain and subsequent ED.

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REPLY BY THE AUTHORS

The principal advantage of RT in PD is a decrease in penile pain and discomfort; we were surprised that 29% of

our patients also reported an improvement in penile angulation. Only 24% of our patients underwent surgery after RT because of persisting severe penile curvature. We advocate RT only if the penile pain is severe and does not spontaneously improve after a 6-month period of observation.

It is true that PD can be self-limiting, but, as reported by Devine and Horton,¹ this occurs in only 50% of patients within 18 months. Given the distressing nature of the symptoms, many patients do not wish to wait so long. Seventy-two percent of our patients reported a decrease in penile pain within 3 months after RT.

No worsening of ED was reported after RT in our study. On the contrary, 13% of our patients had improved erec-

tions. We therefore do not believe that RT results in the aggravation of the ED frequently associated with PD.

The problems with PD remain its mysterious etiology, the limited treatment alternatives, and the lack of randomized trials.

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Chapter 7

Sexual functioning in patients with localized prostate cancer awaiting treatment

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Abstract

This paper evaluates current sexual functioning in patients with prostate cancer awaiting treatment. One-hundred-fifty-eight patients filled out a 15-item questionnaire regarding current sexual functioning. Median age was 67 years. Sixty per cent reported to have spontaneous erections at least once a week with a good firmness in 37%. During sexual activity, 35% reported no difficulty in getting erections and 33% in maintaining an erection. After diagnosis, all patients reported a decrease in sexual interest, activity and pleasure. Diagnosis of prostate cancer does have an impact on sexual functioning, therefore sexual counseling prior to treatment is advised.

Introduction

Prostate cancer (PC) has become the most frequent malignancy in men in Western countries. Over recent years the number of diagnosed patients has increased dramatically because of routine prostate specific antigen (PSA) tests and the awareness of possibility of cure of early disease, with a 5-year relative survival rate of 98% (Parker, Tong, Bolden, & Wingo, 1996).

Standard treatments in The Netherlands comprise radical prostatectomy (RP), external beam radiotherapy (RT) or observation. Randomized trials are in progress to investigate whether RP and RT are superior to observation for long-term survival rates. Treatment choice is often determined by tumor staging, patient's age and co-morbidity, urologist's and patient's preferences. Patient's health related quality of life including sexual functioning is very important in decision making. As reported by Singer, Tasch, Stocking, Rubin, Siegler, & Weichselbaum (1991) some men may choose a treatment with lower long-term survival to increase their chance of remaining sexually potent. The occurrence of erectile dysfunction (ED) after RP varies in the literature from 30% with sparing both neurovascular bundles (Catalona & Bigg, 1990) to 50% when only one bundle is spared (Walsh, Epstein, & Lowe, 1987) and reaches 98% in non-nerve-sparing techniques (Lim, Brandon, Fiedler, Brickman, Boyer, Raub, & Soloway, 1995). After external RT, ED occurs in up to 77% of patients (Mantz, Song, Farhangi, Nautiyal, Awan, Ignacio, Weichselbaum, & Vijayakumar, 1997; McCammon, Kolm, Main, & Schellhammer, 1999; Shrader-Bogen, Kjellberg, McPherson, & Murray, 1997; Turner, Adams, Bull, & Berry, 1999).

However, time is important after RT: erectile function continues to decline after 12 months and reaches a plateau after 24 months (ED in 38% and 59%, respectively) (Mantz, Song, Farhangi, Nautiyal, Awan, Ignacio, Weichselbaum, & Vijayakumar, 1997; Turner, Adams, Bull, & Berry, 1999).

The impact of treatment on potency is difficult to determine unless a baseline, pretreatment assessment of erectile function is included. The present study was carried out to determine pre-treatment sexual functioning in PC-patients awaiting treatment and to evaluate whether the diagnosis of PC had an impact on sexual functioning. Furthermore these data were collected to be used for comparison one and two years later in the same patients following PC-treatment.

Patients and Methods

In the period 1996-1998 166 patients with localized PC were referred to our hospital for treatment. Eighty-five subjects were to be treated with RP and 81 with RT. Treatment choice had been previously determined by urologist's and patient's preferences. All subjects were asked to fill out at home a 15-item questionnaire with items regarding various aspects of sexual functioning of the past two weeks. The questions referred to sexual interest, pleasure and activity and problems with getting erections following PC diagnosis (Appendix A). The questionnaire was adapted from a previously used version (Incrocci, Hop, & Slob, 1996; Slob, Blom, & van der Werff ten Bosch, 1990). The response rate was 91%: 158 out of 166 patients accepted to fill out the questionnaire.

Statistical methods

The statistical analysis was primarily descriptive. Differences between the RP and RT patients in the answers to the different questions and in the distribution of age were tested with the Kruskal-Wallis test and logistic regression.

Results

Median time between diagnosis and survey was 6 weeks (range 4-9 weeks). Patients' characteristics are summarized in Table 1. Median age was 67 years (range 50-80 years). Co-morbidity (diabetes and/or cardiovascular history) was reported in 21% of the patients.

Sixty-five patients (41%) indicated to have (very) much sexual desire. Sex was (very) important to 124 men (78%). Sixty per cent reported spontaneous erections (= outside sexual activity), at least once a week. Firmness of these erections was good in 57 subjects (37%).

Fifty-five patients (35%) reported no difficulty in getting and 52 (33%) no difficulty in maintaining an erection. For 56 patients (35%) these erections were firm enough for sexual activity (masturbation or intercourse). Overall satisfaction with sexual life was (very) high in 84 patients (53%). We found no statistically significant differences in sexual functioning between subjects with or without co-morbidity (all p values > 0.1).

Impact of cancer diagnosis

Receiving the diagnosis of PC (4-9 weeks earlier) had caused an important decrease in sexual activity in 31 patients (20%), in sexual interest in 12 patients (15%), in sexual pleasure in 20 patients (12%) and there was an increase in problems with getting an erection in 16 patients (10%). Before diagnosis 105 subjects (66%) were sexually active; after diagnosis, over the past two weeks, 88 patients (56%) were sexually active; this difference is highly statistically significant ($p=0.008$). The reason of not being sexually active was ED in only 15 men (10%); other reasons were absence of partner or no sexual desire in the partner.

Differences between RP and RT patients

The choice of treatment was not random, but determined by urologist's and patient's preference. As can be seen in Table I, RP patients were significantly younger than RT patients (median age 63 vs 69 years), PSA was significantly lower (4 $\mu\text{g/l}$ vs 8 $\mu\text{g/l}$) and there were less cardiovascular diseases (14% vs 23%). To make comparisons in ED rates after treatment one should be aware of the differences between these two groups of patients. RP and RT patients differed in their current level of sexual activity (77% versus 57%, respectively; $p=0.01$). About half of the RP patients reported no problems in getting (45%) or maintaining an erection (42%) versus only a quarter of the RT patients (25% and 26% respectively), a statistically significant difference ($p=0.01$). More RP patients (60%) than RT patients (46%) indicated high or very high overall satisfaction with sexual life ($p=0.004$). A logistic regression analysis with adjustment for age and the following independent variables:

sexual desire, spontaneous erections, sexual activity, significance of sex and satisfaction with sexual life, showed no statistically significant differences between the RP and RT patients, except for satisfaction with sexual life (lower in RT patients than in RP patients, $p=0.04$).

Discussion

A very commonly ignored aspect of PC therapy is the impact on sexual activity and sexual functioning (McCammon, Kolm, Main, & Schellhammer, 1999; Ofman, 1995). Although the use of advanced surgical techniques as the nerve-sparing RP and the introduction of conformal RT, sexual functioning after PC treatment remains a concern.

In order to carefully evaluate the impact of PC diagnosis and treatment on sexual life it is necessary to assess sexual functioning prior to treatment (Stock, Stone, & Iannuzzi, 1996; Zinreich, Derogatis, Herpst, Auvil, Piantadosi, & Order, 1990). Many published studies used retrospective assessments of sexual functioning prior to treatment (Lim, Brandon, Fiedler, Brickman, Boyer, Raub, & Soloway, 1995; Mantz, Song, Farhangi, Nautiyal, Awan, Ignacio, Weichselbaum, & Vijayakumar, 1997; Shrader-Bogen, Kjellberg, McPherson, & Murray, 1997). Some studies evaluated pre-treatment sexual functioning with a prospective design (Litwin, Flanders, Pasta, Stoddard, Lubeck, & Henning, 1999; Stock, Stone, & Iannuzzi, 1996; Turner, Adams, Bull, & Berry, 1999). Often PC patients are impotent before treatment. Therefore, assessment of this condition is necessary to predict sexual functioning after therapy (Robinson, Dufour, & Fung, 1997; Stock, Stone, & Iannuzzi, 1996; Zinreich, Derogatis, Herpst, Auvil, Piantadosi, & Order, 1990). Preservation of potency is more likely to occur if there is no or minimal impairment before treatment (Turner, Adams, Bull, & Berry, 1999).

Of the 600 articles reviewed by Robinson, Dufour & Fung (1997) on ED in men after PC treatment only 40 (15%) comprised papers in which pre-treatment erectile functioning was assessed. They stated that this is the most important criterion to provide meaningful end comparisons of ED after RP or RT. The lack of consistency in definitions of potency makes it difficult to compare the results from different studies.

In our study, potency was defined as the ability to achieve erections sufficient for sexual activity (masturbation or intercourse). Ideally, besides the questionnaire and in order to possibly differentiate between psychological and organic erectile dysfunction, we would have used also objective measurements as penile Doppler ultrasonography, Visual Sexual Stimulation or Nocturnal Penile Tumescence recording with the Rigiscan, but we felt this to be too time consuming and too cumbersome for our patients.

Because of the multifactorial nature of sexual dysfunction not only erectile function but also libido, satisfaction with sexual life and interest in sex should be assessed (Schover, 1993). Therefore, we adapted a 15-item questionnaire regarding many aspects of sexuality, routinely applied to all new ED patients (Incrocci, Hop, & Slob, 1996; Slob, Blom, & van der Werff ten Bosch, 1990). More recently an international questionnaire, also validated in our country, the International Index of Erectile Function (IIEF) has been introduced (Rosen, Riley, Wagner, Osterloh, Kirkpatrick, & Mishra, 1997), but unfortunately this was not yet available at the moment of our study.

Sexual dysfunction in PC patients can be due to different factors such as age, medical therapy, co-morbidity, use of tobacco, alcohol, previous pelvic surgery or the prostate carcinoma itself (Helgason, Adolfsson, Dickman, Arver, Fredrikson, & Steineck, 1997; Melman & Gingell, 1999). Helgason, Adolfsson, Dickman, Arver, Fredrikson, & Steineck (1999) reported ED in 57% of patients with PC after RT and 53% in the not-treated men, assessed at 1.5-2.5 years after diagnosis. This suggests that PC itself was associated with an increased risk of sexual impairment.

In our study the diagnosis PC resulted in decreased sexual activity. Although sexual functioning prior to diagnosis was assessed retrospectively (it is actually impossible to do this prospectively), the possibility of recall bias was rather limited because of the short time between diagnosis and survey (median 6 weeks).

The prostate gland itself is not essential for normal sexual function but most men express anxiety after diagnosis of PC thinking of losing erectile capacity because of treatment (Schover, 1993). Fear of death and worries about family can also play a role in impairing sexual functioning when men are told they have cancer.

We are aware that a control group of patients without PC would have been interesting, but this was not possible in our case. Of our patients only 35% expressed no problem with getting or maintaining an erection. Reports on the Dutch population reveal that in men 60-69 years and 70 years and older the percentage of problems in getting an erection is 22% and 38%, respectively (Meuleman, Donkers, & Kiemeneij, 2000). Thus, the incidence of ED in a normal population seems to be lower than in our PC patients. In the Meuleman et al. (2000) study 35% of subjects 60-69 years and in 53% in 70-79 years were satisfied with their sexual life; these figures are similar to our PC-patients data.

Bosch, Groeneveld, Bohnen, Prins, & Hop (1999) reported an incidence of ED in 49% of men 70-74 years, in a community-based sample of 1661 men. This percentage is much lower than in the present study (65%).

Forty-one per cent of our patients expressed a high level of sexual desire and 78% considered sex very important. Helgason, Adolfsson, Dickman, Arver, Fredrikson, Göthberg, & Steineck (1996) reported similar percentages in men without PC: 83% stated that sex was (very) important and 76% of men aged 60-69 years were potent.

Before diagnosis, 66% of our patients were sexually active. These percentages are similar to those of Janus & Janus (1993) who reported that 69% of 212 men 65 years and older had weekly sexual activity, and of Brecher (1984) who reported that 79% of 598 men 70 years and older were sexually active.

Diabetes and hypertension are significantly associated with ED, as well certain medications and the use of tobacco (Feldman, Goldstein, Hatzichristou, Krane, & McKinlay, 1994). We found no statistically significant difference regarding sexual functioning in patients with or without co-morbidity, possibly because of the small numbers (only 21% of patients with co-morbidity). None of our patients were on hormonal therapy; use of tobacco or alcohol was not always reported.

A significant difference in age was found between RP and RT patients, similar to earlier published studies (Lim, Brandon, Fiedler, Brickman, Boyer, Raub, & Soloway, 1995; McCammon, Kolm, Main, & Schellhammer, 1999; Shrader-Bogen, Kjellberg, McPherson, & Murray, 1997). Age difference is the main reason of all differences encountered in sexual

functioning, therefore the differences in sexual functioning between patients undergoing RT or RP are mostly related to the doctor's preference for surgical treatment in younger men.

We are aware of the limited value of these mainly descriptive data, but such information is useful to make comparisons of treatment morbidity. Currently, data are been collected on sexual functioning in the same patients, one and two years after therapy.

Conclusions

There is a decrease in all aspects of sexual functioning after the diagnosis of PC. Because of the impact of diagnosis and treatment of PC on sexual function, patients with PC may benefit profoundly from sexual counseling before (and presumably following) treatment. Baseline data on sexual functioning prior to treatment are relevant for later comparison with data after treatment and to detect treatment related morbidity.

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Table 1. Characteristics of $n=158$ patients with localized prostate cancer awaiting treatment, either radical prostatectomy (RP) or external beam radiotherapy (RT)

	Total ($n=158$)	RP($n=77$)	RT($n=81$)
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Median age (range) years	67 (50-80)	63* (50-73)	69 (55-80)
Diabetes Mellitus	5 (3)	1 (1)	4 (5)
Cardiovascular disease	30 (18)	11 (14)	19 (23)
TNM classification:			
T1	20 (13)	11 (14)	9 (11)
T2	97 (61)	52 (68)	45 (56)
T3	34 (22)	14 (18)	20 (25)
T4	3 (2)	0 (0)	3 (4)
unknown	4 (2)	0 (0)	4 (4)
N0	127 (80)	46 (60)	81 (100)
NX	31 (20)	31 (40)	0 (0)
M0	158 (100)	77 (100)	81 (100)
Differentiation grade:			
G1 (good)	78 (49)	40 (52)	38 (47)
G2 (moderately)	60 (38)	29 (38)	31 (38)
G3 (poor)	19 (12)	8 (10)	11 (14)
unknown	1 (1)	0 (0)	1 (1)
Median PSA (range) $\mu\text{g/l}$	9 (1-59)	4* (1-30)	8 (1-59)

* $p < 0.0001$ versus RT patients

Appendix A: Questionnaire on sexual functioning

1. How much sexual desire (sexual thoughts or feelings) did you have in the past 2 weeks?

None at all
Some
Moderately
Quite a bit
Very much

2. How often did you have a spontaneous erection (partly or complete, not during sexual activity) at night or in the morning in the past 2 weeks?

Never (skip next question)
About once
More than once
About once a day
More than once a day

3. How would you rate the quality of those spontaneous night or morning erections?

1	2	3	4	5
rather soft		half soft/half hard		very firm

4. How important is sex to you?

Very unimportant
Unimportant
Somewhat important
Important
Very important

5. How satisfied are you, in general, with your current sexual life?

Very satisfied
Satisfied
Somewhat satisfied
Unsatisfied
Very unsatisfied

6. Were you sexually active (i.e. masturbation or intercourse) before you were informed to have prostate cancer?

Yes, continue with question 7
No, skip questions 7-10

7. Since you were informed to have prostate cancer, were you less interested in sex than before your illness?

Not at all
A little
Quite a bit
Very much

8. Since you were informed to have prostate cancer, were you less sexually active than before your illness?

Not at all
A little
Quite a bit
Very much

9. Since you were informed to have prostate cancer, did you have more difficulty in getting or maintaining an erection than before your illness?

Not at all
A little
Quite a bit
Very much

10. Since you were informed to have prostate cancer, was sex less enjoyable for you than before your illness?

Not at all
A little
Quite a bit
Very much

11. Were you sexually active (i.e. masturbation or intercourse) in the past 2 weeks?

Yes, go to questions 13-15

No, go to question 12, skip questions 13-15

12. I was not sexually active in the past 2 weeks because

I had no sexual desire
I do not have a partner
My partner did not have sexual desire
I could not get an erection
Otherwise, (please describe)

13. Did you have difficulty in getting an erection in the past 2 weeks?

Yes, (almost) always

Yes, sometimes

No, (almost) never

14. Did you have difficulty in maintaining an erection in the past 2 weeks?

Yes, (almost) always

Yes, sometimes

No, (almost) never

15. How would you rate the quality of your erections during sexual activity in the past 2 weeks?

1
rather soft

2

3
half soft/half hard

4

5
very firm

Chapter 8

Sexual dysfunction after radiation therapy for prostate cancer: a review

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submitted

Abstract

Prostate cancer has become the most frequent malignancy in older men in Western countries. With the improvement of treatment efficacy sexual functioning has become more important. In the current review we discussed the various methods used for the evaluation of sexual dysfunction, the definition of potency and the etiology of erectile dysfunction after external beam radiotherapy and brachytherapy. The literature has been summarized and comparative studies of radiation and surgery have been briefly surveyed.

Percentages of erectile dysfunction following radiation reported in the literature vary enormously, from 6 to 84% after external beam radiotherapy to 0-51% after modern brachytherapy techniques. Most of the studies are retrospective, the definition of erectile dysfunction is not always clear, often only one question about sexual functioning is asked.

Time since radiation is very relevant, one should at least wait 18-24 months before drawing final conclusions on impotence occurrence. The most likely cause of erectile dysfunction after radiation for prostate cancer is a vascular damage although the etiology is not completely understood. Sexual desire, satisfaction, frequency of intercourse should also be assessed.

Patients should be offered sexual counseling and informed about the availability of effective treatments for erectile dysfunction such as sildenafil, intracavernosal injection and vacuum devices.

Key-words: prostate cancer, radiation, sexual function, sexual dysfunction

Introduction

Prostate cancer (PC) has become the most frequent malignancy in men in Western countries. In 1996, 6539 new cases were diagnosed in the Netherlands with an incidence of 87.7 per 100.000 persons (Netherlands Cancer Registry, 1998). Over recent years the number of diagnosed patients has dramatically increased because of routine prostate specific antigen (PSA) testing and the awareness of potential for early disease cure, with a 5-year survival rate of 98% (1). A commonly ignored aspect is the impact of PC-therapy on sexual activity and sexual functioning (2,3). Irrespective of the use of advanced surgical techniques, as the nerve-sparing radical prostatectomy and the introduction of 3-Dimensional Conformal Radiotherapy (3D-CRT), sexual functioning after PC treatment remains problematic for many patients.

Standard treatment options for PC comprise radical prostatectomy (RP), external beam radiotherapy (ERT) or observation. In recent years, in a number of institutions, brachytherapy (BT) has become the preferred treatment in small tumors or in combination with ERT for locally advanced tumors. The choice of treatment is usually determined not only by tumor staging, patient's age and comorbidity, but also by urologist's and patient's preferences.

Patients with higher-staged, i.e. T2b-T4, PSA >10 ng/ml, less differentiated tumors, are frequently offered ERT in combination with hormonal therapy (4). Younger patients, i.e. less than 70 years, with smaller tumors and lower PSA are offered RP or BT, if the medical condition is not compromised by a cardiovascular or pulmonary history. Wait and see is mainly offered to older patients (> 80 years) with low-staged tumors. We believe that patient's health-related quality of life (QoL), including sexual functioning, should also be an important factor in decision making. In fact, when given the choice, men might choose a treatment with lower long-term overall survival, if it would increase their chances of remaining sexually potent (5) and enjoying an active sexual life.

The purpose of this paper is to present an overview of the literature dealing with sexual and erectile dysfunction (ED) after ERT and/or BT. Abstracts-only or papers dealing with PC patients with metastatic disease, or on hormonal therapy, have not been included in this review. First, we will discuss the various methods used of evaluating and defining ED. Then the etiology of ED following ERT and BT will be reviewed. The literature will be summarized regarding ERT, BT and sexual functioning. Also papers dealing with sexual dysfunction other than ED will be discussed. Finally, comparative studies of ERT and RP will be briefly surveyed. We end this review paper with the main conclusions and recommendations for radiation oncologists.

Evaluating Erectile Dysfunction: Methodology and Difficulties

Already in 1965 concerns with sexual (dys)functioning in patients following ERT for PC were expressed (6,7). In 1977 Perez *et al.* mentioned impotence as a "vexing complication" (8). Most papers focussed on treatment outcome, and bowel and urinary toxicity; sexual function was only marginally mentioned. The first paper reporting extensively and specifically on potency after radiation treatment appeared in 1988 (9). The most practical and quickest way of evaluation of ED is the use of self-administered questionnaires.

The problem, however, is the variability of the questionnaires used in the published papers, i.e. some validated, some not. Only recently an international questionnaire, the International Index of Erectile Function (IIEF) has been validated in many countries and offers the possibility to make comparisons between different studies (10). However, to our knowledge, it has not been used in the evaluation of ED after radiation for PC.

In most papers from the 70's and 80's no methodological data was reported, that is only the rate of potency/impotence was mentioned (6-9,11-60).

In many of the published questionnaires on sexual function the questions were often limited to 2-6 items and were part of a more general questionnaire on toxicity of radiation treatment and/or on QoL in general (2,29,31,40,43,48,61-81). In the majority of cases the questionnaires as a whole were not included in the paper but, instead, just a few questions were listed (62,63,68,69,72,76,79,81-95). In some papers, fortunately, the complete questionnaire was presented as a table or as an appendix, which offered a more transparent description of the methodology used (2,64,67,75,80,96-98).

In summary, beyond the question on erectile function, the questionnaires used offered limited information on sexuality. There are, however, a few exceptions (9,85-88,91,96,99) where items such as desire, ejaculation, satisfaction with sexual life, frequency of spontaneous erections and frequency of intercourse were also asked.

Examples of extensive questionnaires are the Radiumhemmet scale of sexual functioning (87,91), the Derogatis Interview for Sexual Functioning (DISF) (100), the Brief Sexual Function Inventory (101) and the Psychosocial Adjustment to Illness Scale (PAIS) (102). Other validated instruments were seldomly used (71,73,75,77,78,80,103-105).

Definition of Potency

Another significant aspect in studies dealing with ED after ERT for PC is the lack of a definition for potency and/or impotence (6-8,11-16,18-20,22,23,25-33,35-7,39,41,42,46,47, 52,53,56-58,61-63,66,67,69,71,72,74,75,77-80,84,90,93-95,97,104-107).

The National Institute of Health (NIH) Consensus on ED defined impotence as: the consistent inability to attain and maintain a penile erection sufficient to permit satisfactory sexual intercourse (108). One could argue, however, that such a definition is strictly relevant in the presence of a willing partner.

A definition of (im)potence which is similar to the one advocated by the NIH but with some variations has been used by many authors in ERT and BT studies (17,21,24,34,38,40,43-45,51,54,55,59,60,64,68,70,83,85,87,89,92,96,99).

More detailed and complex definitions had been also advocated by other authors (2,48-50,76,82,86,88,89,91,98,109). A potency graded scale has also been used (48,76,89,98). McCammon *et al.* were the first to define potency as physician's documented erections (2) while Banker used both frequency of intercourse and rigidity of erections as a parameter for potency (9).

Potency does not only mean getting an erection but also the ability to maintain it. This latter aspect is very often ignored by the investigators or not discussed. Because ED is more than just a non-functional penis, other relevant sexual factors such as also libido, satisfaction with sexual life and interest in sex should also be assessed (110). Quality of erections, i.e. firmness of erections, is also very important. Knowledge about the presence of spontaneous erections or the occurrence of morning/night erections is necessary to differentiate between a (mainly) organic or a (mainly) psychological etiology.

One should be aware that in many irradiated patients psychological factors also play a role, albeit somewhat less important than the organic ones. There is a need to differentiate between having ED and not being sexually active. The latter is often due to factors other than erectile insufficiency, e.g. absence of a "willing" partner or lack of interest in sex in the man. Ejaculatory disturbances could also play a role, especially in patients irradiated for PC; sometimes older men cannot differentiate between being impotent and not being able to ejaculate. For this reason more complete questionnaires are recommended.

In conclusion, a simple, unequivocal definition of "potency" is lacking. Usually, the following questions have not been addressed properly: What is a good erection, the one assessed by the patient or by the physician? Is it necessary to use a complicated definition or is it sufficient to refer to the standard definition of the NIH? Is only the presence of an erection important or also the rigidity of these erections which allows sexual activity? We feel that the standard definition of (im)potence advocated by the NIH is appropriate and should be used, in order to make comparisons between different studies possible. Moreover, if a patient defines his own erection as sufficient for sexual intercourse or masturbation he should be considered potent. Nevertheless, for study purposes on potency in general, we believe that a more extensive evaluation of patients' sexuality should be carried out. Is the patient sexually

active, does he have a sexual partner, is his partner interested in sex with him, does he have premature ejaculation, does he have sexual desire. These and other sexuality items are relevant in the assessment of post-radiation (dys)function.

Etiology of Post-Radiation Erectile Dysfunction

To our knowledge only three papers with proper methodology have been published on the etiology of ED after ERT (111-113).

Goldstein *et al.* performed objective tests of erectile functioning in 23 patients, 6-60 months after ERT (30-70 Gy), including Nocturnal Penile Tumescence (NPT) tests, bulbo-cavernosus reflex latency, perineal electromiography, penile Doppler ultrasonography, and endocrine screening (blood levels of luteinizing hormone, prolactin and testosterone) (111). Before ERT, 15 patients were considered potent: erections sufficiently rigid for vaginal penetration and sustained until ejaculation, with regular coitus several times per month and well sustained periods of increases in penile circumference during NPT testing. Twelve patients whose erectile capacity worsened after ERT had normal blood hormone levels, and normal neurological tests. Vascular evaluation by penile Doppler was abnormal in all patients with altered erectile function after ERT. A selective pudendal arteriography performed in 2 patients revealed occlusive vascular disease within the pelvic radiation field (bilateral narrowing of the internal iliac arteries and tortuosity and occlusions of the internal pudendal and penile arteries).

In conclusion, endocrine data corroborated earlier findings of normal Leydig's cell function and testosterone production (8,16,83). Injury to the pelvic nerves could not be identified. The vascular abnormalities found could be explained because portions of the internal pudendal and penile arteries were inevitably exposed to the majority of the radiation delivered to the prostate. The presence of other vascular risk factors (smoking, hypertension) might predispose to develop a pelvic vascular insufficiency because of the synergistic effect of radiation. Furthermore, patients were also interviewed by a psychologist and feelings of anxiety, depression, anger, fear of failure, loss of masculinity were found. Mittal evaluated penile blood circulation and its effect on erectile function in 6 patients, before and 6-9 months after radiation using Penile Brachial Index (PBI) and Penile Flow Index (PFI) (112). No statistically significant difference between pre- and post-radiation values of PBI and PFI testing was found.

However, evaluation at 6-9 months after radiation is too short to show a possible damage to the vessels, and the methods used, nowadays considered obsolete, were possibly not accurate to draw conclusions.

Zelefsky and Eid evaluated 38 patients who became impotent after ERT or I-125 BT, using Duplex ultrasound before and after intracavernosal injection of prostaglandin (113). This method assesses the adequacy of penile blood flow and erectile function, structure and function of the cavernosal arteries and dorsal veins. Diameter of the arteries before and after injection can be used to quantify their distensibility and any increase in diameter of the cavernous arteries less than 95% was considered abnormal. A cavernosal dysfunction (abnormal cavernosal distensibility with a normal penile peak blood flow) was reported in 32% and arteriogenic (peak penile blood flow rates less than 25 cc/min) in 63% of the patients. Both dysfunctions were present in 3% of patients, neurogenic dysfunction (normal distensibility and normal peak blood flow values but poor erectile responses also after prostaglandin injection) in 3% of patients. Comorbidity, hormonal manipulation, smoking and age had no influence on the type of dysfunction observed. The authors concluded that the predominant etiology of radiation-induced impotence was arteriogenic, i.e. due to a disruption of the arteriolar system supplying the corporal muscles, although other unknown factors might also play a role (113). Thus, their conclusions corroborated those of Goldstein *et al.* (111).

In two BT studies mention of possible etiology of post-radiation ED was made (50,96) and two other papers studied specifically the dose to the neurovascular bundles in patients treated with Palladium-103 (Pd-103) or Iodine-125 (I-125) seeds, with or without ERT (114,115). Di Biase *et al.* postulated that BT-related impotence might be due to excessive radiation dose to the neurovascular bundles (114). The authors made a detailed calculation of the dose to these regions, which was higher than the prescription dose (for Pd-103 150-260 Gy, for I-125 200-325 Gy), but they did not correlate these findings with potency data. This was done by Merrick *et al.* in 33 patients who developed ED after BT and in 21 men who remained potent following treatment (115). By using the same methodology as Di Biase *et al.*, they found no significant difference in mean dose to the neurovascular bundles between potent and impotent men, between the two different isotopes (I-125 versus Pd-103) and with or without combination with ERT, after a follow-up time of 37 months (115).

It should be kept in mind that, because of the inability to visualize the bundles on a planning CT, doses had to be estimated and calculations therefore might not be always accurate.

Incidence of Erectile Dysfunction after External Beam Radiotherapy for Prostate Cancer Patients

Studies published in the 70's

To our knowledge, the first two studies on ERT for PC discussing potency were published in 1965 (6,7). Generally ED rates, albeit in small series, varied reportedly between 6 and 84% (11-13,15-17,19,21,22). In two larger studies incidence of ED, determined at 15 months post-ERT, was between 30-40% (15,17).

A compilation of the studies published in the 70's can be seen in Table 1. Unfortunately, because of the non-controlled character of most studies, no meaningful conclusions can be drawn. Treated patients were also younger (mean age 57-65 years) than we see nowadays for ERT treatment, and the percentage of patients potent prior to ERT was often missing except for a few studies (12,15,17,22).

Studies published in the 80's

In the 80's Megavolt energies using linear accelerators were routinely used and interstitial techniques were introduced. Comorbidity was seldom reported, with a few exceptions (9,33,35,99); all studies except one (35) reported ED percentages prior to ERT. A summary of the studies published in the 80's is presented in Table 1.

ED rates ranged from 11 to 73% (9,26,27,33,35-37,83,84,99). For the first time in the 80's sexual (dys)function was assessed prospectively; impotence did not correlate statistically significant with testosterone concentration (83,84) and tumor stage did not seem to influence incidence of ED (37).

In general, papers from the 80's did not differ much from those published in the 70's. However, there were two exceptions: in 1988 two innovative papers appeared which focussed specifically on sexual (dys)function after ERT for PC (9,99) .

Banker studied the relationship of potency before and after ERT (9). The author personally interviewed patients prior to and 8-12 months after treatment and concluded that men who were sexually active before treatment had a good chance of retaining potency after ERT (9).

This was the first prospective study focussing on ED following ERT. Van Heeringen *et al.* queried patients on comorbidity factors, smoking habits, partner availability, libido, erections, frequency of coitus and ejaculation and concluded that taking into account other aspects of sexuality than only ED, a higher proportion of patients had complaints in this regard after ERT. The need of adequate information on sexuality prior to ERT treatment was emphasized (99).

Retrospective studies published in the 90's

In this era of PSA-testing, ERT of PC was frequently characterized by more fields, shaped/customized blocks, a computer planning system and 3D treatment plans (54,55,60,69,86,88). QoL became also important in ERT trials although most questionnaires were still primarily related to urinary and bowel treatment sequelae. An overview of the retrospective studies published in the 90's is given in Table 2. For the first time also partners were interviewed (85,86,88) and percentages of patients potent prior to ERT were reported in nearly all studies, except for a few (51,67,75,80). Post-radiation ED rates varied from 17 to 84% (38,51,54,55,60,61,66,67,74,80,86-88,90,97) and, with regard to 3D-CRT, from 27% to 49% (55,60,74,86). Different and sometimes conflicting results were reported regarding correlation of medical or surgical history and the occurrence of ED. Age correlated positively with ED in one study (61) but not in others (38,54,55,60); comorbidity, a history of TURP or a RP correlated positively in two studies (51,86), but not in others (38,54,55,60,61,86,87).

Tumor stage was not found to influence ED rates (38,51,54,55,60,61,86). Pre-ERT potent patients who received a dose of 75.6 Gy or more had an impotence percentage of 68% at 5 years versus 52% for those treated to 70.2 Gy or less (54,55). Other studies could not corroborate these findings (38,60,86). Hormonal manipulation (54,55,87) was not correlated with ED, while patients marginally potent prior to radiation were more likely to become impotent following treatment (51,86). Volume of tissue irradiated did not influence sexual complications because the neurovascular bundles were always included in the full dose treatment field running along the edge of the prostate (67).

Helgason *et al.* were the first to link the decrease of sexual capacity to a change in QoL (87). The importance of time factor was stressed by some authors reporting an increase of ED occurrence with increasing follow-up (51,60). Nguyen *et al.* randomized 112 patients to conventional or 3D-CRT (70 and 78 Gy, respectively), reporting an overall ED rate of 49%, not different from the 47% and 52% for conventional and 3D-CRT techniques, respectively (74). Special ERT beams such as proton, pion and neutron have also been reported to have a detrimental effect on potency (29,49,79) similar to those reported with the more common used photon beams.

Prospective studies published in the 90's

In the 90's a few studies were performed prospectively, reporting the number of patients potent prior to ERT and in most cases the exact follow-up time of ED evaluation (see Table 2 for an overview). We think this is the only correct way to avoid recall bias of pretreatment potency status. These prospective studies revealed more realistic ED percentages, which appeared to be much lower than those reported in retrospective studies published in the same years. Although these prospective studies were carried out adequately, ED percentages still varied considerably, from 7 to 72% (47,65,69,70,85,98,109). Time factor, i.e. time since radiation, was again found to be very relevant (69,98). Tumor stage, radiation dose, comorbidity, TURP prior to ERT had no predictive value on sexual dysfunction after ERT; good prognostic factors were a lower age and pre-treatment functional erections (109). A trend that radiation field and size had a role in sexual function, i.e. the smaller the field size the better sexual functioning was found for the first time (69).

Incidence of Erectile Dysfunction after Brachytherapy for Prostate Cancer Patients

Results of radium BT in bladder and prostate cancer were reported as early as 1917 (116). Nowadays, much experience has been accumulated with various forms of interstitial techniques (retropubic, suprapubic, transperineal), of prostate visualization through ultrasound and computer tomography (CT) imaging, of treatment planning (pre and post-implantation dosimetry) with the use of various isotopes such as I-125, Iridium-192 (Ir-192) and Pd-103. BT was originally introduced (and gained popularity) to limit the detrimental effects of ERT on bowel and urinary function but also with regard to sexual function.

Because of the very few papers specifically focussing on ED it is difficult to give a meaningful overview (see Table 3). In essence, the same problems as for ERT studies were encountered; there was often no clear definition of potency, most studies were of retrospective nature and did not report on comorbidity, with a few exceptions (24,30,32,39,43,44,50, 52,53,72,106), and in most studies no percentages of patients potent prior to BT were given. Other complicating factors, whose specific effects on erectile function remain unclear, were the combination of BT and ERT and seeds implantation performed after lymph nodes dissection with incision of the endopelvic fascia to mobilize the prostate gland. Percentages of ED after BT monotherapy were usually lower than after ERT alone. However, a selection bias might exist because patients who are highly motivated to maintain potency are more likely to choose BT. Furthermore, a lower average age, a better performance status and a more favorable tumor staging of patients undergoing BT, probably due to selection bias by the referring urologist and the radiation oncologist, could also explain the lower percentages of impotence rates after BT together with a rapid fall-off of isotopes that delivers the lowest radiation dose to the neurovascular bundles.

In studies from the 70's ED ranged from 0 to 25% (14,20,23,24,82), being highest when BT was used in combination with ERT (20). Herr reported specifically on sexual potency following BT and stressed the importance of a thorough explanation to the patient of the procedure and its influence on sexual functioning, advocating the importance of sexual counseling (82). In the 80's percentages of ED following BT seemed to be higher than in the 70's, ranging from 8 to 61%, probably because of the frequent combination with ERT (25,28,30-32,34,106).

In the 90's, advances in radioisotope development, with the introduction of Pd-103, sophisticated 3D computer-assisted dosimetry, intraoperative trans-rectal ultra sound (TRUS) availability, and introduction of the transperineal approach, produced a more homogeneous and reproducible implant than in the past with the retropubic route. In general, in studies using I-125 and/or Pd-103 the ED rates ranged from 2 to 51% (40,41,43-45,48,50,52,53,56-59,68,89,95,96,105), with again the highest percentages found when BT and ERT were combined (41,45,78,95).

The highest ED rates, ranging from 25 to 89%, have been reported following the combination of a temporary Ir-192 implant followed by ERT (39,42,46,72).

With respect to the differences between I-125 and Pd-103, ED rates were 6-21% (40,43,44,56) and 15% (53), respectively. No statistically significant difference was found between I-125 and Pd-103 implants on ED (96), but in another paper Pd-103 resulted in a worsening of sexual function (50). When the exact time of impotence evaluation was indicated in studies of I-125 or Pd-103 without the combination of ERT, ED rates were at 12 months 2-8% (48,50), at 24 months 6-21% (40,50,89) and at 36 months 19% (44). One paper reported no differences in ED occurrence following BT alone or the combination ERT and BT (41). A new concept of "temporarily impotence" was introduced because of painful/uncomfortable erections after BT (43). For the first time an increase in erectile function was found in 21% of patients following BT (48) while a decrease in penile sensitivity suggested a neural component in the etiology of ED (96).

Ejaculatory and other Sexual Dysfunctions

The ability to achieve and sustain erections is only one component of the entire sexuality picture. Loss of libido and ejaculation disorders are very important as well. A deterioration of sexual activity has significantly been associated with the severity of ejaculatory dysfunction, mainly a decrease in volume or an absence of semen (117). Ejaculatory disturbances in BT studies varied from diminishing or absence of ejaculate volume (7%-45%) to discomfort during ejaculation (3-11%) to hemospermia (5%) (24,32,40,43,68,82).

Following ERT lack of ejaculation was reported in 2 to 56% (19,65,87,99). Dissatisfaction with sexual life was reported in 25-60% (83,109), a decreased libido in 8-53% (72,99,109) and a decreased sexual desire in 12-58% (40,66,72,87). One study reported a decreased intensity of orgasm, decreased frequency of erections and less erection rigidity, and decreased importance of sex (87).

Comparative studies of External Beam Radiotherapy versus Radical Prostatectomy

Because of the growing popularity of modern 3D-CRT techniques in the 90's complications of ERT and RP were compared (for a summary of the studies see Table 4). Survival benefits of PC-treatments had to be balanced by acceptable side effects and ED was a bothersome complication of the surgical treatment approach. ED rates after RP seemed to be much higher than following ERT, therefore patients who wanted to preserve sexual potency were more frequently referred to the radiation department.

In comparative studies, ED rates after RP varied from 48 to 98% while after ERT these rates were 31-85% (2,62-64,71,76,81,91, 92,104). A meta-analysis including only men potent prior to treatment showed that the probability of maintaining normal erections after ERT was 0,69 and after RP 0,42, difference statistically significant (118). A comment seems at place. The authors determined ED at one year post-treatment on the assumption that at this time the final effect of ERT is expected to be present and the recovery after surgery is expected to have been achieved. However, this interval might be too short to reveal all ERT effects; as previously reported there is a clear decrease in erectile function between 12 and 24 months following radiation (69,98).

Concluding Remarks and Recommendations

There are still no conclusive data on ERT techniques, field sizes, energy used and their specific influence on sexual function. Conventional and conformal techniques resulted in the same rates of ED. However, prospective studies with larger series, and the use of standardized validated instruments, have to confirm these findings. Conformal techniques using shaped blocks do not spare the neuro-vascular bundles because these are always entirely in the high-dose prostate field. No reliable data is at the moment available on the correlation between doses in this region and the occurrence of ED after ERT. Although the arteriogenic mechanism seems to be mainly involved this is certainly not the only one because radiation dose to the neurovascular region after BT has not been found different in potent and impotent patients. The radiation dose received by the corpora cavernosa, at the crura of the penis, might be also important in the etiology of ED but data are lacking. A multifactorial etiology has to be considered, taking into account comorbidity, previous TURP, drugs, and pre-treatment erectile function. Furthermore, not only a functional penis but a functional man, and also his partner, has to be considered assessing sexual desire, satisfaction with sexual life, libido and frequency of intercourse as well. Prevention is a difficult matter: by accepting the hypothesis that radiation induces vascular damage, any methodology of decreasing the dose to the pelvic vascular structures would decrease ED rate. Thus with the modern Intensity Modulated Radio Therapy (IMRT) techniques, a higher percentage of PC patients might stay sexually potent after radiation. Much work has still to be done on the etiology of radiation-induced impotence. Time post-radiation therapy and ED evaluation has also to be considered.

It is not possible to draw final conclusions when evaluation is made at 6-12 months after ERT or BT, one should wait at least 18-24 months when ED occurrence has reached a maximum and remains stable further on. It is also obligatory to determine pre-treatment sexual functioning; high percentages (up to 60%) of patients may be impotent already before radiation therapy. A "standard" definition of (im)potence as advocated by the NIH should always be used and a standardized methodology of ED evaluation by using, prospectively, validated questionnaires on QoL and sexual functioning is mandatory.

A better understanding of the etiology would allow a more specific knowledge of therapy possibilities. Improved penile blood flow through the cavernosal arteries induced by elective phosphodiesterase inhibitors can be effective when arteriogenic dysfunction is predominant. Sildenafil citrate (Viagra®) has been reported to be effective in up to 74% of patients 2 years or longer after ERT (119-121) and in 80% following BT (122), but in no case a randomized, placebo-controlled trial was performed. Also intracavernosal injection of prostaglandines or phentolamine-papaverine is effective (123), suggesting a predominant vascular etiology.

Patients may also benefit of the implantation of a penile prosthesis (124). New drugs for ED are at the moment under evaluation such as the central agent apomorphine and a new class of phosphodiesterase inhibitors that might be more effective in post-radiation ED. Sildenafil taken at bedtime has been found to significantly increase nocturnal erectile activity, especially in the older age group and in patients with vasculogenic ED (125). We could hypothesize this might be a potential way of preventing or minimizing the vascular deterioration that usually occurs following radiation therapy. Finally, sexual counseling: patients need to be correctly informed on the anatomy of the prostate, on the possible sequelae of radiation on their sexual life and functioning, including ejaculation disturbances, which are quite often neglected. They should also be informed about the various effective treatments for ED available nowadays: sildenafil, autoinjection therapy, vacuum pump and erection prosthesis.

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Table I: Incidence of Erectile Dysfunction after External Beam Radiotherapy (ERT) for Prostate Cancer: studies from the 70's and the 80's

Author (reference)	Year	Patients <i>n</i>	Mean age* years (range)	Patients potent prior to BRT <i>n</i> (%)	Mean total dose Gy (range)	Mean follow-up months (range)	Incidence % (<i>n</i>)
Studies from the 70's							
Loh (12)	1971	36	66 (49-79)	19 (53)	70 (53-76)	n.a. (5-60)	84 (16/19)
Rhamy (13)	1972	15	57 (39-73)	n.a.	n.a.	up to 48	47 (7/15)
Ray (15)	1973	310	63 (39-89)	96 (31)	n.a. (70-82)	n.a.	30 (29/96) at 15 months
Bagshaw (17)	1975	430	59 (n.a.)	110 (26)	n.a. (70-76)	n.a.	41 (65/110) at 15 months
Mollenkamp (18)	1975	88	65 (47-84)	n.a.	n.a. (42-75)	n.a. (12-60)	23 (20/88)
McGowan (19)	1977	107	64 (50-79)	n.a.	n.a. (45-60)	n.a. (24-65)	6 (7/107)
Perez (8)	1977	112	n.a. (40-81)	n.a.	n.a. (40-70)	n.a. (12-60)	13 (15/112)
Taylor (22)	1977	278	n.a.	108 (39)	n.a. (65-75)	n.a.	22 (24/108)
Studies from the 80's							
Tomic (83)	1983	12	66 (55-73)	12 (100)	64 (58-71)	22 (6-66)	25 (9/12)
Forman (33)	1985	240	68 (52-86)	105 (44)	65 (n.a.)	40 [†] (12-108)	43 (45/105)
Asbell (35)	1988	445	68 (n.a.)	n.a.	n.a. (45-72)	84 [†] (n.a.)	11-53 (n.a.)
Bagshaw (36)	1988	914	63 (35-86)	434 (47)	70 (n.a.)	up to 180	14 (n.a.) at 15 months
Banker (9)	1988	85	n.a.	26 (30)	n.a. (45-70)	n.a. (8-12)	73 (19/26)
van Heeringen (99)	1988	18	71 (60-82)	11 (61)	65 (n.a.)	20 (4-45)	27 (3/11)
Shipley (37)	1988	121	68 (n.a.)	54 (45)	n.a. (65-68)	n.a. (60-114)	37 (20/54) at >36 months
n.a. data not available							
* mean age for entire group							
† median							

Table 2: Incidence of Erectile Dysfunction after External Beam Radiotherapy (ERT) for Prostate Cancer: studies from the 90's

Author (reference)	Year	Patients <i>n</i>	Mean age* years (range)	Patients potent prior to ERT <i>n</i> (%)	Mean total dose Gy (range)	Mean follow-up months (range)	Incidence % (<i>n</i>)
Retrospective studies							
Mameghan (38)	1991	218	67 [†] (45-87)	42 (19)	n.a. (50-65)	55 (n.a.)	45 (19/42) at 24 months
Jønler (61)	1994	98	74 [†] (55-89)	68 (77)	n.a. (66-70)	31 [†] (14-60)	84 (57/68)
Helgason (87)	1995	53	70 (53-80)	33 (66)	63 (56-66)	n.a. (18-24)	50 (26/53)
Roach (88)	1996	124	72 [†] (48-87)	60 (48)	n.a. (59-87)	21 [†] (7-40)	38 (23/60)
Crook (97)	1996	192	70 (49-87)	158 (82)	n.a. (60-66)	33 (12-72)	35 (55/158)
Caffo (66)	1996	90	71 [†] (49-83)	45 (50)	n.a. (60-70)	35 [†] (6-86)	67 (30/45)
Fransson (67)	1996	199	71 [†] (51-86)	n.a.	65 (61-69)	48 (24-56)	56 (n.a.)
Mantz (51)	1997	114	68 (52-85)	n.a.	n.a. (65-70)	18 (n.a.)	2 (n.a.) at 1 month 8 (n.a.) at 12 months 25 (n.a.) at 24 months 34 (n.a.) at 36 months
Fosså (90)	1997	114	69 (n.a.)	22 (19)	n.a. (64-66)	n.a.	61 (13/22)
Nguyen (74)	1998	101	n.a.	81 (80)	n.a. (70-78)	>24	49 (40/81)
Zelevsky (54)	1998	743	69 [†] (51-84)	385 (52)	n.a. (65-81)	36 [†] (12-92)	27 (104/385)
Zelevsky (55)	1999	743	69 [†] (51-84)	544 (73)	n.a. (65-81)	42 [†] (18-109)	39 (211/544)
Fransson (75)	1999	83	73 (55-85)	n.a.	65 (n.a.)	96 (72-104)	65 (54/83) at 96 months
Johnstone (80)	2000	46	80 [†] (62-90)	n.a.	67 (63-70)	167 [†] (120-276)	76 (35/46)
Wilder (60)	2000	51	68 [†] (n.a.)	35 (69)	74 (66-79)	15 [†] (n.a.)	0 at 12 months 17 (9/51) at 24 months 37 (19/51) at 36 months

Table 2: continued

Author (reference)	Year	Patients <i>n</i>	Mean age* years (range)	Patients potent prior to ERT <i>n</i> (%)	Mean total dose Gy (range)	Mean follow-up months (range)	Incidence % (<i>n</i>)
Prospective studies							
Zinreich (85)	1990	27	68 (52-80)	10 (37)	n.a.	n.a.	20 (2/10) at 12 months
Pilepich (47)	1995	230	71 [†] (49-84)	102 (44)	n.a. (65-70)	54 [†] (n.a.)	72 (74/102)
Beckendorf (109)	1996	67	68 (54-84)	40 (60)	68 (58-70)	n.a. (8-12)	33 (13/40)
Beard (69)	1997	121	n.a.	69 (57)	n.a (65-72)	n.a.	57 (39/69) at 3 months 64 (44/69) at 12 months
Borghede (70)	1997	184	67 (46-83)	134 (73)	70 [†] (60-72)	46 (24-96)	7 (9/134)
Turner (98)	1999	290	69 (44-82)	182 (63)	66 [†] (60-70)	23 [†] (n.a.)	38 (56/146) at 12 months 59 (40/68) at 36 months
n.a. data not available							
* mean age for entire group							
† median							
‡ at survey							

Table 3: Incidence of Erectile Dysfunction after Brachytherapy (BT) for Prostate Cancer

Author (reference)	Year	Isotope/Technique	ERT	Patients <i>n</i>	Mean age* years (range)	Patients potent prior to BT <i>n</i> (%)	Prescribed dose Gy (range)	BT Total dose Gy (range)	ERT Mean follow-up months (range)	Incidence % (<i>n</i>)
Whitmore (14)	1972	I-125/RTP	-	26	n.a.	15 (58)	n.a. (80-160)	-	n.a. (3-24)	13 (2/15)
Carlton (20)	1976	Au-198/RTP	ERT	109	n.a.	n.a.	n.a. (25-35)	n.a. (40-50)	n.a. (12-120)	25 (23/109)
Hilaris (23)	1976	I-125/RTP	-	112	58 (36-77)	n.a.	n.a.	-	42 (24-72)	0
Fowler (24)	1979	I-125/RTP	-	116	60 (36-77)	109 (94)	n.a.	-	23 (1-90)	7 (8/109) at 15 months
Herr (82)	1979	I-125/RTP	-	51	65 (52-74)	41 (80)	n.a.	-	>6	2 (1/41) at 6 months
Shipley (25)	1980	I-125/RTP	ERT	30	64 [†] (52-76)	19 (63)	160	10	>12	11 (2/19)
Ross (28)	1982	I-125/RTP	ERT	57	65 (51-75)	n.a.	100	40	22 (1-52)	50 (29/57)
Flanigan (30)	1983	I-125/RTP	ERT	25	61 (51-70)	23 (88)	n.a.	10	30 (12-48)	26 (6/23)
Schellhammer (31)	1983	I-125/RTP	-	90	62 (46-77)	n.a.	160	-	>12	8 (n.a.) at 12 months 25 (n.a.) at 36 months
Kwong (32)	1984	I-125/RTP	-	65	63 (45-78)	45 (69)	160-180	-	n.a.	13 (6/45)
Bosch (34)	1986	Ir-192/TPR	ERT	43	64 (53-73)	31 (73)	30	40	n.a.	61 (19/31)
DeLaney (106)	1986	I-125/RTP	ERT	64	64 (48-79)	34 (53)	160	10	60 (24-108)	29 (10/34)
Syed (39)	1992	Ir-192/TPR	ERT	200	65 (49-81)	100 (50)	30-35	30-40	n.a.	25 (n.a.)
Arterbery (40)	1993	I-125/TPR	-	21	67 (59-78)	18 (86)	160	-	13 (2-24)	6 (1/18) at 24 months
Blasko (41)	1993	I-125; Pd-103/TPR	ERT	469	n.a.	n.a.	160-115 [‡]	45	38 (12-78)	<70 15;>70 50
Stromberg (42)	1993	Ir-192/TPR	ERT	57	63 (40-77)	46 (80)	30-35	36	72 [†] (0-102)	57 (26/46) at 24 months
Kleinberg (43)	1994	I-125/TPR	-	31	67 [†] (58-80)	18 (58)	140-160	-	>12	6 (1/18)
Wallner (44)	1994	I-125/TPR	-	62	67 [†] (58-80)	38 (61)	160	-	19 [†] (6-55)	19 (7/38) at 36 months
Kaye (45)	1995	I-125/TPR	ERT	72	71 (50-83)	44 (61)	120-160	45	26 (11-60)	25 (11/44) at 12 months
Martinez (46)	1995	Ir-192/TPR	ERT	59	n.a.	n.a.	15-19	46	19 (4-36)	38 (n.a.)

Table 3: continued

Author (reference)	Year	Isotope/Technique	ERT	Patients <i>n</i>	Mean age* years (range)	Patients potent prior to BT <i>n</i> (%)	Prescribed dose BT Gy (range)	Total dose ERT Gy (range)	Mean follow-up months (range)	Incidence % (<i>n</i>)
Stone (48)	1995	I-125; Pd-103/TPR	-	58	68 (49-75)	12 (21)	n.a.	-	12 (6-24)	8 (1/12) at 12 months
Chaikin (96)	1996	I-125; Pd-103/TPR	-	37	n.a.	27 (73)	n.a.	-	18 (5-32)	45 (12/27)
Stock (89)	1996	I-125; Pd-103/TPR	-	97	69 [†] (49-82)	64 (66)	160-115 [‡]	-	18 [†] (6-51)	21 (13/64) at 24 months
Stock (50)	1996	I-125; Pd-103/TPR	-	89	69 [†] (49-82)	65 (73)	160-115 [‡]	-	15 [†] (1-52)	2 (2/64) at 12 months 6 (4/65) at 24 months
Arterbery (68)	1997	I-125; Pd-103/TPR	-	51	n.a.	35 (69)	n.a.	-	n.a.	13 (4/35) at 6 months
Koutrouvelis (52)	1998	I-125; Pd-103/n.a.	-	130	71 [†] (49-90)	n.a.	160-120 [‡]	-	n.a. (6-24)	5 (n.a.)
Joly (72)	1998	Ir-192/TPR	ERT	71	68 (51-82)	n.a.	15	40-45	n.a.	89 (n.a.)
Sharkey (53)	1998	Pd-103/TPR	-	434	73 (52-83)	n.a.	n.a.	-	28 (12-60)	15 (n.a.)
Zelevsky (56)	1999	I-125/TPR	-	145	64 [†] (n.a.)	128 (88)	140-160	-	24 [†] (6-103)	21 (28/132)
Kestin (57)	2000	Ir-192/TPR	ERT	161	69 [†] (n.a.)	n.a.	6-10	46	34 [†] (5-86)	29 (47/161)
Sánchez-Ortiz (105)	2000	I-125; Pd-103/TPR	-	114	69 (n.a.)	81 (71)	115	-	23 (4-72)	51 (41/81)
Sharkey (58)	2000	Pd-103/TPR	-	299	73 (48-88)	n.a.	n.a.	-	n.a.	15 (n.a.)
Zelevsky (59)	2000	I-125/TPR	-	248	65 [†] (45-80)	221 (89)	140-160	-	48 [†] (12-126)	29 (64/221)

Isotope: Gold-198 (Au-198); Iridium-192 (Ir-192); Iodine-125 (I-125); Palladium-103 (Pd-103)

Technique: Retropubic (RTP); Transperineal (TPR)

Combination with external beam radiotherapy (ERT)

n.a. data not available

* mean age for entire group

† median

‡ I-125/Pd-103 respectively

Table 4: Incidence of Erectile Dysfunction in studies of Radical Prostatectomy (RP) versus External Beam Radiotherapy (ERT) for Prostate Cancer

Author (reference)	Year	RP patients <i>n</i>	ERT patients <i>n</i>	Mean age* RP years (range)	Mean age* ERT years (range)	Patients potent prior to RP <i>n</i> (%)	Patients potent prior to ERT <i>n</i> (%)	NS/NNS RP
Lim (64)	1995	89	46	65 (41-78)	71 (62-85)	73 (82)	n.a.	NS/NNS
Litwin (62,63)	1995	98	56	70 (n.a.)	76 (n.a.)	n.a.	n.a.	NS/NNS
Helgason (91)	1997	22	37	69 (54-79)	69 (55-78)	n.a.	n.a.	n.a.
Shrader-Bogen (71)	1997	132	142	66 (n.a.)	75 (n.a.)	n.a.	n.a.	n.a.
Yarbro (104)	1998	68	53	69 (n.a.)	75 (n.a.)	n.a.	n.a.	n.a.
Talcott (92)	1998	125	135	61 (41-72)	68 (49-86)	n.a. (68)	n.a. (55)	NS/NNS
McCammon (2)	1999	203	257	63 (43-74)	70 (n.a.)	n.a.	n.a.	NS/NNS
Lilleby (76)	1999	108	154	63 (47-78)	66 (48-81)	n.a.	n.a.	NS/NNS
Smith (81)	2000	1247	189	68 [†] (n.a.)	74 [†] (n.a.)	<70 (81); >70 (55)	<70 (61); > 70 (50)	n.a.

NS=nerve-sparing RP; NNS=non-nerve sparing RP

n.a. data not available

* mean age for entire group

[†] median

[‡] at survey

Table 4: continued

Mean total dose Gy (range)	Mean follow-up RP months (range)	Mean follow-up ERT months (range)	Incidence RP % (n)	Incidence ERT % (n)
n.a. (65-72)	n.a. (3-18)	n.a. (3-18)	97 (71/73)	54 (25/46)
66 (n.a.)	n.a. (60-72)	n.a. (60-72)	71 (n.a.)	64 (n.a.)
63 (n.a.)	n.a. (18-24)	n.a. (18-24)	86 (n.a.)	57 (n.a.)
n.a.	32 (12-60)	41 (12-60)	83 (110/132)	70 (99/142)
n.a.	30 (n.a.)	25 (n.a.)	98 (n.a.)	65 (n.a.)
n.a.	n.a.	n.a.	95 (n.a.) at 3 months	48 (n.a.) at 3 months
			91 (n.a.) at 12 months	61 (n.a.) at 12 months
n.a.	40 [†] (12-144)	31 [†] (12-121)	67 (132/198)	60 (147/246)
n.a. (64-66)	41 (12-116)	31 (12-121)	48 (52/108) at 12 months	31 (45/154) at 12 months
n.a.	34 (n.a.)	33 (n.a.)	<70 75; >70 94	<70 71; >70 85

Chapter 9

Summary and Conclusions

Summary and Conclusions

The use of visual sexual stimulation (VSS) in the differential diagnosis of men with erectile dysfunction (ED) has been suggested by different authors and strongly advocated by our group (see Appendix). The combination of VSS with penile vibration (VIB) using a small vibrator, attached to an erectionmeter and applied to the frenulum area of the glans penis, proved to be an excellent method in determining (remaining) erectile capacity in ED-patients. Following priming with VSS and VSS plus VIB, a low dose intracavernosal injection (ICI) of a vasoactive drug was in the vast majority of patients effective in eliciting an erection sufficiently rigid for sexual intercourse. To the patient and the doctor such a penile response means that the neurovascular mechanism is intact and that the male is potentially sexually potent. However, in cases of no penile response, this has no significant diagnostic meaning. Various reasons can be responsible for the absence of penile response, i.e. somatic or psychological, e.g. psychic inhibition, or the video may not be sexually arousing.

When using this psychophysiological screening method on a routine basis in 406 consecutive patients with various ED etiologies it appeared that up to 80% of the patients responded with a good erection (Chapter 2). Although men under 40 years of age responded significantly better than men over 40, no difference in penile response was found between ages 40 and 80. This demonstrates that this methodology also has its significance in testing older men with sexual dysfunction. Also the addition of VIB and ICI increased penile response in virtually all patients of all ages. In summary, VSS alone caused a penile response in one third of the patients, the combination of VSS and VIB caused 52% of the patients to respond, while VSS with ICI elicited a good penile response in 82% of the patients. Nowadays we would advise to use this psychophysiological diagnostic screening (PDS) only in those ED-patients where medical history reveals no erection whatsoever: not during the night, not in the morning, not with sexual activities, either with the partner or solo with masturbation. PDS remains a very useful instrument for research purposes since it nicely shows the erectile capacity of a patient.

In the same group of 406 patients a follow-up investigation was carried out in order to ascertain current sexual functioning 1 to 4 years after the consultation at the psychophysiological laboratory (Chapter 3). An extensive questionnaire was developed and mailed to all patients; a representative sample of 237 (54%) patients responded.

About half of the patients reported to have undergone some form of ED treatment (autoinjection treatment, vacuum device, sex therapy/counseling). It is important to note that this study was carried out before sildenafil (Viagra®) had become available. More than half of the patients reported no change in their original complaint, about a quarter had improved and another quarter reported a further deterioration of their sexual dysfunctioning. No statistically significant correlation was found between original psychophysiological responding and current satisfaction scores. Only the occurrence of daytime spontaneous erections and the frequency of morning/night erections (information easily obtained through history taking) correlated positively with present satisfaction with sexual functioning. Overall, these results are somewhat disappointing because they clearly show the need for a more appropriate therapeutic approach to patients with erectile difficulties. Furthermore, we believe that the results of this follow-up study clearly indicate that effective somatic treatments such as autoinjection therapy, vacuum device therapy or drug medication (even sildenafil treatment) should be combined with sexual counseling or sex therapy in order to further improve their efficacy.

Surgical castration, trauma or agenesis of a testicle may produce psychosexual problems, especially in young men. Testicular prostheses (TP's) are easy to insert, complications are mild and cosmetic results are quite satisfactory. We retrospectively studied 30 patients (mean age 30 years) who had received a TP earlier in their life (**Chapter 4**). About 40% of the men considered their body appearance greatly improved and 27% slightly improved after receiving a TP. About 60% of the patients were satisfied with their current sexual life, 10% complained of ED and 45% were bothered by premature ejaculation. The relatively low frequency of sexual problems may be related to the positive body image and the high satisfaction rate after the insertion of a TP. Men of all ages and their partners benefited from the restoration of a normal social and sexual functioning.

Peyronie's disease (PD) is a mysterious condition; a genetic predisposition for a fibrotic response most likely leads to rupture of microvasculature followed by fibrosis in the penis in these subjects. This results in a plaque of scar tissue in the tunica albuginea of the penis and consequently in penile curvature, usually with discomfort during sexual activity. Many treatment options have been advocated, all more or less with positive study outcomes: vitamin E, Potaba, colchicine, tamoxifen or intralesional injections with corticosteroids or Verapamil. PD is self-limiting in 50% of the patients within 12-18 months. However, if penile discomfort

is long lasting therapy is indicated. In cases of severe penile curvature surgery remains the therapy of first choice. We investigated through questionnaires 179 patients who had received external beam radiotherapy (ERT). This proved to have been effective in a decrease of penile pain in 83% of the patients and of penile curvature in 23%, mostly within 3 months. No side effects were observed (**Chapter 5**).

Sexual functioning in patients following ERT for PD is a much neglected area. We evaluated 106 patients (mean age 69 years) who had received ERT a mean of 9 years earlier, by analyzing the answers to an extensive questionnaire regarding sexual desire, significance of sex, frequency and rigidity of spontaneous erections (=morning/night erections), difficulty in getting and maintaining an erection (**Chapter 6**). About one third of the patients never had spontaneous erections, about half had sometimes or always difficulty in getting an erection. A decrease had occurred in sexual interest, in sexual activity and in sexual pleasure after ERT for PD in 28%, 67% and 49%, respectively, but patients were also 9 years older. About half of the patients reported not being satisfied with their current sexual life. All these variables were correlated with age. Thus, complaints in sexual functioning following ERT for PD were age-related. Therefore, sexual counseling before and after ERT is highly recommended, since we found that after ERT for PD erectile function improved only in 13% of patients.

Prostate cancer (PC) has become the most frequent malignancy in men in Western countries. Standard treatments comprise radical prostatectomy (RP), ERT or brachytherapy (BT) with or without hormonal therapy, or observation. Choice of treatment is often determined by tumor staging, patient's age and comorbidity, urologist's and patient's preferences. The impact on sexual activity and sexual functioning of PC diagnosis and subsequent therapy is quite frequently ignored. Receiving the diagnosis of PC causes a significant decrease in sexual activity, interest and pleasure. We studied 158 PC-patients awaiting treatment (RP or ERT) (**Chapter 7**). An increase in problems with getting an erection has been observed in up to 20% of the patients. A significant decrease of patients who are sexually active after receiving the diagnosis compared to 4-9 weeks previously has also been observed. Patients awaiting RP were significantly younger with a lower incidence of cardiovascular diseases than patients awaiting ERT. The RP-group was significantly sexually more active and reported significantly fewer problems in getting or maintaining an erection than patients in the ERT-group. Age was the most relevant variable responsible for the differences encountered in sexual functioning between RP- and ERT-patients.

This can easily be explained by a physician's bias: i.e. the doctor's preference for surgical treatment in younger men. Baseline data on sexual functioning prior to treatment are relevant for later comparisons with data after treatment and to detect treatment related morbidity.

Reviewing the literature on sexual (dys)function following radiotherapy (ERT and/or BT) for PC appeared cumbersome and not without caveats (**Chapter 8**). There are many studies published on this subject but conclusive data are still lacking on the influence of techniques, e.g. field sizes and energy on sexual functioning. Methodological problems encountered were manifold: which questionnaire was used? Was it validated? Was it dealing only with erections or did it offer a more comprehensive picture of patient's sexuality: his desire, ejaculation, satisfaction with sexual life, frequency of erections and of intercourse? In very few studies extensive, validated questionnaires were used. Furthermore, the definition of potency/impotence was quite variable. We strongly recommend the use of a standardized definition, for instance the one proposed by the National Institute of Health and somewhat adapted: impotence is the consistent (or prevailing) inability to attain and maintain a penile erection sufficient to permit satisfactory sexual activity, i.e. intercourse or masturbation. ED is, of course, more than only a non-functional penis, other sexual parameters of the ED-patient such as libido, interest in sex and satisfaction with sexual life should also be taken into account. Therefore, a simple unequivocal definition of potency/impotence is needed. For study purposes a more complex evaluation of patients' erectile function should be carried out; if a patient defines his own erection as sufficient for sexual intercourse or masturbation he should be considered potent. With these shortcomings it is difficult to summarize from the literature the incidence of ED after ERT for PC. This varies in fact from 6 to 84% in studies published in the 70's, from 11 to 43% in studies of the 80's, from 0 to 84% in retrospective studies of the 90's and presumably more reliably from 7 to 64% in prospective studies of the 90's. After BT these percentages range from 25 to 89% with the combination of ERT and from 2 to 51% using Iodine-125 or Palladium-103 seeds. Conformal and conventional techniques do not seem to differ much in the occurrence of ED, 52% versus 47% respectively.

A much neglected parameter in many studies is the time of ED evaluation following treatment. There is a clear increase in the occurrence of ED with increasing follow-up time. Therefore, it is obligatory to wait at least 18-24 months before final conclusions can be drawn. The common belief that the incidence of ED after radiation is lower than after RP has

to be changed. If one waits long enough the ED-percentages following ERT and BT will reach similar values as after RP.

The etiology of ED after radiation for PC is not completely understood. The most likely cause is a damage of the neurovascular bundles by the radiation. A better understanding of the etiology would certainly allow more therapeutic options. Sildenafil citrate (Viagra®) has been reported to be effective in up to 74% of patients two years or more after ERT and 80% after BT (no follow-up time indicated). These results cannot be considered conclusive because in no case a randomized, placebo-controlled, double-blind trial has been performed. In an ongoing study (randomized, placebo-controlled, double-blind) in 60 patients, performed in the Department of Radiation Therapy of the University Hospital Rotterdam-Daniel den Hoed Cancer Center, our first results indicate that 100 mg sildenafil citrate is effective in 50% of our patients. In this study patients using nitrates for cardiovascular comorbidity were excluded. For those patients autoinjection therapy or penile prosthesis still remain a good alternative in the treatment of radiation-induced ED.

In summary, we believe that patients awaiting treatment for PC should be correctly informed about the possible sequelae of radiation on their sexual life and sexual functioning, including ejaculatory disturbances. Patients should also be informed about the various effective and available treatments for ED, should such a condition occur following PC-treatment.

Finally: sex: does it matter in cancer patients? The answer comes from a 71 years old patient after 4 years of unsatisfactory sexual activity following ERT for his prostate carcinoma, using sildenafil (Viagra®): "At 7 a.m. I took the "pill", at 8.15 a.m. I started with foreplay, with quite reasonable results. At penetration I knew right away...it is going to be as in the old days; after a few minutes I did get a good erection and it felt as in the past! A fantastic experience!" (letter of a patient).

Samenvatting

Samenvatting

Visuele seksuele stimulatie (VSS) gecombineerd met vibrotactiele stimulatie van de penis (VIB), met een kleine vibrator in het frenulum gebied van de penis, is een excellente methode in de differentiaal diagnose van mannen met erectiele disfunctie (ED) om de (nog) aanwezige potentie te bepalen (zie Appendix). Na voorbereidende stimulatie met VSS en VSS+VIB is een intracaverneuse injectie (ICI) met een lage dosis van een vaso-actief middel (bijvoorbeeld prostaglandine of de combinatie papaverine/fentolamine) vrijwel altijd voldoende voor het veroorzaken van een (vrijwel) volledige erectie, stijf genoeg voor seksuele activiteit. Deze penisrespons laat dus zien dat het neurovasculaire mechanisme intact is en dat de man in principe seksueel potent is. Indien er geen respons optreedt hoeft dit geen diagnostische waarde te hebben. Meerdere oorzaken zouden dit “falen” kunnen verklaren, somatisch (gebruik van bepaalde medicijnen; vasculaire insufficiëntie), maar ook psychologisch (bijvoorbeeld een psychische inhibitie, of de video is seksueel niet opwindend voor de man op dit moment).

We hebben routinematig VSS, VSS+VIB and ICI gebruikt bij 406 opeenvolgende patiënten van verschillende ED etiologie; 80% van de patiënten reageerde met een goede erectie (**Hoofdstuk 2**). Mannen onder de 40 jaar gaven een betere respons dan mannen boven de 40, maar er werden geen verschillen gevonden tussen de leeftijdsgroepen 40-60 en 60-80 jaar. VSS alleen gaf een goede penisrespons in éénderde van de patiënten, de combinatie van VSS en VIB bracht de respons tot 52% en VSS+ICI tot 82%. Momenteel adviseren wij deze diagnostische methode bij patiënten met ED indien anamnestic géén erecties meer worden gerapporteerd, niet ‘s nachts, niet bij het wakker worden en niet tijdens seksuele activiteit (met partner of bij solo-masturbatie).

In diezelfde groep van 406 mannen werd een follow-up onderzoek uitgevoerd om het seksueel functioneren te bepalen 1-4 jaar na de eerste onderzoeken in het psychofysiologische laboratorium (**Hoofdstuk 3**). Van de 237 mannen (54%, representatief voor de gehele groep) die reageerden, gebruikte (of had gebruikt) ongeveer de helft enige behandeling voor ED (autoinjectie therapie, vacuüm pomp, seksuele counseling). Tijdens deze studie was sildenafil citraat (Viagra®) nog niet op de markt. Meer dan de helft van de patiënten rapporteerde geen verschil ten opzichte van de oorspronkelijke klachten, een kwart was verbeterd en een kwart was seksueel slechter gaan functioneren.

Er werd geen significant verschil gevonden tussen de oorspronkelijke respons in het laboratorium en de huidige tevredenheid scores; alleen spontane erecties en het hebben van erecties bij het wakker worden of 's nachts, correleerde positief met het huidige seksueel functioneren. Deze resultaten zijn enigszins teleurstellend want zij tonen aan dat de somatische therapie bij mannen met ED (zoals autoinjectie therapie, vacuüm pompen en ook tegenwoordig sildenafil) in veel gevallen toch niet voldoende is. Ons advies is dat de somatische therapie gecombineerd wordt met begeleiding, of met seksuologische counseling.

Chirurgische castratie, een trauma of agenesie van een testikel kan psychoseksuele problemen veroorzaken, vooral bij jonge mannen. Testis prothesen zijn eenvoudig te implanteren, complicaties zijn gering en de cosmetische resultaten zijn zeer redelijk. In **Hoofdstuk 4** hebben wij gerapporteerd over een onderzoek bij 30 mannen (gemiddelde leeftijd 30 jaar) die eerder een prothese hebben gekregen. Ongeveer 40% van deze mannen vond hun "body image" sterk, en 27% licht verbeterd na de implantatie. Zestig procent was tevreden met hun huidige seksuele leven, 10% klaagde over ED en 45% over vroegtijdige zaadlozing. Het lage percentage van seksuele problemen kan gerelateerd worden aan een positieve "body image" en een hoge tevredenheid na implantatie van een testis prothese.

De ziekte van Peyronie is een mysterieuze aandoening met een onduidelijke oorzaak. Een trauma van de penis in erectie veroorzaakt mogelijk schade aan de microvasculatuur met als gevolg fibrosis van de penis bij mannen met predispositie voor zulk een fibrotische respons. Het gevolg is een plaque van littekenweefsel in de tunica albuginea met als gevolg een kromming van de penis in erectie en pijnklachten, meestal tijdens seksuele activiteit. In de loop van de jaren zijn er verschillende behandelmethodes geprobeerd, met uiteenlopende resultaten, bijvoorbeeld: vitamine E, Potaba, colchicine, tamoxifen, en verder corticosteroiden of Verapamil toegediend lokaal in de plaque. De ziekte van Peyronie is "self-limiting" bij 50% van de mannen, binnen 12-18 maanden. Bij een forse verkromming is chirurgie de eerste behandeloptie, doch ook radiotherapie is een geaccepteerde behandeling. We analyseerden het effect van uitwendige radiotherapie in 179 patiënten (**Hoofdstuk 5**). 83% rapporteerde een vermindering van de pijn en 23% had een vermindering van de verkromming, meestal binnen 3 maanden en zonder bijwerkingen.

Het seksueel functioneren van patiënten met de ziekte van Peyronie krijgt in de internationale literatuur weinig aandacht. Wij evalueerden 106 patiënten (gemiddelde leeftijd 59 jaar), die gemiddeld 9 jaar eerder bestraald waren, met een uitgebreide vragenlijst over hun

huidige seksueel functioneren: zin in seks, seksuele verlangens, frequentie en rigiditeit van erecties en eventuele problemen met het krijgen en behouden van een erectie (**Hoofdstuk 6**). Ongeveer éénderde van de mannen ervaaarde nooit spontane (=ochtend/nacht) erecties, de helft had soms of altijd problemen bij het krijgen van een erectie. Een vermindering in seksuele interesse, seksuele activiteit en seksueel plezier na radiotherapie in vergelijking met vóór behandeling werd gerapporteerd in respectievelijk 28%, 67% en 49%. Het is belangrijk te bedenken dat de patiënten ook gemiddeld 9 jaar ouder waren geworden. Ongeveer de helft van de patiënten was ontevreden over hun huidige seksuele leven. Deze variabelen waren gecorreleerd met leeftijd. Op grond van deze resultaten bevelen wij seksuele counseling sterk aan, zowel vóór als na radiotherapie voor de ziekte van Peyronie, aangezien de erectiele functie bij slechts 13% van de patiënten verbeterde.

Prostaatkanker wordt behandeld met een radicale prostatectomie, uitwendige of inwendige radiotherapie (brachytherapie), met of zonder hormonale therapie, of observatie (=geen behandeling). De therapiekeuze wordt vooral bepaald door tumorstadium, de leeftijd en comorbiditeit van de patiënt, en de voorkeur van de uroloog en de patiënt. De invloed van de diagnose "prostaatkanker" en van de daarbijbehorende therapie op de seksuele activiteit en het seksueel functioneren van de patiënt wordt regelmatig onderschat of vergeten. Alleen al de diagnose "prostaatkanker" veroorzaakt frequent een vermindering van seksuele activiteit, interesse en plezier. Bij 20% van de patiënten wordt een toename gevonden van problemen bij het krijgen van een erectie en tevens is er een vermindering in seksuele activiteit vergeleken met 4-9 weken voorafgaande aan de diagnose (**Hoofdstuk 7**). Onderzocht werden 158 patiënten die prostaatkanker hadden en in afwachting waren van behandeling, òf een prostatectomie, òf radiotherapie. Patiënten die een prostatectomie zouden ondergaan waren meestal jonger en hadden minder vaak een cardiovasculaire voorgeschiedenis dan patiënten die bestraald zouden gaan worden. Voorts waren de patiënten in de chirurgiegroep vaker seksueel actief en hadden ze minder frequent erectiestoornissen dan patiënten in de radiotherapiegroep. Leeftijd was de meest relevante variabele bij het verklaren van alle verschillen tussen de twee groepen. Deze verschillen in seksueel functioneren zijn dus in belangrijke mate te verklaren door de therapiekeuze van de dokter: jongere mannen wordt vaker een operatie voorgesteld. Data over het seksueel functioneren voorafgaande aan de behandeling zijn belangrijk om later te kunnen vergelijken met data na de behandeling en voor de evaluatie van de latere morbiditeit van de behandeling.

Het laatste **Hoofdstuk (8)** in dit proefschrift is een literatuuroverzicht over seksuele (dis)functie na radiotherapie voor prostaatkanker. Er zijn geen definitieve gegevens over de invloed van de radiotherapeutische techniek, zoals veldgrootte en energie, op het seksueel functioneren. In de literatuurstudie bleken er veelvuldig methodologische onduidelijkheden: welke vragenlijst werd gebruikt? was deze gevalideerd? werd er alleen vragen over erecties gesteld? of ook over andere aspecten van het seksuele leven van de patiënt: interesse in seks, tevredenheid met seksuele leven, frequentie van erecties en van coïtus? Slechts in een klein aantal studies werden gevalideerde vragenlijsten gebruikt. Ook de definitie van potentie/impotentie was heel verschillend. Naar ons idee zou een gestandaardiseerde definitie gebruikt moeten worden, bijvoorbeeld die van de 'National Institute of Health', met enige aanpassingen: impotentie (=ED) is het constante (of overwegend) onvermogen om een erectie te krijgen en te behouden die voldoende is voor seksuele activiteit (coïtus of masturbatie). Maar ED is meer dan alleen een niet-functionele penis, ook andere seksuele aspecten zijn van belang zoals libido, interesse in seks en tevredenheid met het seksuele leven. Voor fysiologisch laboratoriumonderzoek kan een complete evaluatie van de erectiele functie nodig zijn, maar als de patiënt zelf zijn erecties definieert als voldoende voor seksuele gemeenschap of masturbatie dient hij als potent beschouwd te worden. Gezien de eerdere genoemde moeilijkheden bleek het lastig om uit de literatuur tot een betrouwbare schatting te komen van de incidentie van ED na radiotherapie voor het prostaatcarcinoom. Percentages variëren tussen 6 en 84% in studies uit de jaren 70, van 11 tot 43% in studies uit de jaren 80, van 0 tot 74% in retrospectieve studies uit de jaren 90 en -waarschijnlijk reëler- percentages van 7 tot 64% in prospectieve studies uit de jaren 90. Na de brachytherapie zijn de ED-percentages 25 tot 89% in combinatie met uitwendige bestraling en 2 tot 51% met het gebruik van I-125 of Pd-103 zaadjes. Conformatie en conventionele radiotherapie lijken niet verschillend te zijn in het percentage van ED na behandeling: 52% en 47% respectievelijk.

Een ander belangrijk aspect was de tijdsperiode na behandeling wanneer ED werd geëvalueerd. Er werd een duidelijke toename waargenomen van ED bij een langere follow-up. Daarom is het noodzakelijk om minstens 18-24 maanden te wachten voordat betrouwbare conclusies getrokken kunnen worden. Een en ander betekent dat het idee dat de incidentie van ED na radiotherapie lager is dan na prostatectomie, niet langer meer opgaat. Immers, indien men lang genoeg wacht worden de percentages van ED na uitwendige en inwendige radiotherapie vergelijkbaar met die na (zenuwsparende) radicale prostatectomie.

De etiologie van ED na radiotherapie is nog onduidelijk. De meest waarschijnlijke oorzaak is schade aan de neurovasculaire bundels door de dosis van de radiotherapie. Meer duidelijkheid over de oorzaak zou meer therapeutische opties bieden. Sildenafil citraat (Viagra®) is effectief gebleken in 74% van de patiënten na uitwendige radiotherapie (2 jaar of langer) en 80% na brachytherapie (tijd niet vermeld). Maar deze resultaten komen uit studies die niet gerandomiseerd, niet placebo-gecontroleerd en niet dubbel-blind zijn. Wij hebben een onderzoek verricht bij 60 mannen (wel gerandomiseerd, placebo-gecontroleerd en dubbel-blind) en de eerste resultaten tonen een effectiviteit van 100 mg sildenafil in 50% van de patiënten aan. Patiënten die werden behandeld met nitraten in verband met een cardiovasculaire aandoening waren geëxcludeerd voor de studie. Voor deze categorie mannen zou autoinjectietherapie, of vacuümpomp of in het laatste geval een erectieprothese een goed alternatief kunnen zijn als behandeling van ED als gevolg van radiatieschade.

Naar ons idee dienen patiënten die behandeld moeten gaan worden voor hun prostaatacarcinoom goede voorlichting krijgen over de mogelijke consequenties van de radiotherapie op hun seksuele leven en hun seksueel functioneren, en tevens over de mogelijke ejaculatiestoornissen. Patiënten dienen op dat moment ook volledig geïnformeerd te worden over de verschillende behandelingsopties voor erectiestoornissen, indien die zouden gaan optreden.

Seks, is het relevant bij kankerpatiënten? Het antwoord komt van een 71 jarige man die, na 4 jaar lang onbevredigende seksuele gemeenschap als gevolg van radiotherapie voor zijn prostaatacarcinoom, sildenafil (Viagra®) gebruikte: “'s morgens rond 7 uur heb ik een pil ingenomen, om 8.15 uur ben ik begonnen met voorspel, met redelijk succes. Bij het binnendringen wist ik het meteen...dit wordt als vanouds, na een aantal minuten, kreeg ik een erectie, die was zoals weleer, een waardevolle beleving!” (brief van een patiënt).

List of abbreviations

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3D-CRT	three-dimensional external beam radiotherapy
AIT	autoinjection therapy
BT	brachytherapy
ED	erectile dysfunction
ERT	external beam radiotherapy
Gy	gray
ICI	intracavernosal injection
IMRT	intensity modulated radiotherapy
KV	kilovolt
MeV	megaelectronvolt
MV	megavolt
NIH	National Institute of Health
NPT	nocturnal penile tumescence
PBI	penile brachial index
PC	prostate cancer
PD	Peyronie's disease
PDS	psychophysiological diagnostic screening
PE	premature ejaculation
PFI	penile flow index
PPS	psychophysiological screening
PSA	prostate specific antigen
QoL	quality of life
RP	radical prostatectomy
RT	radiotherapy
TP	testicular prosthesis
TRUS	trans-rectal ultrasound
TURP	trans-urethral resection of the prostate
VES	visual erotic stimulation
VIB	vibrotactile stimulation
VSS	visual sexual stimulation

List of Publications

List of publications

1. **L. Incrocci** and A.K. Slob: Visual sexual stimulation and penile vibration in screening men with erectile dysfunction. *Int J Impotence Res* 1994;6:227-229 [*Letter to the Editors*].
2. **L. Incrocci**, W.C.J. Hop and A.K. Slob: Visual erotic and vibrotactile stimulation and intracavernous injection in screening men with erectile dysfunction: a 3 year experience with 406 cases. *Int J Impotence Res* 1996;8:227-232.
3. A.K. Slob, P.E.M. Lottman, W.C.J. Hop, **L. Incrocci** and J.J. van der Werff ten Bosch: Diagnosis and treatment of erectile dysfunction in retrospect. *Sexual Dysfunction* 1998;1:43-47.
4. **L. Incrocci**, J.L.H.R. Bosch and A.K. Slob: Testicular prostheses: body image and sexual functioning. *BJU International* 1999;84:1043-1045.
5. **Luca Incrocci**, Arendjan Wijnmaalen, A. Koos Slob, Wim C.J. Hop, and Peter C. Levendag: Low-dose radiotherapy in 179 patients with Peyronie's disease: treatment outcome and current sexual functioning. *Int J Radiation Oncology Biol Phys* 2000; 47:1353-1356.
6. **Luca Incrocci**, Wim C.J. Hop and A. Koos Slob: Current sexual functioning in 106 patients with Peyronie's disease treated with radiotherapy 9 years earlier. *Urology* 2000;56:1030-1034.
7. **Luca Incrocci**, Joanna B. Madalinska, Marie-Louise Essink-Bot, Wim L.J. van Putten, Peter C.M. Koper, Fritz H. Schröder: Sexual functioning in patients with localized prostate cancer awaiting treatment. *Journal Sex & Marital Therapy* 2001, *in press*.
8. **Luca Incrocci**, A. Koos Slob and Peter C. Levendag: Sexual dysfunction after radiation therapy for prostate cancer: a review. *Submitted*.

Appendix

LETTER TO THE EDITORS

Visual sexual stimulation and penile vibration
in screening men with erectile dysfunction

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With great interest we read the December 1993 issue of this journal, an NIH consensus statement on impotence and comments and suggestions of about 38 experts in the field from all over the world.

We thoroughly appreciated the attempts of the editors of this journal. At the same time we were somewhat disappointed by the organizers of the NIH congress that apparently an important aspect in the process of differential diagnosis of men with erectile problems was totally neglected: the use of visual sexual stimulation (VSS). Only Morales & Heaton¹ mentioned it and were somewhat reluctant to really advocate this method because of their inability to satisfactorily deal with negative results. In an earlier paper they have discussed the use of VSS as a possible alternative to NPT². During the past 15 to 20 years various scientists and clinicians have proposed and discussed the use of VSS, with or without vibrotactile stimulation (VIB), eg Bancroft³, Rosen & Leiblum⁴, Wagner and co-workers⁵⁻⁷.

In our psychophysiology laboratory we have used VSS routinely for many years in the evaluation of more than 550 men with erectile difficulties. In our first paper⁸ we reported on the usefulness of an erectionmeter for NPT measurements and VSS penile response measurements. The erectionmeter measures increase in penile circumference as well as rigidity of the erection. In a follow-up study⁹ we found that a positive VSS response and the occurrence of nocturnal erections were of relatively high prognostic significance with respect to treatment outcome. In that study we suggested that the positive outcome itself is facilitated by the experience of a penile response during VSS. Over the years we have optimized our VSS methodology by administering concomitant vibrotactile stimulation (VIB) to the underside of the tip of the penis¹⁰⁻¹². It appeared that the enhancing effect of the combined stimulation on objective and subjective penile response was greater when VIB followed VSS than when it preceded it, a finding which was recently also reported by Janssen et al¹³. To the patient, we always reinforce the penile response positively: it shows that nothing serious is wrong, that the genital apparatus is capable of responding sexually. When no response occurs, we are very keen to

reassure the man and explain that such a response has *no diagnostic significance!* We emphasize that there are many psychological reasons why a man does not react in the laboratory: the film is not sexually stimulating, the man could be afraid to lose control, the man could be too tense, etc. When no response occurs, we combine VSS and VIB with an intracavernous injection (ICI) of a vasoactive substance. This appears to be very successful. Of the last 74 consecutive men treated this way, 58 (78%) showed a full or almost full erection (usually including a swollen phallus, indicating partial psychogenic erection activity). It is worth mentioning that Virag and his collaborators routinely used the combination of a low dose ICI with VSS when screening men with erectile difficulties¹⁴.

Currently, we are pleased with our investigative procedures. They are not very invasive, they provide information relevant both to the doctor and to the patient: a positive penile response to a sexual stimulus proves that the neurovascular mechanism is intact and that the man is potentially sexually potent. Quite frequently, the positive response has a positive, therapeutic effect on the patient. Similar findings were recently published by Janssen and collaborators¹³.

A remark about age: in our process of differential diagnosis all men are exposed to VSS and VIB. Although Buvat and co-workers¹⁵ have suggested that many men of over 50 do not respond to VSS, we have obtained different results. A recent unpublished analysis of 406 consecutive patients with ED in the years 1991 through 1993 revealed that many older men showed a good penile response to VSS. Men under 40 years of age responded better than men over 40 years; between 40 and 80 years men did not differ in their VSS response. The addition of VIB to the VSS significantly increased penile response with approximately 30% in men of all ages.

Finally, we would like to repeat a suggestion we made earlier¹⁶. In screening men with erectile dysfunction it is important to carry out diagnostic tests (VIB, ICI) in a sexually positive atmosphere (ie a quiet private room, provided with sexually stimulating materials: video or magazine) to reduce the occurrence of false-negative results. When such a goal cannot be reached in a urology clinic, close collaboration with a psychophysiology lab should be initiated.

We hope that this letter will invite many colleagues to start using VSS plus VIB, with or without ICI, early in the screening process of men with erectile difficulties. It is stimulating to discover how many men with erectile difficulties are still potentially able to function sexually. Although the diagnosis reads 'psychogenic', many relatively simple and effective treatments are available nowadays which can be used, in many cases only temporarily because the problems disappear: vacu-pump, intracavernous self-injections, elastic band around base of penis, yohimbine. Ideally these treatments coincide with simple sexual counselling and positive reinforcement by the doctor.

ACKNOWLEDGMENTS—Thanks are due to Professor F. H. Schröder, MD, urologist, for his continuous interest in this research and to two reviewers for critical comments on an earlier version of this manuscript.

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Curriculum Vitae

Curriculum vitae

Luca Incrocci was born on January 7, 1962 in Lucca (Italy). After graduating from high school he started studying Medicine at the University of Pisa (Italy) where he graduated cum laude in April 1992. In July 1992 he went to The Netherlands where he worked as a resident in the Department of Urology of the University Hospital Rotterdam-Dijkzigt (Chairman Professor F.H. Schröder, M.D., Ph.D., urologist) till December 1994. During that period he started research projects in collaboration with the Department of Endocrinology & Reproduction of the Erasmus University Rotterdam (Professor A.K. Slob, Ph.D., medical physiologist/sexologist). In 1995 and 1996 he followed the postgraduate training in Sexology under the auspices of the Dutch Society for Sexology. In January 1996 he started his residency training in the radiation oncology at the University Hospital Rotterdam-Daniel den Hoed Cancer Center (Chairman Professor P.C. Levendag, M.D., Ph.D, radiation oncologist) which was completed in December 2000. In January 2001 he was registered as a radiation oncologist, he joined the staff and he is now working at the University Hospital Rotterdam-Daniel den Hoed Cancer Center. He is an active member of the International Society for Sexual and Impotence Research (ISSIR) and is Associate Editor of the ISSIR NewsBulletin. He is married to Nicole Bootsma and is father of Jonathan (1996) and Carlotta (2000).

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Dankwoord

Dankwoord

Onderzoek verrichten is een passie geweest sinds mijn eerste studie jaren. Ik heb geleerd dat je onderzoek niet alleen kan doen, maar afhankelijk bent van vele mensen met wie je ideeën, interpretaties, discussies kunt delen.

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