Review Article

Radiotherapy for prostate cancer and sexual health

Luca Incrocci

Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Correspondence to: Luca Incrocci, MD, PhD. Associate Professor, Department of Radiation Oncology, Erasmus MC Cancer Institute, PO Box 2040, Rotterdam 3000 CA, The Netherlands. Email: L.Incrocci@erasmusmc.nl.

Abstract: Sexual dysfunction is very common after treatment of prostate cancer. Radiation therapy together with radical prostatectomy is the most effective treatment for localized disease. Percentages of erectile dysfunction (ED) reported in prospective studies after external-beam radiotherapy (RT) vary from 60-70%, and these are similar after brachytherapy. In randomized trials more realistic percentages of 30-40% are reported. Modern techniques do not seem to decrease post-radiation ED. No final conclusions can be drawn whether or not the radiation dose to the penile structures correlates with post-radiation ED in patients treated for prostate cancer. The etiology of ED after RT of prostate cancer is most probably multi-factorial. The phosphodiesterase type 5 inhibitors (PDE5-I) sildenafil and tadalafil have been shown to be effective to treat post-radiation ED in about half of the patients in randomized trials. Patients and their partners need to be adequately counselled on the effects of cancer treatment on their sexual life and relationship, and about the different treatment possibilities. Sexual counselling has not become yet a routine part of oncology care in most hospitals, but this should be provided. Due to the lack of robust data, prevention of post-radiation ED with PDE5-I cannot be recommended so far.

Keywords: Prostate cancer; radiotherapy (RT); erectile dysfunction (ED); sexual dysfunction; sexual counseling

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Introduction

The number of cancer survivors continues to increase due to the aging and growth of the population, and improvement in early detection and treatment (1). Among men, the most common cancer affects the prostate. About 60% of prostate cancer survivors are aged 70 years or older, and many remain interested in sex (2). Therefore it is important to understand the medical and psychosocial needs of prostate cancer survivors and proactively address sexual health.

Primary treatments for prostate cancer are radical prostatectomy, radiotherapy (RT) (external-beam, brachytherapy or a combination), or observation. The choice of treatment depends on tumor staging, patient's age and comorbidity, urologist's and patient's preferences (3). More often, patient's quality of life, including sexual functioning, plays a significant role in the decision making on which treatment the patient prefers. The introduction of sildenafil (Viagra®) in the late 1990s, with media attention towards erectile dysfunction (ED), has made sexual problems more normative and has increased acceptance of help-seeking (2,3). This paper is an extension on a previous published paper (3) and aims at specifically address sexual health after RT for prostate cancer.

Definition and evaluation of erectile (dys) function

The 3rd International Consultation on Sexual Medicine defined ED as the consistent or recurrent inability to attain and/or maintain a penile erection sufficient for sexual performance (4). Such a definition is strictly relevant in the presence of a willing partner, therefore the general term sexual activity (intercourse or masturbation), would be more appropriate (5). Rigidity of erections, presence of spontaneous morning and night erections should be addressed as well (5). Psychological factors may play a role in post-radiation ED. In most of the published studies,

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authors referred to the general terms potency or impotence without giving a proper operational definition (5). The most practical way to evaluate erectile function is by using questionnaires, and different questionnaires have been used in the literature so far. In most of the cases questions on sexual functioning were limited to a few items, or were incorporated into a questionnaire on toxicity of radiation treatment, or on quality of life in general. With a few exceptions, the entire questionnaire was not included in the papers. Since the end of the 1990s, the International Index of Erectile Function (IIEF) has been introduced (6), followed later by the shortened IIEF-5 questionnaire (also known as the Sexual Health Inventory for Men or SHIM) (7). The IIEF and the SHIM have been translated and validated in many languages, though they have not been specifically developed for cancer patients. More recently a specific questionnaire on sexual functioning after treatment of cancer has been developed in the USA, but has not been validated yet in other countries (8).

Incidence of post-radiation sexual dysfunction

Only studies that prospectively evaluated erectile functioning, by using validated questionnaires and using a proper definition of potency are useful to draw conclusions on the incidence of post-radiation ED (5). In general, this reaches about 60-70% in prospective studies (5,9,10). Three recent prospective studies have shown an incidence of ED in 30-40% of the patients treated by external-beam RT. They showed an increase of post-radiation ED between one and two years, with no changes after three years (11-13). Brachytherapy was originally introduced not only to limit the detrimental effects of external-beam RT on bowel and urinary function, but also to help preserve sexual function. The introduction of sophisticated 3D-computer-assisted dosimetry, and the availability of intra-operative transrectal ultrasound in the late 1990s, led to more accurate and reproducible implants. In general, after permanent seed implantation, ED rates range from 5-51% (5,14).

A deterioration of sexual activity has also been associated with the severity of ejaculatory dysfunction, particularly with decreased volume or absence of semen (15). After RT for prostate cancer, ejaculatory disturbances vary from a reduction or absence of ejaculate volume (2-56%) to discomfort during ejaculation (3-26%) and hemospermia (5-15%) (5,14). Dissatisfaction with sex life has been reported in 25-60%, decreased libido in 8-53%, and decreased sexual desire in 12-58% of the patients (5). A decreased intensity of orgasm, decreased frequency and rigidity of erections, and decreased importance of sex have also been reported (5,9,10,14).

New radiation techniques and sexual (dys) function

In the last decade substantial improvements have been made in the irradiation techniques and doses, therefore post-radiation outcome and toxicity in prostate cancer patients have improved. Sophisticated planning systems have allowed the introduction of intensity-modulated RT (IMRT), which enables adequate dose delivery with better sparing of the normal tissues. IMRT has almost completely replaced the older conformal RT techniques (16,17). Image-guided RT techniques such as implanted fiducials and cone-beam computed tomography (CT) equipped linear accelerators have added even more precision and will hopefully allow for further decrease in toxicity. Several trials on hypofractionated RT for prostate cancer (higher dose per fraction) are on-going. These schedules could improve therapeutic gain, reduce toxicity as well offer economic and logistic advantages (18,19). Stereotactic body RT has been used for several years now in patients with prostate cancer, often using 2-5 fractions, with encouraging results and acceptable toxicity (18,19). Though the clinical advantages of all these new techniques have not been proven in randomized trials yet but only in comparative studies. These techniques, unfortunately, seem to cause post-treatment ED similarly to conventional RT (18,20) or even worse outcome (16,17). Proton therapy is a relatively new conformal technique to treat prostate cancer. This modality delivers less radiation dose to normal tissues compared to traditional RT. Few data are available on the effects of proton therapy on erectile function. Only one study has reported prospectively on the rates of potent patients before and after proton therapy using a validated questionnaire (21). It seems that this technique reduces the percentage of post-radiation ED: at 2 years 73% of patients reported no or mild ED compared to baseline levels. This study only included men of 60 years and younger, which may bias the results as seen in daily practice (21).

Mechanisms of post-radiation ED

Post-radiation ED in patients with prostate cancer has already been extensively and critically reviewed (5,9,10,14). Zelefsky and Eid concluded that the predominant etiology

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of radiation-induced impotence was arteriogenic (22). Several studies investigated the relationship between the radiation dose to the neurovascular bundles, the penile bulb and the penile bodies and the incidence of post-radiation ED, presenting contradictory results (23). In a randomized dose-escalation trial comparing 68 and 78 Gy, the proximal corpora cavernosa (crura), the superiormost 1-cm segment of the crura, and the penile bulb were contoured on the planning CT-scan and dose-volume parameters were calculated in 96 patients (24). Two years after RT, 35 patients had developed ED. No statistically significant correlations between post-radiation ED and dose-volume parameters in the crura, the most superior 1-cm segment of the crura, or the penile bulb were found (24). Magnetic resonance imaging (MRI) appeared to be superior to CT for the imaging of erectile tissues, and showed that the dose to the penile bulb and corporal bodies is low, but the dose has not been correlated to post-radiation ED (25). Post-radiation ED has more likely a multi-factorial etiology, and is not only based on the radiation dose to one single anatomical structure. It is very likely that the structure responsible for ED has not been investigated yet (24). Carrier *et al.* conducted an experiment in which 47 male rats were treated at the prostatic area with a single fraction (10 or 20 Gy) and found a decrease in nitric oxide synthase (NOS)-containing nerve fibers in the proximal shaft of the penis (26). They concluded that there were defects in the vascular supply of the erectile tissue and a decrease in cavernous smooth muscle (26). The first animal experimental study demonstrating fibrotic changes in the arteries of the rat penis after fractionated irradiation of the prostatic area was conducted by van der Wielen and colleagues (27). The prostate of twelve rats was irradiated in 5 daily fractions of 7.4 Gy. Three control rats were sham irradiated. Prostatic and penile tissue was evaluated for general histology and the penile tissue was further evaluated after combined staining for collagen and a-smooth muscle actin (SMA) (27). The prostate showed adequate irradiation with fibrosis occurring at 9 weeks after irradiation. The corpora cavernosa showed arteries that had developed loss of smooth muscle cells expressing SMA, thickening of the intima, and occlusions (27). All the control rats maintained normal anatomy. These data suggest that post-radiation ED might be caused by radiation damage to the arterial supply of the corpora cavernosa (26,27). Further experimental studies are needed to support these data.

To date, no final conclusions can be drawn whether or not the radiation dose to the penile structures correlates with post-radiation ED in patients treated for prostate cancer.

Therapy of post-radiation ED

Prior to the introduction of sildenafil in 1998, only very limited data were available on treatment of post-radiation ED. Sildenafil citrate is a selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 inhibitors (PDE5-I), and hence inhibits the degradation of cGMP in the cavernosal smooth-muscle cells, restoring erectile response to sexual stimulation in patients with ED of different etiologies. Sildenafil has been reported to be effective in the treatment of post-radiation ED in up to 90% of the patients in open-label studies (28-32), but less effective in double-blind studies (33-35). Incrocci and colleagues performed a randomized, double-blind, placebo-controlled, cross-over trial in 60 patients, who complained of post-radiation ED (33). Sildenafil 100 mg improved erections significantly as compared to placebo; 55% of the patients had successful intercourse with sildenafil. In a follow-up study of patients who had participated in the sildenafil double-blind study only 24% were still using the drug two years after (34). Reasons were lack of efficacy (60%), costs (24%) and side effects (16%). Almost half of the patients were dissatisfied with their sexual life. This indicates that patients with a history of prostate cancer treatment and subsequent ED should be informed on treatment modalities but also followed-up, and adequately counseled to improve their sexual life (34). Similar results on the efficacy of oral drugs have been reported in randomized, double-blind trials using tadalafil (36-38). Tadalafil once-daily showed similar efficacy, and even better compliance, than on-demand in a recently published randomized trial (38). In patients treated with both RT and androgen deprivation therapy sildenafil seems to be less effective (35).

Prevention of post-radiation erectile ED

If one accepts the hypothesis that radiation induces vascular damage, then decreasing the dose to pelvic vascular structures could decrease ED incidence (24). Even modern techniques do not appear to spare the neuro-vascular bundles as these are always entirely in the high-dose prostate field (10). So far, no conclusive data are available that show a correlation of the radiation doses in these structure with ED (23). It has been written a lot in the literature about

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the role of PDE5-I in the penile rehabilitation process for patients after radical surgery for prostate cancer (39). This is not the case for patients undergoing radiation therapy (40). As PDE5-I have been found effective in the treatment of post-radiation ED in randomized trials of prostate cancer (33,35,36,38), one may speculate that these drugs might be useful in the rehabilitation process as well (40). Schiff and colleagues reported in a non-randomized, non-blinded study, that the early use of PDE5-I after brachytherapy was associated with a significant improvement in and maintenance of erectile function compared with late use (41). Recently two large trials have been published on the use of sildenafil (42,43) and tadalafil (44) for the prevention of post-RT ED. An Australian trial randomized 27 men undergoing RT for localized prostate cancer to receive daily sildenafil 50 mg or placebo starting one month after completion of radiation therapy for 6 months (42). Primary end point was erectile function measured by the IIEF at 2 years. The results showed no difference in erectile function between the two groups (42). Zelefsky and coauthors randomized 279 patients to double-blinded daily sildenafil 50 mg or placebo (43). Medication was started 3 days before RT (external-beam, brachytherapy or both) through 2 weeks after, and used daily for 6 months. The IIEF questionnaire was administered at 3, 6, 9, 12, 18 and 24 months (43). At 12 months erectile function scores were statistically significantly better for the active drug; 73% of the patients taking sildenafil reported no or mild ED compared to 50% of those taking a placebo. Erectile function and IIEF scores were not better anymore for sildenafil at 24 months (43). Sexual desire and overall satisfaction scores though were still better for those patients who received sildenafil. Patients on hormonal manipulation experienced worse erectile function than those who were not, regardless of treatment arm (43). No difference in erectile function was found in patients treated with external-beam RT, brachytherapy or a combination of these. The authors concluded that a longer course of treatment with sildenafil might be required to provide better functional outcomes beyond 12 months after therapy (43). Pisansky and coauthors performed a placebo-controlled, multicentre, double-blinded, randomized trial (n=242) to assess the efficacy of tadalafil once-daily in maintaining erectile function in patients undergoing radiation therapy for localized prostate cancer (44). Almost two thirds of the patients received external-beam RT (almost all them IMRT), one third received brachytherapy. Patients received tadalafil 5 mg or placebo for 24 weeks. Two-hundred-twenty-one patients were evaluable. Primary outcome was spontaneous erectile function at 28-30 weeks after RT was started (i.e., 4-6 weeks after tadalafil was stopped). The patient was considered to maintain erectile function without the study drug at week 28-30 if he answered "about half of the time" or more (score 3-5) to question 1 of the IIEF: how often were you able to get an erection during sexual activity? Seventy-nine per cent and 74% of the participants assigned to the tadalafil group or to placebo maintained spontaneous erections, respectively, showing a difference of 5% (P=0.49), at primary end-point (44). Although patients younger than 65 years seemed to maintain erectile function more frequently than older patients, the difference did not reach a statistically significant difference. At one year similar results were found: 72% of the patients who received tadalafil versus 71% who received placebo maintained erectile function (P=0.93) (44).

The strengths of the trial are the multicentre distribution, covering different types of medical practices, the use of standardized, modern radiation techniques and doses, the use of validated questionnaires, and the assessment of other aspects of sexual functioning than erectile function only (45). Though it might be doubted whether question 1 of the IIEF is the right choice to evaluate erectile function, getting an erection does not mean that this is rigid enough for penetration (question 2) and whether this is maintained during sexual performance (question 4) (45). Another possible limitation might be the relatively short administration of the study drug; 24 weeks might be too short to prevent penile fibrosis as a consequence of radiation therapy (45). We can speculate that a PDE5-I, by increasing nightly, spontaneous, and voluntary erections, might improve oxygenation of the corporal bodies and therefore preserve endothelial and cavernosal function. This could prevent fibrosis occurring in the first 6-12 months after RT by restoration and preservation of nitric oxide-mediated vasodilation in the irradiated corporal bodies and maintain erectile function of patients undergoing radiation therapy (45). The previously mentioned animal studies (26,27) may also help to explain the beneficial effect of PDE5-I in patients complaining about ED after radiation therapy and their possible role in preventing post-radiation ED. Because of the extended period of effectiveness, tadalafil, which lasts up to 36 hours after intake, might have advantages above other PDE5-I because of its prolonged and continuous enhancement of vascular responsiveness. Unfortunately the results of the prevention trials, similar to the one with sildenafil, do not allow us yet to advice patients to take

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PDE5-I to prevent ED when undergoing RT for localized prostate cancer (45).

Sexual counseling

Quality of life in general and sexual functioning in particular has become very important in cancer patients. Patients need to be correctly informed on the pelvic anatomy and on the possible sequelae of radiation on their sexual life and functioning (40). Sexual desire, satisfaction with sexual life, libido and frequency of intercourse has to be discussed as well. Patients should be offered sexual counseling and informed about the availability of effective treatments for sexual dysfunction. Being treated for prostate cancer is detrimental to patient's frequency of sexual activity. Sexual activity dropped from 2 times weekly to once a month in one study (46). The stability of sexual function in husbands and wives of cancer patients suggest that the problem developing after cancer treatment are caused by the emotional and medical impact of illness rather than by stress in the couple's relationship (46). In busy oncology clinics where outpatient visits must include educating patients about their disease, prognosis and treatment, physicians and nurses often do not have the time of assessing quality of life issues (47). Sexuality in general, and in relation to cancer in particular, should be an integral part of training at the undergraduate and postgraduate level (48). This does not happen in most medical schools and training programs in most countries around the world. The great majority of oncology professionals are scared to address sexuality and the great majority of sexological professionals are scared by cancer (48). It is time that cancer specialists and sexologists better understand each other. The challenge for any health care professional is to address both components with compassion. The recommendations of the Committee on chronic disease and cancer of the 3rd International Consultation on Sexual Medicine (4) are very useful to help developing research and educational programs in oncology and sexual medicine (40).

Conclusions

Although vascular damage to the pelvic organs seems to play a role in post-radiation ED, no reliable data are available to correlate the radiation dose received by the penile bodies and the penile bulb and ED. Furthermore, nerve injury cannot be excluded. A multi-factorial etiology has to be considered, taking into account age, comorbidity, previous pelvic surgery, drugs, pre-treatment erectile function and hormonal manipulation. The time elapsed between RT and ED evaluation is important as one should wait at least 18-24 months when ED occurrence reaches a maximum, and remains stable further on. It is important to standardize procedures to assess quality of life and sexual functioning in cancer patients, using validated questionnaires and using the definition of (im)potence advocated by the 3rd International Consultation on Sexual Medicine (4,40). Patients need to be correctly informed on the pelvic anatomy, on the possible sequelae of radiation on their sexual life and functioning, and about the availability of treatments for sexual dysfunction. Cancer clinics should offer a specific consultation for sexual function and dysfunction. Cancer affects quantity and quality of life. Any health care professional should address both components with compassion.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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