

LONG-TERM POTENCY AFTER IODINE-125 RADIOTHERAPY FOR PROSTATE CANCER AND ROLE OF SILDENAFIL CITRATE

RUPESH RAINA, ASHOK AGARWAL, KUSH K. GOYAL, CHERYL JACKSON, JAMES ULCHAKER, KENNETH ANGERMEIER, ERIC KLEIN, JAY CIEZKI, AND CRAIG D. ZIPPE

ABSTRACT

Objectives. To assess the long-term sexual potency and attrition in sexual function after iodine-125 (¹²⁵I) seed radiotherapy and the effect of sildenafil on radiation-induced erectile dysfunction (ED).

Methods. This prospective study consisted of 86 sexually active patients (mean age 63.5 ± 7.7 years) who underwent ¹²⁵I seed implantation from 1997 to 1999 to treat low-volume prostate cancer (prostate-specific antigen less than 10 ng/mL, Gleason score 6 or less, stage T1-T2). All patients were followed up every 6 to 8 months for 4 years. Patients prescribed sildenafil citrate for ED completed the abridged five-item version of the International Index of Erectile Function (IIEF) and the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaires.

Results. The median follow-up was 49.7 months (range 36 to 66). Of 86 patients, 43 (50%) did not initiate drug therapy; and only 36 (83.7%) of the 43 were interviewed at 4 years. Twenty-three (63.8%) of the 36 patients had erections sufficient for vaginal penetration, with a total mean ± SD IIEF-5 score of 15.76 ± 1.13. The other 50% (43 of 86) initiated sildenafil citrate for treatment of ED after seed implantation, with a minimal follow-up of 6 months. At 4 years, 32 (74%) of the 43 were responding positively to sildenafil citrate, with a total IIEF-5 score of 18.3 ± 1.2. The mean EDITS ± SD score was 76.5 ± 3.2, and the spousal satisfaction rate was 72% (31 of 43). The dropout rate was 37% (16 of 43); 10 (63%) of the 16 discontinued because of a lack of efficacy, 3 (19%) because of a return of natural erections sufficient for vaginal penetration, and 3 (19%) discontinued because of side effects (headaches).

Conclusions. ED is a major long-term issue after ¹²⁵I seed radiotherapy, with a long-term potency rate of 29%. Sildenafil citrate improves erections in most patients after ¹²⁵I seed implantation. UROLOGY 62: 1103–1108, 2003. © 2003 Elsevier Inc.

Erectile dysfunction (ED) is an important morbidity factor among patients with localized prostate cancer who are treated with brachytherapy.^{1–3} The published rates of ED after iodine-125 (¹²⁵I) seed implantation range from 15% to 30%,^{3–6} depending on the reported interval after treatment. In the past, most patients with prostate cancer undergoing brachytherapy were elderly.

Thus, postradiation potency was not a major factor in their decision to undergo radiation. Since the advent of the prostate-specific antigen (PSA) measurement, prostate cancer is diagnosed more frequently in younger patients, many of whom choose radiotherapy for treatment. In these younger patients, the issue of postradiation potency is a major concern.

ED after brachytherapy is most often associated with arteriogenic causes.¹ Because sildenafil increases cyclic guanosine monophosphate levels, leading to smooth muscle relaxation in the corpus cavernosum and increased blood flow, oral therapy may be effective in ED attributable to arteriogenic etiologies.² Merrick *et al.*² reported that brachytherapy-induced impotence was amenable to sildenafil treatment. At median follow-up of 13 months, 80.6% of patients who underwent brachytherapy

C. D. Zippe is a member of the speaker's bureau for Pfizer.

From the Center for Advanced Research in Human Reproduction, Infertility, and Sexual Function, Glickman Urological Institute, and Department of Radiation-Oncology, Cleveland Clinic Foundation, Cleveland, Ohio

Reprint requests: Craig D. Zippe, M.D., Glickman Urological Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk A100, Cleveland, OH 44195

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and had radiation-induced ED regained potency with sildenafil citrate. Recently, Potters *et al.*⁵ reported that sildenafil effectively restored sexual function in 80% of the patients with ED who were sexually potent before permanent prostate brachytherapy for localized prostate cancer. However, it remains unclear what impact oral therapy would have on sexual function with longer follow-up. Most of these reported potency rates were not derived from complete, validated questionnaires designed to assess ED and the studies lacked long-term follow-up. In addition, no study prospectively assessed long-term potency and attrition in sexual function after ¹²⁵I seed radiation.

This study was designed to assess long-term sexual potency and attrition in sexual function after ¹²⁵I seed radiotherapy and the effect of sildenafil on radiation-induced ED; and is the very first published report to the best of our knowledge. Unlike previous studies, we used a prospective design. In addition, the patients' response to sildenafil citrate was assessed using two validated questionnaires: the International Index of Erectile Function (IIEF-15) questionnaire abridged to the 5-item version (IIEF-5) referred to as the Sexual Health Inventory for Men (SHIM) and the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire.⁷⁻⁹

MATERIAL AND METHODS

PATIENT RECRUITMENT

The Cleveland Clinic Institutional Review Board approved this study, and all patients provided written informed consent. This study consisted of all patients with low-grade, clinically localized prostate cancer who underwent ¹²⁵I seed implantation at the Cleveland Clinic Department of Urology and Radiation Oncology from September 1997 through May 1999 (n = 97). Low-risk prostate cancer was defined as a PSA level of less than 10 ng/mL and a Gleason score of 6 or less.

In a multidisciplinary Prostate Cancer Clinic, we requested that all patients with prostate cancer complete the IIEF-15 questionnaire before (baseline and pretreatment) and after treatment as part of their initial and routine follow-up evaluation. The 97 patients who agreed and signed the informed consent form to participate in the study were initially evaluated with a comprehensive sexual history, physical examination, and pertinent laboratory testing. All 97 patients had completed the IIEF-5 questionnaire in the office before (before seed implantation, within 1 month of the screening) and at a mean interval of 6 months after ¹²⁵I seed implantation during their follow-up visit. Eighty-six patients (88.6%) were potent (ability to achieve an erection sufficient for penetration during intercourse) before ¹²⁵I seed implantation. The 11 patients who were not sexually potent before seed implantation were not included in this analysis.

All brachytherapy treatments were administered by the same physician (J.C.). The median radiation dose in the brachytherapy series was 14,400 cGy. Patients were followed up after ¹²⁵I seed treatment at 3 months and then every 6 to 8 months for 4 years. The data of all patients were entered into the database of the Prostate Cancer Registry of the Cleveland Clinic Foundation to ensure appropriate follow-up. The me-

dian follow-up for all 86 patients was 49.7 months (range 36 to 66) after ¹²⁵I seed implantation. Those patients not seen in the Cleveland Clinic Foundation were interviewed by questionnaire to provide follow-up serum PSA values, details of complications, and information pertaining to their ability to maintain potency. Any patients who were prescribed sildenafil citrate were analyzed separately based on their initial treatment course to assess the efficacy of this therapy.

DRUG THERAPY

Of these 86 men, 43 (50%) initiated sildenafil citrate for treatment of ED at least 6 months after ¹²⁵I seed implantation. These study participants were a self-selected, nonrandomized group who had undergone ¹²⁵I seed radiotherapy and who desired treatment with an oral medication. None had received any concurrent form of therapy for their ED or had any contraindications for the use of sildenafil (eg, ischemic cardiovascular disease and use of oral, sublingual, or transdermal nitrates).

All 43 patients had a minimal follow-up of 6 months after the initiation of sildenafil citrate. The starting dose was 50 mg, which was titrated to 100 mg if the patient did not have a positive response. Patients were instructed to take one sildenafil tablet approximately 1 hour before sexual activity as per the manufacturer's instructions and to engage in adequate foreplay before attempting sexual intercourse.

SURVEYS AND DATA ASSESSMENT

The patients' response to sildenafil citrate was assessed using the IIEF-15 questionnaire, and the efficacy of sildenafil citrate for ED after ¹²⁵I was assessed using the EDITS questionnaire.⁷⁻⁹

The EDITS questionnaire is a psychometrically validated measure of patient satisfaction with ED treatments. We asked 2 of the 11 questions that comprise the questionnaire:

1. How satisfied are you with sildenafil citrate?
2. How has sildenafil citrate met your expectations?

The two questions were scored using a 5-point scale from 0 (no satisfaction or dissatisfaction) to 4 (high satisfaction). The mean satisfaction score for each patient was calculated. To place scores in an easily interpretable metric, each mean score was multiplied by 25 to get the total EDITS score. The total scores were calculated as follows: 0, extremely low treatment satisfaction; 25, unsatisfied with the treatment; 50, neither satisfied nor dissatisfied with the treatment; 75, satisfied with the treatment; and 100, extremely high treatment satisfaction. A score of 50 or more was defined as "satisfied with treatment" and a score of less than 50 was defined as "not satisfied with treatment."⁹

A third questionnaire (the Cleveland Clinic Post Prostatectomy Questionnaire) was used to determine the sexual satisfaction of the patients' spouses/partners.⁷ The spouses/partners were specifically asked how often they were satisfied with intercourse and how often the patient was able to achieve and maintain an erection. This questionnaire was scored from 1 to 5: 1, never/occasionally; 2, less than half of the time; 3, sometimes/half of the time; 4, more than half of the time; and 5, almost always. Total spousal satisfaction was calculated from these questions and expressed as a percentage.

All 86 patients completed the IIEF-15 questionnaire⁷ and spouse/partner questionnaire before (before seed implantation and baseline)⁷ and after a mean interval of 36 weeks (range 24 to 48) after ¹²⁵I seed implantation (but before sildenafil therapy). All three surveys were mailed to all 43 patients and their spouses/partners 4 years after sildenafil citrate was started and to the 43 patients in the no-treatment arm. At that time, we performed a follow-up chart review to determine any

TABLE I. SHIM (IIEF-5) analysis: baseline, after ¹²⁵I seed implantation, and after sildenafil citrate (n = 43) at 4 years

IIEF-5 Domain*	Before Brachytherapy (n = 43)	After ¹²⁵ I Seed Implantation (n = 43)	After Sildenafil Use (n = 43)
Q5 (ability to maintain erection)	4.12 ± 0.19 (4–5)	1.84 ± 0.13 (1–2)	3.42 ± 0.36 [†] (3–4)
Q15 (erection confidence)	3.91 ± 0.28 (3–4)	2.11 ± 0.04 (2–3)	3.87 ± 0.29 [†] (3–4)
Q4 (ability to penetrate)	4.31 ± 0.22 (4–5)	2.07 ± 0.06 (2–3)	3.61 ± 0.06 (3–4)
Q2 (erection firmness)	3.85 ± 0.29 (3–4)	1.64 ± 1.46 (1–2)	3.57 ± 0.12 [†] (3–4)
Q7 (satisfactory intercourse)	3.98 ± 0.28 (3–4)	2.16 ± 0.12 (2–3)	3.83 ± 0.40 (3–4)
Total mean IIEF-5 score [‡]	20.17 ± 1.26 (20–25)	9.82 ± 0.43 (5–10)	18.30 ± 1.23 (15–20)
Spousal satisfaction [§] (%)	34/43 (79)	20/43 (46.5)	31/43 (72)

Key: SHIM = Sexual Health Inventory for Men; IIEF = International Index of Erectile Function; Q = question.
 Data presented as the mean ± SE, with the range in parentheses, unless otherwise noted.
 * Each IIEF-5 domain was scored from 0 to 5, see text for details.
[†] Statistically significant difference; P < 0.05 for IIEF-5 domains between "After ¹²⁵I" and "After Sildenafil Use" (Student's t test).
[‡] Calculated by totaling and taking mean of response to all 5 domains.
[§] Spousal questionnaire scored from 1 to 5; total calculated from these questions and expressed as a percentage; see text for details.

change in drug efficacy, dose, frequency of use, compliance, return of natural erections, and development of new side effects. All 43 patients who initiated drug therapy and their spouses/partners responded to the IIEF-15, EDITS, and spousal questionnaires before seed therapy, after seed therapy but before sildenafil, and 4 years after sildenafil.

Data from the IIEF-15 questionnaire was condensed into the IIEF-5 questionnaire, an abridged five-item version of the IIEF-15 questionnaire (SHIM). The SHIM is a validated, multidimensional, self-administered questionnaire that is a sensitive indicator of changes in erectile function and treatment outcomes. It is scored from 1 to 5: 1, never/occasionally; 2, less than half of the time; 3, sometimes/half of the time; 4, more than half of the time; and 5, almost always. The total IIEF-5 score was calculated by totaling the response to all five questions.^{7,8} A positive response to drug therapy was defined as successful vaginal intercourse.

We also mailed to the other 43 patients (no-treatment arm) the IIEF-15 and spousal questionnaires 4 years after ¹²⁵I seed implantation to assess prospectively the long-term potency and attrition in sexual function. At this time, we also performed a retrospective chart review to collect data on the mean duration of intercourse, number of patient attempts at intercourse, and number of successful attempts (vaginal penetration). Data from the IIEF-15 at 4 years was also condensed into the IIEF-5 (SHIM). Thirty-six (83.7%) of the 43 patients in this control group completed the IIEF-15 and spousal satisfaction questionnaire.

STATISTICAL ANALYSIS

An algorithm for determining potency was devised such that the patients' pretreatment status was assessed; then for each patient, the last potency status was recorded based on the time of their follow-up visit. Probability values for statistical significance were computed using Student's *t* tests, assuming unequal variances for patient age (at treatment and at brachytherapy), sexual frequency, and dose of implantation. Statistical significance was assessed with two-tailed test at *P* < 0.05. Computations used Statistical Analysis Systems, version 8.1, software (SAS Institute, Cary, NC). Summary statistics for the continuous variables are expressed as the mean ± standard deviation.

RESULTS

The mean age of the 86 men who were potent before seed implantation was 63.5 years (range 47

to 80). At a median follow-up of 49.7 months (range 36 to 66) after ¹²⁵I seed implantation, 43 (50%) patients did not initiate therapy and 36 (83.7%) if those 43 were interviewed at 4 years. However, all 43 (50%) of the patients who initiated sildenafil citrate for treatment of ED after seed implantation responded to the survey at 4 years. The mean PSA level was 5.8 ng/mL and mean Gleason score was 5.7.

LONG-TERM EFFICACY AND COMPLIANCE OF SILDENAFIL CITRATE FOR ED AFTER ¹²⁵I SEED IMPLANTATION

The mean age of the 43 patients who initiated sildenafil therapy was 66.7 years. The mean interval from ¹²⁵I seed insertion to the use of sildenafil was 24 ± 5 weeks. With a mean follow-up of 48.7 ± 7.1 months (range 36 to 66 weeks), 32 (74%) of the 43 patients responded positively to sildenafil citrate, with a total IIEF-5 score of 18.3 ± 1.2. The mean EDITS ± SD score was 76.5 ± 3.2, and the spousal satisfaction rate was 72% (31 of 43).

Of the positive responders, 9 (28.2%) required the 50-mg dose and 23 (71.8%) required the 100-mg dose. The two most common side effects were transient headache (30.7%) and flushing (21%), which were not related to the dose increase. Of the 32 positive responders, 7 (22%) augmented their dose from 50 to 100 mg (mean use 1.2 years) with no correlation between the frequency of use and need to increase the dose.

Table I shows the baseline (after ¹²⁵I insertion, before sildenafil use) and post-treatment scores for the abridged IIEF-5 questionnaires completed by the 43 patients who initiated sildenafil therapy. The dropout rate was 37% (16 of 43); 10 (63%) of the 16 discontinued because of a lack of efficacy and 3 (19%) because of a return of natural erections sufficient for vaginal penetration. Only 3 patients (7% of 43) discontinued the drug because of side effects (headaches).

TABLE II. SHIM (IIEF-5) analysis: baseline ¹²⁵I, after ¹²⁵I (4-year) overall and potent group (at 4 years)

IIEF-5 Domain	Before Brachytherapy (Baseline Score; n = 36)	After ¹²⁵ I Seed Implantation (n = 36)	Potent After ¹²⁵ I Seed Implantation* (n = 23/36)
Q5 (ability to maintain erection)	4.36 ± 0.19 (4–5)	2.60 ± 0.11 (2–3)	3.00 ± 0.36 [†] (2–3)
Q15 (erection confidence)	3.43 ± 0.28 (3–4)	2.22 ± 0.19 (2–3)	3.05 ± 0.29 (3–4)
Q4 (ability to penetrate)	4.21 ± 0.22 (4–5)	2.54 ± 0.19 (2–3)	3.13 ± 0.06 (3–4)
Q2 (erection firmness)	3.35 ± 0.29 (3–4)	2.36 ± 0.19 (2–3)	3.11 ± 0.12 [†] (3–4)
Q7 (satisfactory intercourse)	3.78 ± 0.28 (3–4)	2.45 ± 0.19 (2–3)	3.47 ± 0.40 [†] (3–4)
Total mean IIEF-5 score	19.13 ± 1.26 (15–20)	12.17 ± 1.76 (10–15)	15.76 ± 1.13 [†] (15–17)

Abbreviations as in Table I.

See text for details regarding scoring.

Data presented as the mean ± SE, with the range in parentheses.

* Percentage potent (erection sufficient for vaginal penetration) after 4 years in no-treatment group.

[†] P < 0.05, IIEF-5 domains after ¹²⁵I in potent group vs. before ¹²⁵I considered significant (Student's t test).

LONG-TERM SEXUAL POTENCY AND ATTRITION IN SEXUAL FUNCTION AFTER ¹²⁵I SEED IMPLANTATION (NO-TREATMENT GROUP)

At a median follow-up of 49.7 months (range 36 to 66), 43 (50%) of the 86 patients did not initiate therapy. Of the 43 patients, only 36 (83.7%) were interviewed after 4 years. The mean ± SD follow-up for these 36 patients was 49 ± 2.3 months (range 38 to 67). The patients had a mean ± SD age of 68.9 ± 3.46 years. Overall, these 36 patients had a total mean IIEF-5 score of 12.17 ± 1.76. Potency, defined as erections sufficient for vaginal penetration, was preserved in 23 (63.8%) of the 36 patients at mean follow-up of 4 years. In these 23 potent patients, the total mean IIEF-5 score was 15.76 ± 1.13, with a spousal satisfaction rate of 69.5% (16 of 23; Table II). Thus, the mean 4-year natural potency rate for the 86 patients was 29% (23 of 79). When including those who used sildenafil citrate, the overall potency rate increased to 70% ([23 + 32]/79).

COMMENT

One of the main goals in this study was to assess prospectively the long-term sexual potency and attrition in sexual function after ¹²⁵I seed radiotherapy using validated questionnaires. Previous reports on ED after brachytherapy have shown a broad range of impotence rates ranging from 25% to 40%.^{3–5} In a study by Stock *et al.*,¹⁰ 21% of the men experienced ED after brachytherapy at 2 years of follow-up. In another report, Zelefsky and associates^{11,12} reported a 53% rate of ED at 5 years after implantation. Unlike these earlier reports, we found, at 4 years, that 29% of ¹²⁵I seed patients were potent, comparable to another recent report on ED after ¹²⁵I seed implantation.¹³

We found that, excluding patients with ED who used sildenafil citrate, the 4-year natural preserva-

tion of potency was 29% (23 of 79). However, with sildenafil citrate, 70% ([23 + 32]/79) of the patients were potent and able to successfully engage in vaginal intercourse. This finding was consistent with the findings of Merrick *et al.*¹³ who showed a 6-year potency preservation rate after permanent prostate brachytherapy with and without pharmacologic support of 54% and 39%, respectively. Similarly, Schover *et al.*¹⁴ reported that only 49% of the men who survive prostate carcinoma were able to maintain potency after 4.3 years.

The other main goal of our study was to assess the effect of sildenafil on brachytherapy-induced ED. Merrick and associates¹³ were among the first to determine the incidence of potency and efficacy of sildenafil after permanent prostate brachytherapy using the validated IIEF-15 questionnaire. They reported that 85% of the patients had a favorable response to sildenafil citrate after brachytherapy.¹³ Our long-term data showed that sildenafil citrate can be effective in treating this complication. The 74% response rate from sildenafil in our series (in patients who were sexually active before treatment) is nearly identical to the percentage of patients who responded to sildenafil after bilateral nerve-sparing radical prostatectomy (mean age 58 years) and external beam radiotherapy, 76% and 71%, respectively.^{15,16} Although the three series were not comparable in age, with the radiation groups having a higher mean age of 65 to 66 years, both groups were highly motivated and represented sexually active individuals before their respective treatment. It appears that the use of sildenafil in motivated patients can equally improve the morbidity of ED from either of the standard definitive local therapies for prostate cancer.

Sildenafil should be offered as the first treatment option for the subset of patients with ED after radical prostatectomy, external beam radiotherapy,

and brachytherapy. Various factors may be correlated with the sildenafil response in men with ED after treatment for localized prostate cancer.^{13,16} The pretreatment variables included preoperative sexual function and frequency, patient age, degree of postoperative potency before drug therapy, and length of time after surgery before sildenafil administration.¹³⁻¹⁶

The age of the patient may influence the return of sexual activity. A 70-year-old man tends to have a lower probability of pretreatment erectile function than a 60-year-old man with or without brachytherapy. Another crucial factor may be the time of drug administration in relation to postoperative ED. Stock *et al.*¹⁷ reported that sexual function diminishes gradually from 79% at 3 years to 59% at 6 years after prostate brachytherapy. Thus, long-term follow-up after implantation is necessary before determining the overall efficacy of sildenafil citrate after ¹²⁵I radiotherapy. The follow-up in our study ranged from 36 to 66 months.

We observed that some patients who received sildenafil with good initial responses experienced a reduction or complete loss of efficacy. This loss resulted in some patients requiring a higher dose or eventually discontinuing treatment. Seven of the 32 patients who responded to the sildenafil citrate (22%) observed a reduction in efficacy that required them to augment the dose from 50 to 100 mg to achieve adequate results. A trend, but no statistically significant relationship, was noted between the frequency of use and need to increase the dose. The percentage of the reduction in efficacy of sildenafil ranged from 15% to 50%, and the time for diminished efficacy was 15 months (average 12 to 18). Patients who received treatment four or fewer times per month (51%) had to increase the dose more often than those who received it four or more times per month (16%), but this difference was not statistically significant.

El-Galley and associates¹⁸ evaluated the long-term efficacy and tachyphylaxis effect of sildenafil in patients who initially responded to the drug and frequently became resistant with time. This study suggested a possible tachyphylaxis effect with sildenafil after 2 years of use. Twenty percent of the patients increased their dose to sustain the same effect and 17% discontinued the drug because of a loss of efficacy.¹⁸ Tachyphylaxis is a pharmacologic process referring to a reduction in tissue response to a drug that occurs in the presence of a constant concentration of the drug. Additional confirmatory studies are required to document the possible causes and the time interval for the reduction or loss of efficacy in subgroups of patients using sildenafil citrate for ED after ¹²⁵I seed implantation.

At the 4-year mark, 16 of the 43 patients who had initiated treatment with sildenafil citrate had stopped using it after mean use of 1.8 years. Of the 16 patients who reported a good initial response on the first survey, 3 had spontaneous erections (mean time 2.1 years after ¹²⁵I seed implantation) and no longer needed treatment, suggesting a potential therapeutic benefit. However, 10 (12%) of the 43 patients stopped taking sildenafil because of a gradual loss of efficacy (mean use of drug 1.5 years), and 3 patients discontinued treatment because of side effects.

CONCLUSIONS

ED is a major long-term issue after ¹²⁵I seed radiotherapy. The overall 4-year natural potency rate was 29%. When including patients who used sildenafil citrate, the overall potency rate increased to 70%.

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