

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0215

**TREATMENT OF ERECTILE DYSFUNCTION IN PATIENTS TREATED
ON RTOG 99-10 FOR PROSTATE CANCER: IMPACT ON PATIENT AND PARTNER
QUALITY OF LIFE**

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TREATMENT OF ERECTILE DYSFUNCTION IN PATIENTS TREATED ON RTOG 99-10 FOR PROSTATE CANCER: IMPACT ON PATIENT AND PARTNER QUALITY OF LIFE

SCHEMA (11/7/03)

Sildenafil Study Schema begins a minimum of 6 months and a maximum of 5 years after RT completion on RTOG 99-10

S	<u>History of Prior Use of Sildenafil after RTOG 99-10 Protocol Treatment</u>	R	<u>Arm 1</u>
T		A	Sildenafil with dose escalation as needed from 50 to 100 mg/day prn x 12 weeks
R	1. No	N	
A	2. Yes – Unsatisfactory Response†	D	<u>Arm 2</u>
T	3. Yes – Satisfactory Response†	O	Placebo with similar “dose escalation” opportunity x 12 weeks
I	<u>IIEF Question #1 Score</u>	M	<u>One Week Break*</u>
F	1. responses 0-1	I	
Y	2. responses 2-3	Z	<u>CROSSOVER at 13 Weeks</u>
	<u>RTOG 99-10 Arm</u>	E	<u>Arm 1</u>
	1. Arm 1		Placebo with similar “dose escalation” opportunity x 12 weeks
	2. Arm 2		<u>Arm 2</u>
			Sildenafil with dose escalation as needed from 50 to 100 mg/day prn x 12 weeks

† A satisfactory response is defined as a patient who was able to get an erection during sexual activity sometimes, most of the time, or almost always/always while previously using sildenafil after RTOG 99-10 protocol treatment. Otherwise, the patient had an unsatisfactory response while previously using sildenafil after RTOG 99-10 protocol treatment.

* During this period, the patient’s (and partner’s) sexual function and marital adjustment will be assessed, any remaining drug will be collected, and new medication for crossover treatment will be given.

Eligibility (see Section 3.0 for details) **[11/7/03]**

- Eligible patients treated on RTOG 99-10 who completed RT a minimum of 6 months and a maximum of 5 years ago
- Completion of entire IIEF Form (Appendix IV) prior to registration
- Pretreatment (prior to enrollment on this study) erectile dysfunction as measured by IIEF (Appendix IV) question # 1 – “How often were you able to get an erection during sexual activity?” -- with responses of:
 - “no sexual activity” or “almost never/never” (responses 0-1) **or**
 - “a few times (much less than half the time)” or “sometimes (about half the time)” (responses 2-3)
- Patients with erectile dysfunction before starting prostate cancer treatment are eligible.
- Zubrod Performance Status 0, 1, or 2

(Continued on next page)

- No participation in another research study (other than RTOG 99-10) involving prostate cancer treatment
- No previous or concomitant invasive cancer, other than localized basal cell or squamous cell skin carcinoma (AJCC Stage 0-II), unless continually disease free for at least 5 years
- No history of myocardial infarction within the last year
- No current use of any organic nitrate or need for prn nitrates
- No use of ketoconazole, itraconazole, erythromycin, sildenafil, mechanical (vacuum) devices, intracorporeal, intraurethral, topical, or oral agents as therapy for erectile dysfunction at study entry or throughout study treatment (25 weeks); patients who discontinue these therapies remain eligible.
- No prior penile implant or bilateral orchiectomy
- No use of androgen suppression (Lupron, Zoladex), anti-androgen (Casodex, Eulexin, Nilandron), or estrogenic (diethylstilbestrol) agents within the last six months
- No anatomical genital abnormalities or concurrent conditions that in the estimation of the physician would prohibit sexual intercourse or prevent study completion
- Patients (and partners, if willing to participate) must sign a study-specific consent form prior to study entry.

Required Sample Size: 332

RTOG Institution # _____

RTOG 0215 Case # _____

RTOG 99-10 Case # _____

ELIGIBILITY CHECKLIST (11/7/03)

(page 1 of 3)

- _____ (Y) 1. Did patient complete both hormone and radiation therapies on RTOG 99-10?
- _____ (N) 2. Was patient considered ineligible for RTOG 99-10 after he was randomized to that study?
- _____ (Y) 3. Has it been a minimum of 6 months and a maximum of 5 years since completion of RT on RTOG 99-10?
- _____ (Y) 4. Was the entire IIEF form completed by the patient?
- _____ (Y) 5. Does the patient have erectile dysfunction as measured by IIEF question #1, "How often were you able to get an erection during sexual activity?" – responses of: "no sexual activity" or "almost never/never" (responses 0-1) or "a few times (much less than half the time)" or "sometimes (about half the time)" [responses 2-3]?
- _____ (Y) 6. Is the Zubrod Performance Status 0, 1, or 2?
- _____ (N) 7. Is the patient participating in a research study other than RTOG 99-10 that involves prostate cancer treatment?
- _____ (N) 8. Has the patient had previous or concurrent invasive cancer within the past 5 years other than localized basal cell or squamous cell skin carcinoma?
- _____ (N) 9. Is there a history of myocardial infarction within the last year?
- _____ (N) 10. Does the patient currently use organic nitrates or need prn nitrates?
- _____ (NA/Y) 11. If use of any ketoconazole, itraconazole, erythromycin, sildenafil, mechanical (vacuum) devices, intracorporeal, intraurethral, topical, or oral agents as therapy for erectile dysfunction, has the patient discontinued these therapies?
- _____ (Y/N) 12. Does the patient have a history of prior use of sildenafil? (Regardless of past experience, the patient is eligible if he agrees to take only sildenafil/placebo while on study.)
- _____ (Y/N) If yes, did the patient have a satisfactory response? (Able to get an erection during sexual activity sometimes, most of the time, or almost always/always while previously using sildenafil after RTOG 99-10 protocol treatment)

(Continued on next page)

RTOG Institution # _____

RTOG 0215 Case # _____

RTOG 99-10 Case # _____

ELIGIBILITY CHECKLIST (11/7/03)

(page 2 of 3)

- _____(N) 13. Has there been prior penile implant or bilateral orchiectomy?
- _____(N) 14. Has there been use of androgen suppression (Lupron, Zoladex), anti-androgen (Casodex, Eulexin, Nilandron), or estrogenic (diethylstilbestrol) agents within the last six months?
- _____(N) 15. Are there anatomical genital abnormalities or concurrent conditions that in the estimation of the physician would prohibit sexual intercourse or prevent study completion?
- _____(N) 16. Are there any major medical or psychiatric illnesses, which would prevent completion of treatment and/or interfere with follow up?
- _____(Y) 17. Has the patient (and partner, if willing to participate) signed the study-specific consent form?

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (above) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)
- _____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence

(Continued on next page)

RTOG Institution # _____

RTOG 0215 Case # _____

RTOG 99-10 Case # _____

ELIGIBILITY CHECKLIST (11/7/03)

(page 3 of 3)

- _____ 13. Zip Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Would the patient's partner be willing to participate in this study? (not mandatory for partner to participate)
- _____ Married partner will participate.
- _____ Married partner will not participate.
- _____ Unmarried partner will participate.
- _____ Unmarried partner will not participate.
- _____ 17. Specify age (≤ 65 years, > 65 years)
- _____ 18. Specify IIEF question #1 score (0-1, 2-3)
- _____ 19. Specify Patient's RTOG 99-10 Arm (1 or 2)
- _____ 20. Patient's RTOG 99-10 Case Number
- _____ 21. Specify history of prior use of sildenafil after RTOG 99-10 protocol treatment (No; Yes—Unsatisfactory Response; Yes—Satisfactory Response)
- _____ 22. Treatment Start Date for this study
- _____ 23. Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Antiandrogens, originally used in the treatment of metastatic prostate cancer, are being used in earlier stages of the disease. Antiandrogens may be administered before, during, or after radiation therapy or surgery in an attempt to decrease the risk for disease relapse and improve survival. The benefit of androgen ablation in the treatment of prostate cancer has been known for over 60 years, yet the optimal use of antiandrogen therapy remains controversial. Controversies exist with respect to the timing of therapy, the use of intermittent androgen ablation, and the role of total androgen suppression (TAS). The Radiation Therapy Oncology Group (RTOG) recently activated a clinical trial to study the optimal duration of TAS administered as neoadjuvant (that is, prior to definitive therapy) treatment. RTOG 99-10 is a large-scale, multi-institutional phase III trial evaluating the duration of neoadjuvant TAS given with radiation therapy in patients with intermediate-risk (clinical stage II-III) prostate cancer. Specifically, TAS is administered for 8 weeks prior to, and then during, radiation therapy in patients assigned to the standard arm. In the experimental arm, a 28-week course of neoadjuvant TAS is followed by radiation therapy with concurrent TAS. TAS consists of a gonadotropin-releasing hormone (*GnRH*) agonist, Zoladex or Lupron [subject to physician preference], along with a non-steroidal antiandrogen, Casodex or Eulexin. The primary hypothesis of this trial is that the extended duration of TAS prior to radiation therapy (the experimental arm) will reduce the mortality rate due to prostate cancer. Its accrual goal is 1540 patients entered over four years.

1.2 Quality of Life

One of the consequences of antiandrogen therapy in the combined modality treatment of non-metastatic prostate cancer is that men with an otherwise long life expectancy may have to live with side effects for the rest of their lives. This also means that the adverse effects of antiandrogen and combined modality therapy and their impact on quality of life have greater importance as the anti-cancer therapy prolongs survival duration.¹ One significant quality of life concern that has received much attention after prostate cancer therapy is erectile dysfunction (ED). The importance of sexual functioning as a quality of life issue should not be underestimated. In a study of 413 impotent men and 109 controls, satisfaction with sexual life was found to be a powerful predictor of satisfaction with life as a whole.² Further, the importance of sexual functioning as a major issue in patient decision making regarding prostate cancer treatment has been demonstrated. Quality versus quantity of life trade-offs have been documented in up to two-thirds of men with prostate cancer who are willing to accept at least a 10% decrement in survival for a treatment that offered a better chance of preserving erectile function.³ The long-term impact of cancer treatments also highlights the consequences of cure on quality of life. One study, which used a battery of quality-of-life instruments, concluded that cancer survivors enjoy quality of life similar to their neighbors in all but one aspect of daily life: sexual functioning.⁴

1.3 Prostate Cancer Therapy & Erectile Dysfunction

Erectile dysfunction has been reported in 40% to 60% of men after radiation therapy.⁵⁻⁶ In comparison, radical prostatectomy has at least an 85% risk of ED,⁷ and reports of ED after nerve sparing radical prostatectomy have ranged widely from 25% -79%.⁸ In one study of 287 patients that compared the rate of ED after conformal radiation therapy to nerve-sparing radical prostatectomy, 29% of the former versus 34% of the later group experienced ED. For patients older than 70 years, 39% of radiation therapy patients and 67% of nerve-sparing radical prostatectomy patients experienced ED after treatment. At months 1, 20, 40, and 60, actuarial ED rates for the conformal radiation therapy group were 4%, 25%, 41%, and 47%, respectively. Factors identified as significant predictors of post-RT ED included pre-treatment ED, diabetes, coronary artery disease, and anti-androgen medication usage.⁹ Further, 69% of men treated with surgery and 62% of men treated with radiation therapy have reported dissatisfaction with post-treatment sexual function.¹⁰

Although the specific mechanism by which radiation therapy reduces erections is uncertain, it has been suggested that radiation therapy does not damage the corporal nerves, but rather it causes vascular damage. This, in time, interferes with penile hemodynamics which results in ED, even though desire and sexual sensations may be present.¹¹ The prognosis of erectile function has been found to be related to a number of factors including radiation dose to the bulb of the penis, patient age, and pretreatment sexual function. Animal studies and retrospective clinical data suggests that the dose of radiation therapy to the penile bulb is the vascular insult that plays a causal etiology in the development of ED. A recent analysis based on prospectively collected data regarding erectile function and dosimetry from RTOG, 94-06, a Phase II dose escalation trial, found that the mean dose to the penile bulb (< 52.5 Gy vs. > 52.2 Gy) was associated with a higher risk of ED at 2 years ($p=0.048$, hazard ratio ~ 5.0).¹²

As prostate cancer is primarily a disease of advancing age, it is important to distinguish between age-related ED and its treatment-induced counterpart. For instance, one study of 43 men (mean age 67.7 years) found that almost 63% were impotent prior to therapy.¹³ In contrast, in a study of 67 men treated with radiation therapy, (mean age 68 years), only 37% had pre-treatment ED. In this study, ED was preserved in 67% of patients 24 months after the end of radiation therapy, although 50% observed worsening erectile function.¹⁴

The differentiation between age- and treatment-related ED is particularly important in light of recent work showing a high level of ED in the general population. The most recently reported population study of physiologic ED demonstrated age to be the most significant independent predictor of ED. And although other factors were found to correlate with ED (i.e., heart disease, hypertension, diabetes, cigarette smoking, etc.), no other variable, whether it correlated with age or not, was found to diminish the predictive power of age alone. Conducted as part of the Massachusetts Male Aging Study, sexual function was assessed with nine questions addressing sexual activity, erection, and satisfaction, and an additional question asking the men if they considered themselves as not, minimally, moderately, or completely impotent. Of the 1,290 subjects between 40 and 70 years of age analyzed in this study of 'normal' male aging, 17.2% reported minimal ED, 25.2% reported moderate ED, and 9.6% reported complete ED. The probability of complete ED tripled with increased age, from 5.1% in men age 40 years to 15% in men age 70 years, and the probability of moderate ED doubled from 17% to 34%. An estimated 40% of men age 40 had minimal, moderate, or complete ED while that estimate rose to 67% by age 70 years. As prostate cancer is most common in men age 69 years or older, distinguishing treatment-related dysfunction from age-related dysfunction becomes even more important in determining cause and effect and in exploring corrective treatment options.¹⁵

In addition, studies have demonstrated that men who are potent and sexually active prior to external beam radiation therapy tended to maintain their erectile function after radiation therapy was completed. One study found that erectile function was related to the initial frequency and quality of intercourse. For men with sexual activity that amounted to more than three times per month, the prognosis remained good, whereas for others, it was poor. In this study, the patient's age was a predictive factor for the frequency of intercourse.¹⁴

1.4 Antiandrogens & Erectile Dysfunction

Antiandrogens alone carry a risk of erectile dysfunction of at least 80% to 100%.¹⁶⁻¹⁷ Studies indicate that antiandrogen therapy may significantly impair the physical and emotional health of asymptomatic patients with nonmetastatic prostate cancer.¹⁸ Specifically, gonadotropin-releasing hormone (GnRH) agonists cause suppression of the hypothalamic pituitary axis. GnRH, a decapeptide synthesized and released by the hypothalamus, regulates production and release of the luteinizing hormone (LH) by the adenohypophysis.¹⁹ Unlike radiation therapy that causes mechanical ED over time,

antiandrogenic treatment affects the central mechanisms mediating sexual activity by reducing plasma testosterone levels similar to that of castration.²⁰ Men with low levels of testosterone may experience lowered sexual desire, difficulty in achieving a functional erection, less pleasurable orgasm or difficulty in reaching orgasm, decreased semen production, and diminished spermatogenesis.²¹

Since antiandrogens were only used in metastatic disease until recently, most of the published research on antiandrogens and sexual consequences were published in patients with metastatic disease. A study of 44 patients with metastatic prostate cancer indicated that before beginning treatment, most had an active sexual life, as illustrated by normal erotic imagery, an adequate sexual desire, and satisfactory frequency of intercourse. Slightly more than 50% were able to easily achieve an erection by erotic imagery or sexual fantasy, and 50% claimed they never experienced erectile problems. More than three-quarters (80%) of subjects had intercourse at least once a week. When compared with their previous sexual functioning, 70% of subjects noticed a major reduction in their desire for sexual intercourse during antiandrogenic treatment. Nevertheless, almost 40% were able to maintain the ability to induce an erection by erotic imagery. However, only 19% claimed an ability to maintain an erection during sexual activity, as compared to 56% before treatment, but erection usually lacked full rigidity.¹⁷

Another study of anti-androgen therapy, a combination of finasteride and flutamide, for metastatic prostate cancer found a dose-time response to ED. Eleven of 20 men (55%) had erectile function at baseline. During treatment with flutamide and finasteride, 9 (82%) of 11 men maintained erectile function at six-month follow up, whereas 2 (18%) of 11 experienced ED. With longer follow up (median 16.4 months), 6 (55%) of 11 men maintained erectile function, 2 (18%) of 11 had partial ED, and 3 (27%) of 11 had complete ED. Erectile function was preserved initially in most patients who had erectile function pre-treatment, although there was a reduction in function and libido on longer follow up.²² Even with monotherapy, flutamide or cyproterone acetate, 80-90% of men experienced complete ED by about two years if they continue on therapy. However, loss of erectile function under monotherapy with either flutamide or cyproterone acetate is slow, with median times of 12.9 and 5.8 months versus 13.7 and 8.9 months respectively for spontaneous erections and sexual activity.²³

In combination with radiation therapy, conventional wisdom held that after radiation therapy plus neoadjuvant or concurrent antiandrogens, erectile function would be equivalent to that after radiation therapy alone (once the antiandrogens are discontinued). However, in our own work,²⁴ rates of ED are higher with combination radiation therapy and antiandrogens even after the antiandrogens are discontinued. This has been corroborated in at least one other study (Mack Roach, MD, UCSF, unpublished data, personal communication, June 12, 1999). The cause of the higher rate of ED is unknown; however, we can hypothesize two possible mechanisms: 1) a physiologic synergistic radiation therapy-antiandrogen interaction, or 2) a lingering psychological response to complete ED. In the former, ED therapy may or may not improve erectile function depending on the extent and specific physiologic etiology; in the latter, ED therapy should improve erectile function.

1.5 Current Interventions for ED

Despite these well-documented levels of ED following prostate cancer therapy, there has been, until the recent availability of sildenafil, a deficit in acceptable interventions for maintaining erectile function. Pharmacological and non-pharmacological interventions such as intracavernous vasoactive injections, oral drug therapy with yohimbine, vacuum constriction devices, penile prosthesis implants, and venous and arterial surgery that can restore voluntary erectile function for sexual intercourse have been available for years but have gained little attention from physicians and patients alike, probably due to both inconvenience and cost (including both physical and financial).

1.5.1 Sildenafil: Despite of the options available to treat ED, there has been a poor overall success rate in patient acceptance of medical and surgical techniques used in the treatment of ED.²⁵ The risks and obvious difficulties with compliance with the previously discussed alternative treatments along with the small samples of subjects and lack of prostate cancer specific studies, suggest the need for evaluating other potential agents in the treatment of ED after prostate cancer therapy. Sildenafil citrate (Viagra™) is an oral agent that works by enhancing smooth muscle relaxation and inflow of blood in the corpus cavernosum. This occurs in conjunction with sexual stimulation. Sildenafil has demonstrated significant improvement in ED patients with various histories and concomitant disease states, including radical prostatectomies and in small, single institution studies of radiation therapy.²⁶⁻³²

In a study to assess the efficacy and safety of sildenafil in a double-blind, placebo-controlled, dose-escalation study over a period of 26 weeks in men with ED of a broad etiologic spectrum (not including radiation therapy or antiandrogens), 315 patients from five countries were randomized to receive treatment with placebo (156 men) or sildenafil (159 men).³³ Concomitant medical conditions included hypertension (20%), a history of pelvic surgery (19%), diabetes mellitus (15%), and ischemic heart disease (10%). Patients randomized to treatment received a starting dose of 25 mg of sildenafil (or matching placebo), which could be increased to 50 mg and then to 100 mg of sildenafil, based on efficacy and tolerability. Efficacy was based on patient response to the 15-item International Index of Erectile Function (IIEF), including questions on the ability to achieve an erection and the ability to maintain an erection, a partner questionnaire, an overall efficacy question, and event-log data. After 12 weeks of treatment, 26%, 32% and 42% of patients were taking 25, 50 and 100 mg of sildenafil, respectively, similar to the distribution of doses reported after 26 weeks of treatment. Treatment with sildenafil significantly improved the patients' abilities to achieve and maintain an erection compared to treatment with placebo ($p < 0.001$). Scores for four of the five sexual function domains of the IIEF (erectile function, orgasmic function, intercourse satisfaction and overall satisfaction) also improved significantly ($p < 0.001$). There was a significant improvement in the mean score for the erectile function domain, regardless of the etiology of ED ($p < 0.001$). After 12 weeks and 26 weeks of treatment, 82% and 79% of patients receiving sildenafil reported improved erections, compared with 24% and 23% of patients receiving placebo, respectively ($p < 0.001$). Treatment-related adverse events were mild to moderate and occurred in 27% of patients receiving sildenafil, compared with 8% of patients receiving placebo.³³

1.5.1.1 Sildenafil and Prostate Cancer: Recently, there has been a small series of studies undertaken to assess the efficacy of sildenafil in patients treated with radiation therapy for prostate cancer (Table 1).

Table 1: Studies of Sildenafil in the Improvement of Erections Post-Radiation Therapy

Author	N	Age	Age Range	Treatment	+ Response
Kedia ²⁹	21	Mean 65	--	Implant n = 2 3DCRT n= 19	71%
Weber ³¹	30	Mean 69	54-79 years	4-6 field RT	77%
Zelefsky ³²	50	Median 68	54-78 years	3DCRT	70%
Merrick ³⁰	62	Mean 65	50-78 years	Implant	81%
Valicenti ³⁴	24	Median 68	51-77 years	3DCRT	91%

An improved response in erections was seen in approximately 70-80% of patients, about twice the rate Pfizer reported after radical prostatectomy. Across all trials, sildenafil improved erections in 43% of radical prostatectomy patients compared to 15% with placebo. However in contrast to the radical prostatectomy studies, all of the radiation therapy studies used small convenience samples and were open-label,

nonrandomized trials. In addition, few studies assessed patients treated with TAS and only one assessed partner satisfaction.

Kedia²⁹, Zelefsky³², Valicenti³⁴ and colleagues evaluated the response of sildenafil in patients with prostate cancer treated with three-dimensional conformal radiation therapy (3DCRT). Kedia et al. assessed 19 patients treated with 3DCRT and two patients treated with iodine-125 seed implantation. All 21 patients were considered to have erectile dysfunction as assessed by the IIEF and were prescribed sildenafil (50 mg, with titration to 100 mg as needed). The mean time between the completion of radiation therapy and initiation of sildenafil was 24.6 +/- 5.8 months. A positive response to sildenafil on the IIEF questionnaire was defined as an erection sufficient for vaginal penetration. Overall, 15 (71%) patients had a positive response, with a mean duration of 12.7 +/- 2.5 minutes of intercourse, and a corresponding spousal satisfaction rate of 71%. Twelve (80%) of the 15 responders required titration to the 100-mg dosage for maximal effect. The most common side effects were transient flushing (19%), abnormal color vision (14%), and headaches (10%). No patient discontinued the drug because of side effects. On the IIEF questionnaire, the responses to frequency of penetration, maintenance of erection, satisfactory intercourse, and erection confidence, improved from mean baseline scores of 1.3, 1.1, 1.2, and 1.8 to final mean scores of 4.0, 3.9, 3.2, and 3.4, respectively ($p < 0.001$). On the global efficacy question (ability to achieve firm erections), 71% of the patients responded positively.

Zelefsky et al.³² also sought to ascertain the efficacy of sildenafil in 50 patients with ED after 3DCRT. Patients in this study were given 50 mg doses of sildenafil and instructed to use the medication on at least three occasions. Thirty-seven patients (74%) reported significant and 2 (4%) reported partial improvement in the firmness of the erection after sildenafil, and 11 (22%) had no response. In terms of the durability of the erection, significant improvement was reported in 33 patients (66%), 3 (6%) had partial improvement, and 14 (28%) reported no improvement. Patients with partial or moderate erectile function before using sildenafil were more likely to benefit from the medication compared with those with complete ED. Among 29 patients with erections classified as partial after radiation therapy, 26 (90%) had a significant response to the medication, in contrast to only 11 (52%) of 21 with erections classified as flaccid after radiation therapy ($p = 0.007$).

Valicenti et al.³⁴ evaluated 24 men who started taking sildenafil for ED at a median time of one year after completing 3DCRT. Sexual function and overall satisfaction were assessed at three time points using the O'Leary Brief Sexual Function Inventory. These points were (a) before initiation of all therapies (3DCRT or antiandrogens) for prostate cancer, (b) before starting sildenafil (50 mg or 100 mg) but after completion of all therapies, and (c) at least 2 months afterward. Prior to cancer treatments, 20 (87%) of 23 men were sexually potent, with 8 (36%) of 22 fully potent (little or no difficulty for penetration at intercourse). After 3DCRT with or without antiandrogens and prior to sildenafil use, 13 (65%) of the 20 potent patients remained potent, with only 2 (11%) of 19 being fully potent. The use of sildenafil resulted in 21 (91%) of 23 men being potent, with 7 (30%) being fully potent. In 16 men responding to the satisfaction question, 10 (63%) and 12 (75%) were mixed to very satisfied with their sex life before 3DCRT with or without antiandrogens and after sildenafil use, respectively. This response corresponded to potency and satisfaction scores significantly decreasing after 3DCRT and subsequently increasing (on average by one unit) after sildenafil use ($p < 0.05$).

Weber et al.³¹ assessed the efficacy and safety of sildenafil in patients treated with 4-6 field external beam radiation therapy. Patients received sildenafil 100 mg orally once a week for 6 consecutive weeks. Response also was assessed using the IIEF

and was defined as at least one successful attempt at sexual intercourse per week. Eighty-six percent (30/35) of patients completed the 6-week study. Seventy-seven percent of these patients had significantly improved erectile function, allowing recovery of full capacity for sexual intercourse. Of 27 patients not receiving concomitant hormone treatment, failure to respond was observed in only four patients (15%) compared with four (50%) of eight patients receiving hormonal treatment during the study. The time course of response was gradual, with 40%, 57%, 66%, 69%, and 74% responding at weeks 1 through 5, respectively. Therapy was generally well tolerated. The most frequently reported side effects in patients were flushing (37%), transient headache (17%), and dyspepsia (9%). After responding to but then discontinuing sildenafil, 12 patients (34%) reported the ability to achieve and maintain an erection sufficient for intercourse (i.e., 24 hours to 6 days after taking the medication).³¹ Finally, Merrick et al.³⁰ assessed the efficacy of sildenafil in 62 patients with ED either before or after prostate brachytherapy, who were interested in ED treatment. Patients were prescribed 50 mg of sildenafil; if three attempts on 50 mg were unsuccessful at producing an erection sufficient for vaginal penetration, the dosage was increased to 100 mg. Fifty (80.6%) of 62 patients responded favorably to sildenafil, meaning they could obtain and maintain an erection sufficient for vaginal penetration. None of the treatment parameters predicted medication failure, and among the clinical parameters, only diabetes predicted failure (3 of 5) with borderline statistical validity ($p = 0.046$).

Overall, these studies suggest that about two-thirds of patients with ED after treatment with radiation therapy will respond to sildenafil. Patients with less severe dysfunction are most likely to benefit from this intervention. However, these studies shed little light on the response to ED after treatment with neoadjuvant total androgen suppression and radiation therapy. In addition, antiandrogens affect erectile function through a different mechanism than the etiologies previously studied, most of which were associated with penile vascular damage, or in some cases, neurologic damage.

1.5.1.2

Partners' Satisfaction with Sildenafil: Erectile dysfunction affects and is affected by not only the patient, but also their partner and the relationship. Despite the fact that pharmaceutical breakthroughs are allowing for renewed or expanded sexual activity among many couples, the psychosocial impact of these agents on the dyad have largely been ignored. Yet, the few studies conducted in this area have indicated that the couples' relationship is prognostic for both the incidence and the success or failure of the treatment of ED.³⁵⁻³⁷ Although the FDA approval of sildenafil has produced a flurry of research into male ED, little attention has been given to the sexual partner in any role except to confirm the presence of erection. In fact in one recent study, partners of patients taking sildenafil were asked only two questions, "During sexual activity with your partner, how often did he get an erection?" and, "How often did he maintain his erection?"³⁸ Although partners in this study indicated that the patients on sildenafil had erections that improved their ability to have intercourse 80% of the time as compared to 20% for men on placebo, questions regarding the effect of improved erectile function on the relationship or sexual satisfaction of the partner were not mentioned in the publication. Only one study has been identified to date that asked the partner whether the patient's ED treatment had improved their own sex life. In a study of the efficacy of sildenafil for treating ED in non-cancer patients, men were randomized in a double-blind study to placebo ($n = 95$) or sildenafil ($n = 250$), once daily for 28 days. Compared to the placebo group, patients receiving sildenafil reported significantly improved erections ($p < 0.001$), frequency, hardness and duration of erections ($p < 0.01$), and improvements in enjoyment of sexual intercourse and satisfaction with sex life ($p < 0.05$). The results of the partner questionnaire ($n=231$) were consistent with the results reported by patients. In addition, response to a question that asked the partner, "Has the quality of your sex life changed since your partner started

treatment,” (scored on a 1=much worse to 5=much better scale) indicated that treatment with sildenafil was associated with significant improvement in the partners' own sex lives ($p < 0.001$).³⁹

On the other hand, the media is replete with stories of relationship conflicts associated with sildenafil. The literature cites four case reports of psychosocial and interpersonal problems associated with sildenafil. Two cases occurred in couples whose marital situation worsened after the husband refused to take sildenafil for ED following radical prostatectomy.⁴⁰ Two additional cases of homicidal ideation toward their wives were documented in men in their mid-seventies who took sildenafil. In one case, a wife's rejection of her husband's advances seemed to uncover many hidden resentments that they bore toward each other. In the other, sildenafil failed to restore potency to a patient with diabetes, and he developed a jealous delusion that his wife was having an affair. Both men required admission to a locked psychiatry unit.⁴¹ As one author affirmed, the scientific community's emphasis on erection ignores the relationship issues and education/counseling efforts important to the successful treatment of sexual dysfunction. According to Westheimer and colleagues, “The most significant factors affecting sexual performance are not physical but psychological. Therefore, the same scientific rigor applied to the physical side of sexual function must be applied to the emotional and psychological aspects as well.”⁴²

In the current study, patients will be asked if they have a spouse or a sole partner and if they will permit contact to recruit the spouse or partner to the study. If the partner consents to participate, the patient/partner will be asked if they are married. The patient, patient's spouse or unmarried/same sex partner can complete the two-item partner questions of the International Index of Erectile Function Questionnaire (IIEF) [for partner convenience, these two items appear on the SAQ-P form] and Sexual Adjustment Questionnaire (SAQ-P); only married patients and their spouses will complete the Locke's Marital Adjustment Test (LMAT).

- 1.5.1.3.** Significance of the Study of Sildenafil: Currently, there are no large randomized trials of the efficacy of sildenafil for the treatment of erectile dysfunction after radiation therapy ± antiandrogens. Antiandrogens frequently are being studied and commonly used as adjuvant, neoadjuvant or concurrent therapy for the treatment of localized prostate cancer. Based on the literature, radiation therapy and antiandrogens, as prescribed in RTOG 99-10, will have a significant impact on erectile function. If interventions are available to treat ED after prostate cancer therapy, the quality of sexual life impairments may be minimized for many patients. This in turn may have a direct effect on treatment decision-making and subsequent cost-effectiveness analyses for prostate cancer, as well as adding impetus for the use of these interventions. In addition, for patients weighing the pros and cons of radiation therapy versus radical prostatectomy, it may be very helpful to have reliable data addressing the efficacy of ED treatment options. Sildenafil, an oral agent with minimal side effects, has shown efficacy in treating ED after radiation therapy in several small, single institution non-randomized studies. Overall, these studies suggest that approximately two-thirds of the patients will respond to sildenafil. However, these studies shed little light on the response to ED after treatment with total androgen suppression. In addition, antiandrogens affect erectile function through a different mechanism than the etiologies previously studied in sildenafil research. Most published studies of the efficacy of sildenafil were in diseases or conditions associated with penile vascular damage or in some cases neurologic damage. Antiandrogens, on the other hand, affect the hormonal milieu required not only for a physiologic erectile response, but also a psychologic response (desire).

Men in RTOG 99-10 will have discontinued antiandrogen treatment, but our own work shows higher rates of ED after discontinuation of antiandrogens as compared to radiation therapy alone.⁴³⁻⁴⁵ Although the cause of this is uncertain, the need to test ED treatment options is heightened since combination radiation therapy and TAS prolongs survival. Further, interventions to treat ED do not work in a vacuum. Sildenafil in particular works in combination with sexual arousal. It is important that the complex psychosexual components of the individual's sexual experience be recognized and assessed as critical to the subjective experience of sexual function. Since the majority of men diagnosed and treated with prostate cancer have partners, a critical part of the sexual experience would be an assessment of relationship factors that may interact with ED therapy to predict or modify response to treatment. This knowledge would allow for more effective treatment approaches based on a clinical strategy that provides instruction both on the technical use of the medication as well as on the importance of creating an appropriate psychosexual environment.²⁵ Findings from this study would also aid patient education, counseling and decision-making regarding treatment related ED, symptom management and quality of life.

2.0 OBJECTIVES

- 2.1 To determine if there is a difference in erectile function between men treated with sildenafil versus placebo after radiation therapy + antiandrogens for prostate cancer
- 2.2 To determine if there is a difference in overall sexual function and satisfaction between men treated with sildenafil versus placebo after radiation therapy + antiandrogens for prostate cancer
- 2.3 To determine if there is a difference in partner sexual satisfaction between the sildenafil versus placebo arms of this study
- 2.4 To determine if there is a difference in patient and partner marital adjustment between the sildenafil versus placebo arms of this study
- 2.5 To assess factors that may predict response to sildenafil therapy (for example: age, pretreatment sexual function, tobacco use, and comorbidities)

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (11/7/03)

- 3.1.1 Patient registered to RTOG 99-10 for intermediate relapse-risk clinical stage II or III prostate cancer as determined by any of the following combinations of factors:
 - Clinical stage T1b-4, Gleason score 2-6, and prostate-specific antigen >10 but ≤ 100.
 - Clinical stage T1b-4, Gleason score 7, and prostate-specific antigen < 20.
 - Clinical stage T1b-1c, Gleason score 8-10, and prostate-specific antigen <20;
- 3.1.2 Patient suitable for analysis for RTOG 99-10 after RTOG Headquarters' evaluation of RTOG 99-10 eligibility status;
- 3.1.3 Minimum of six months and maximum of 5 years since completion of radiotherapy on RTOG 99-10;
- 3.1.4 Completion of entire IIEF Form (Appendix IV) prior to registration;
- 3.1.5 Pretreatment (prior to enrollment on this study) erectile dysfunction as measured by IIEF (Appendix IV) Question # 1, "How often were you able to get an erection during sexual activity?" – with responses of:
 - "no sexual activity" or "almost never/never" (responses 0-1) or
 - "a few times (much less than half the time)" or "sometimes (about half the time)" [responses 2-3].
 Patients with erectile dysfunction before starting prostate cancer treatment are eligible;
- 3.1.6 Zubrod Performance Status 0, 1, or 2;
- 3.1.7 Although patients with partners are targeted for recruitment, patients without partners or without partners willing to participate are eligible;

- 3.1.8 Patients (and partners, if willing to participate) must sign study-specific informed consent form (Appendix I) prior to randomization.

3.2 Patient Ineligibility (11/7/03)

- 3.2.1 The patient's participation in another medical research study (other than RTOG 99-10) that involves prostate cancer treatment;
- 3.2.2 Previous or concomitant invasive cancer, other than localized basal cell or squamous cell skin carcinoma (AJCC Stage 0-II), unless continually disease free for at least 5 years;
- 3.2.3 History of myocardial infarction within the last year;
- 3.2.4 Current use of any organic nitrate or need for prn nitrates (e.g., use of nitroglycerin on an as-needed basis);
- 3.2.5 Use of ketoconazole, itraconazole, sildenafil, or erythromycin; or use of mechanical (vacuum) devices, intracorporeal, intraurethral, topical, or oral agents as therapy for erectile dysfunction at study entry or throughout study treatment (25 weeks); patients who discontinue these therapies remain eligible;
- 3.2.6 Prior penile implant or history of bilateral orchiectomy;
- 3.2.7 Use of androgen suppression (Lupron, Zoladex), anti-androgen (Casodex, Eulexin, Nilandron), or estrogenic (diethylstilbestrol) agents within the last six months;
- 3.2.8 Anatomical genital abnormalities or concurrent conditions that in the estimation of the physician would prohibit sexual intercourse or prevent study completion;
- 3.2.9 Major medical or psychiatric illness which, in the opinion of the investigator, would prevent completion of treatment or would interfere with follow up.

4.0 PRETREATMENT EVALUATION (11/7/03)

- 4.1 History, physical examination, and Zubrod Performance Status;
- 4.2 History of prior sildenafil use: Document usual dosage per sexual encounter, date of last dose, and patient's response (No; Yes—Unsatisfactory Response; Yes—Satisfactory Response). Regardless of past experience, the patient is eligible if he agrees to adhere to protocol and take only sildenafil or placebo prescribed on study.
- 4.3 Evaluation of erectile function with question # 1 of the IIEF (Appendix IV);
- 4.4 Testosterone level;
- 4.5 Completion of baseline questionnaires prior to distribution of study pills.

5.0 REGISTRATION PROCEDURES (8/22/03)

- 5.1 Each institution must submit a Study Agent Shipment Form (Appendix IX) to the CTSU Regulatory Office (Fax 215-579-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0330).** This must be done prior to registration of the institution's first case. Allow adequate processing time (7-10 days) before calling to register the first patient.
- 5.2 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at 215-574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY

6.1 RTOG 99-10

Radiation therapy and androgen suppression therapy to be administered per RTOG 99-10; No additional radiation therapy or androgen suppression therapy is planned as a part of this study.

7.0 DRUG THERAPY

7.1 Sildenafil

7.1.1 *Description*

Sildenafil works by enhancing the effect of nitric oxide by inhibiting phosphodiesterase type 5 (PDE5), which causes increased levels of cyclic guanosine monophosphate (cGMP) in the corpus cavernosum and results in smooth muscle relaxation and inflow of blood. This occurs in conjunction with sexual stimulation. Sildenafil is rapidly absorbed following oral administration, with absolute bioavailability of approximately 40%. Absorption rate is significantly reduced when sildenafil is taken with a high fat meal, producing a delay in the time to maximum serum concentration (T_{max}) and a reduction in maximum serum concentration (C_{max}); however, extent of absorption is unaffected (Pfizer, personal communication, June 9, 1998). Pharmacokinetics are dose-proportional over the recommended dose range. Sildenafil is primarily eliminated by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to those of the parent compound. Both sildenafil and its metabolite have terminal half-lives of approximately four hours.²⁶ Sildenafil is excreted as metabolites predominantly in the feces and to a lesser extent in the urine.

7.1.2 *Storage*

Sildenafil should be stored in a dry place at room temperature between 59°-86° F.

7.1.3 *Administration (11/7/03)*

A double-blind crossover design will be used in this study to prevent compensatory equalization, probably the most severe threat to the validity of a standard treatment/control group design. Compensatory equalization is a concern since sildenafil has received almost unprecedented media coverage and consumer popularity since it received FDA approval. Those with ethical considerations regarding the withholding of treatment will be more likely to participate in a crossover design where all patients receive treatment.

Sildenafil administration begins a minimum of 6 months and a maximum of 5 years after completion of radiation therapy on RTOG 99-10. Patients randomized to Arm 1 will receive sildenafil for twelve weeks. A flexible dosing schedule, as used in the original Pfizer clinical trials, will be used starting with a 50 mg dose (one tablet) PRN, 1 hour prior to desired sexual intercourse and increasing to 100 mg (two tablets) as needed, once daily. Patients randomized to Arm 2 will receive placebo for 12 weeks with similar "dose escalation" opportunity.

Medication will be dispensed after randomization to the experimental or control period (enough for 100 mg per day, 4 times per week, for 12 weeks). Patients will be issued pill diaries to record the date and number of pills used (See Appendix VIII). If more drug is required (i.e. if the patient requires enough drug for once per day for 7 times per week), the patient must bring in his pill diary and any remaining drug to get a renewed prescription.

At the end of the twelfth week after beginning the drug/placebo (during the one-week break between twelve-week arms), the patient's (and partner's, if participating) sexual function and marital adjustment will be assessed, any remaining drug will be collected, and new medication for crossover treatment will be given (again, enough for 100 mg per day, 4 times per week, for 12 weeks). At the twelfth week after beginning crossover (twenty-fifth week of the study), the patient's (and partner's, if participating) sexual function and marital adjustment will be assessed and any remaining drug again will be collected.

The time point of the one-week break between twelve-week arms is based on a previous dose escalation study,⁴⁰ in which approximately 42% of patients advanced to the full dose of 100 mg of sildenafil, no more than once per day, by 12 weeks. In reviewing 5 double-blind crossover studies of sildenafil in populations other than

cancer,⁴⁶⁻⁵⁰ only one included a wash out period (2 weeks, Giuliano et al.). With a terminal half-life of 4 hours, a wash out period is not necessary.

Following the end of study treatment, we will assess sexual function and marital adjustment at one year post-entry and will assess the number of men who chose to continue on sildenafil and those who discontinued use, as well as the reasons for discontinuation.

7.1.4 Compliance/Accountability

Patients will be issued pill diaries to record the date and number of pills used (See Appendix VIII). A minimum of 3 pills, (a total of 150 mg) per 12-week period must be taken in order not to cause a dilution effect of efficacy. Patients will be requested to take at least two pills (a total of 100 mg) per month. Pill diaries should be collected as specified in Section 11.1. Unused drug should be tallied and returned to distributor (to the address in Section 7.1.5); unused drug should not be recycled.

7.1.5 Supply and Distribution (8/22/03)

The drug is commercially available as a 50 mg tablet under the trade name Viagra™. Pfizer, Inc. will supply drug and placebo free of charge to patients on study, and Biologics, Inc. will distribute the drug and placebo.

The Study Agent Shipment Form must be submitted to the CTSU Regulatory Office (Fax 215-579-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0330).** This must be done prior to registration of the institution's first case. Allow adequate processing time before calling to register the first patient. Upon receipt of the Shipment Form, RTOG will notify Biologics, Inc. to initiate shipment of drug to the institution. Both of the bottles will be labeled "Sildenafil or Placebo". In addition, one of the bottles will be labeled "Phase 1" which the patient will take for the first 12 weeks and the other bottle will be labeled "Phase 2" which the patient will take for the second 12 weeks. The Phase 1 and Phase 2 bottles will be distributed by the radiation oncologist at time points described in Section 7.1.3 and specified in Section 11.1.

The patient-specific drug supply will not be shipped by Biologics, Inc. until the patient has been randomized. Study drug/placebo for patients will be shipped second business day air to the site. Note: Biologics does not ship drug for weekend or holiday delivery. There also will be no drug/placebo shipped on or between December 23 and January 1. If an institution needs drug/placebo prior to a holiday, the institution should provide 3 days notice. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date.

If the patient requires enough drug/placebo for 100 mg once per day for 7 times per week (see Section 7.1.3), the institution is responsible for contacting the distributor as noted below. After all study patients have completed protocol treatment at the site, the institution will be responsible for returning all remaining supplies to Biologics, Inc. for accountability and destruction at the address below. Returned, unused study drug/placebo will not be used again during the study.

William Vance, R. Ph.
Pharmacy Services Manager
Biologics, Inc.
625 Oberlin Road
Raleigh, NC 27605
(800) 850-4306
FAX (919) 546-9816

Leigh Hancock
Clinical Trials Manager
Biologics, Inc.
625 Oberlin Road
Raleigh, NC 27605
(800) 850-4306 ext. 106
FAX (919) 546-9816
lhancock@biologicstoday.com

7.1.6 Drug Interactions

Many of the patients in sildenafil clinical trials were taking other medications concomitantly to treat such diseases as hypertension, depression, ulcers, diabetes, and arthritis. Analysis of the safety database showed no difference in the side effect profile in patients taking sildenafil with any other medication, excluding nitrates.²⁷

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoenzymes 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance. On the other hand, concomitant administration of CYP3A4 inducers (such as rifampin) will decrease plasma levels of sildenafil (Pfizer, personal communication, June 9, 1998).

In healthy volunteers, cimetidine (800 mg) a non-specific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg). A 182% increase in sildenafil systemic exposure (AUC) was observed with a single inhibitor, at steady state (500 mg twice daily for five days). Stronger CYP3A4 inhibitors (such as ketoconazole, itraconazole, or mibefradil) would be expected to have even greater effects, and population data from patients in clinical trials indicated a reduction in sildenafil clearance when it was co-administered with CYP3A4 inhibitors such as ketoconazole, erythromycin, or cimetidine.

Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 50 mg should be considered in patients treated with potent cytochrome P450 inhibitors such as ketoconazole, itraconazole, and erythromycin (Pfizer, personal communication, June 9, 1998).

7.1.7 Toxicity

Sildenafil was well tolerated in 3,700 patients (aged 19 to 87 years) in clinical trials worldwide. Adverse events were generally transient and mild to moderate in nature. In placebo-controlled clinical trials, the rate of discontinuation due to adverse events for sildenafil (2.5%) was not significantly different from placebo (2.3%). Across trials of all designs, the profile of adverse events was similar with a rate of discontinuation similar to that of placebo (Pfizer, personal communication, June 9, 1998).

When sildenafil was taken as recommended in prn flexible-dose studies, the following adverse events were reported by 2% or more of patients and were more frequent with sildenafil than with placebo: headache (16% versus 4%), flushing (10% versus 1%), dyspepsia (7% versus 2%), nasal congestion (4% versus 2%), urinary tract infection (3% versus 2%), abnormal vision (color tinge or light sensitivity; 3% versus 0%), diarrhea (3% versus 1%), dizziness (2% versus 1%), and rash (2% versus 1%). Other adverse events that occurred at a rate greater than 2%, but were equally common with placebo, were respiratory tract infection, back pain, flu syndrome, and arthralgia (Pfizer, personal communication, June 9, 1998).

In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at the 100 mg dose than at lower doses. At doses above the recommended dose range, adverse events were similar to those mentioned above but were generally reported with greater frequency. No cases of priapism were reported (Pfizer, personal communication, June 9, 1998).

Single oral sildenafil doses of up to 100 mg produced no clinically relevant ECG changes in normal male volunteers. Single 100 mg oral sildenafil doses produced an average decrease in blood pressure of approximately 10 mmHg in normal volunteers, which is similar to its effect in ischemic heart disease patients given 40 mg sildenafil intravenously. Larger but similarly transient effects on blood pressure were recorded in patients receiving concomitant nitrates. These may be related to activity of PDE5 in vascular smooth muscle.²⁸

7.2 Toxicity Reporting

- 7.2.1** This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for grading of study agent toxicity. A copy of the CTC version 2.0 can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC version 2.0. See Appendix III for Adverse Event Reporting Guidelines. This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.
- 7.2.2** The following guidelines for reporting adverse drug reactions (ADR's) apply to any research protocol that uses commercial anticancer agents. The following ADR'S experienced by patients accrued to this protocol and attributed to the commercial agent(s) should be reported by telephone to RTOG Headquarters within 24 hours of discovery and then a written report sent to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within ten working days:
- 7.2.2.1** Any ADR which is both serious (life-threatening [grade 4] or fatal [grade 5]) and unexpected;
- 7.2.2.2** Any increased incidence of a known ADR which has been reported in the package insert or the literature;
- 7.2.2.3** Any death on study if clearly related to the commercial agent(s).
- 7.2.3** The ADR report should be documented on FDA Form 3500 and mailed or faxed to the address on the form, as well as to the IDB and RTOG Data Management Department:

Investigational Drug Branch P.O. Box 30012 Bethesda, MD 20824 (301) 230-2330, available 24 hours Fax (301) 230-0159	RTOG Data Management 1101 Market Street, 14 th floor Philadelphia, PA 19107 Phone (215) 574-3214 Fax (215) 923-1737
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All MedWatch forms submitted to RTOG Headquarters must include the RTOG study and case numbers; the non-RTOG intergroup study and case numbers must be included, when applicable.

- 7.2.4** Death from any cause while the patient is receiving protocol treatment or up to 30 days after the last protocol treatment must be telephoned to the RTOG Headquarters Data Management department within 24 hours of discovery.
- 7.2.5** Acute myeloid leukemia (*AML*) or myelodysplastic syndrome (*MDS*) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at <http://ctep.info.nih.gov>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification. This form will take the place of the FDA Form 3500 and must be mailed within 30 days of AML/MDS diagnosis to the address on the form and to the RTOG Data Management Department:

Investigational Drug Branch (<i>NCI/CTEP</i>) P.O. Box 30012 Bethesda, MD 20824	and	RTOG Headquarters AML/MDS Report 1101 Market Street, 14 th floor Philadelphia, PA 19107
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All forms submitted to RTOG Headquarters must include the RTOG study and case numbers; the non-RTOG intergroup study and case numbers must be included, when applicable.

8.0 SURGERY

Not applicable to the study.

9.0 OTHER THERAPY (11/7/03)

No current use of any organic nitrate or need for prn nitrates. No use of ketoconazole, itraconazole, erythromycin, or sildenafil, or use of mechanical (vacuum) devices, intracorporeal, intraurethral, topical, or oral agents as therapy for erectile dysfunction at study entry or throughout study treatment (25 weeks); No use of androgen suppression (Lupron, Zoladex), anti-androgen (Casodex, Eulexin, Nilandron), or estrogenic (diethylstilbestrol) agents within the last six months.

10.0 PATHOLOGY

Not applicable to the study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (11/7/03)

Assessments	Pre-Entry^a	12 weeks after start of drug/placebo	12 weeks after start of crossover	1 year post-entry follow up^{c,d}
History/physical, Zubrod	X			
IIEF (QF)	X ^b	X	X	X
SAQ Patient (SA)	X ^b	X	X	X
SAQ Partner (SB)	X ^b	X	X	X
LMAT Patient (PF) ^f	X ^b	X	X	X
LMAT Spouse (PQ) ^f	X ^b	X	X	X
Pill Diary (DP)		X ^e	X ^e	
Testosterone level	X			
Toxicity Assessment		X ^e	X ^e	X

- This corresponds to a minimum of 6 months and a maximum of 5 years after completion of RT on RTOG 99-10; **NOTE:** It is strongly recommended that the patient's future visit during the one-week break between twelve-week arms be scheduled at the pre-entry visit.
- Quality of life questions must be reviewed with the patient, and patient's partner if the partner is participating, prior to study entry (See Section 11.2).
- Follow-up patient questionnaires will not be excused because of institutional error or omission. The only acceptable reasons for omitting a questionnaire are death and documented patient refusal. See Section 12.1.2 for additional submission instructions.
- Death information: if the study subject expires before the final questionnaire is due, a follow-up form must be submitted.
- The patient will be seen by the physician at these time points to monitor the pill count and assess for potential side effects that may require intervention.
- Completed by married patients and their spouses; unmarried patients and their partners will not complete the LMAT

11.2 Quality of Life Measures

The schedule of quality of life questionnaires is to be reviewed with the patients before study entry. **The patients (and partners) are to be reassured that these sexually explicit and sensitive questionnaires will not be placed into their medical charts. The questionnaires will be kept separately and confidential in their research charts at the site and in their research records at RTOG headquarters.**

Patients will be asked if they have a spouse or a sole partner and if they will permit contact to recruit the spouse/partner to the study. If the partner consents to participate, the patient/partner will be asked if they are married. The patient's spouse or unmarried/same sex partner can complete the two-item partner questions of the IIEF (for

convenience, these two items appear on the SAQ-P form) and the SAQ-P; only married patients and their spouses will complete the LMAT.

11.2.1 International Index of Erectile Function Questionnaire (IIEF)⁵¹ (Appendix IV): The IIEF was developed as a measure of erectile function. Relevant cross-cultural domains of sexual function were identified via the literature and were reviewed and endorsed by an international panel of experts. The resulting 15-item questionnaire underwent linguistic validation in ten languages. Psychometric testing was conducted, and a principal components analysis identified five factors with eigenvalues greater than 1.0: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Internal consistency was high with Cronbach's alphas for the five domains ranging from .73 to .92 with an overall alpha of .91. Scale reliability was determined with high test-retest correlation coefficients ranging from $r = 0.64$ to $r = 0.84$ depending on the domain. Discriminant validity was demonstrated by the scales' ability to differentiate between patients with ED and age-matched controls. IIEF was positively correlated with clinical interviews of sexual function but not with measures of marital adjustment and social desirability, exhibiting acceptable convergent and divergent validity. Sensitivity and specificity were demonstrated with those patients responding to ED treatment over time showing significant change while patients who did not respond to treatment showed no change in IIEF scores.⁵¹ In addition, the two-item partner questions (for spouse or unmarried/same sex partner) developed as a companion to the IIEF will be given to the patient's partner and include: "Has the quality of your partner's erections changed since your partner started treatment?"; "Has the quality of your sex life changed since your partner started treatment?" scored on a 1 to 5, (1=much worse to 5=much better) scale.³⁹ For partner convenience, these two items appear on the SAQ-P form.

11.2.2 Sexual Adjustment Questionnaire (SAQ)⁵²

11.2.2.1 Patient Version (Appendix V): The SAQ is a 20-item patient self-assessment questionnaire modified from the 30-item version developed by Metcalfe and Waterhouse. The original psychometric testing was conducted on 84 healthy and 8 head and neck cancer patients. SAQ rates most responses on a 5-point Likert-type scale, with a higher score indicating a higher level of sexual adjustment. Combined data from two RTOG prostate cancer studies was used to assess the psychometric properties of the RTOG modified SAQ. Seven hundred and thirty-three patients were accrued on two RTOG studies as of March 1997. All patients were treated with external beam radiation therapy (RT) ± neoadjuvant androgen deprivation therapy (ADT). SAQ was given to the patients pre-treatment and at follow up. If there were more than 5 missing answers, the questionnaire was rejected as incomplete. The RTOG modified SAQ retained 5 of the original 8 subscales, including: desire, activity, arousal, orgasm, and satisfaction, and dropped relationship, technique, and miscellaneous, due to concern for patient burden in large clinical trials.⁵³

An exploratory factor analysis with oblique rotation was performed to discern the underlying structure. With the factors identified, a confirmatory factor analysis was performed to test construct validity. A total of 471 patients completed the pre-treatment SAQ. The factor analysis yielded a 5-factor solution and on the basis of content, was labeled as follows: 1. Dysfunction, 2. Satisfaction, 3. Desire, 4. Activity, and 5. Fatigue. Reliability was demonstrated with Cronbach's alpha for the new subscales ranging from 0.66 to 0.86 with an overall alpha of 0.77. Construct validity was demonstrated with empirical testing of similar and dissimilar clinical measures. Specificity was exhibited by SAQ's ability to discriminate among younger patients (≤ 60) and older patients (> 70). All five domains demonstrated a high degree of sensitivity to changes over time. There was a clear relationship among certain pre-treatment demographic and prognostic variables and SAQ scores, including age, ejaculation and erection. Patients who were younger (≤ 60), able to have erections, and were not having problems with ejaculation at the time of study enrollment had

superior scores compared to patients who were older (60-69 or > 70), or having difficulties with erection or ejaculation pre-treatment. There was no difference in scores by race. Of additional interest, physician and patient assessment of the patient's ability to have an erection differed in up to 47% of cases. The RTOG modified SAQ appears to provide more accurate assessment of patient sexual function compared to physician assessment in the same study, reinforcing the value of quality of life patient self-assessments in clinical trials.⁵³

11.2.2.2 Partner Version (SAQ-P) (Appendix VI) The RTOG modified SAQ has been adapted for partner participation in this study. The same questions as in the patient version are asked of the patient's spouse or unmarried/same sex partner, with the modification that the spouse/partner is to fill out the questionnaire from their own perspective.

11.2.3 Locke's Marital Adjustment Test (LMAT)⁵⁴ (Appendix VII) The LMAT is a well established 23 item self-administered instrument that measures marital adjustment. The same instrument is completed by married patients and their spouses (unmarried patients and their unmarried/same sex partners will not complete the LMAT), with weighted scoring allowing for a possible range for men of 48 to 138 and for women of 50 to 138. A principal components factor analysis with varimax rotation identified a three-factor solution labeled sexual congeniality, compatibility, and closeness. Criteria for factor loading included a minimum of 2 items with loadings greater than .50. Two to four year test-retest correlations were remarkably stable at .76 for wives and .78 for husbands.

12.0 DATA COLLECTION

Data should be submitted to:

**RTOG Headquarters
1101 Market Street, 14th Floor
Philadelphia, PA 19107**

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Initial Evaluation Form (I1)	Within 2 weeks of study entry.
Quality of Life Measures: QOL Cover Sheet (CS) IIEF (QF) SAQ [patient] (SA) SAQ-P* [partner] (SB) †LMAT [patient] (PF) †LMAT* [spouse] (PQ)	
Pill Diary (DP)	12 th week after beginning drug; 12 th week after beginning crossover
Follow-Up Form (F1) Quality of Life Measures: QOL Cover Sheet (CS) IIEF (QF) SAQ [patient] (SA) SAQ-P* [partner] (SB)	12 th week after beginning drug; 12 th week after beginning crossover; 1 year after randomization

†LMAT [patient] (PF)
†LMAT* [spouse] (PQ)

*If spouse/partner consents to participate
† Completed by married patients and their spouses; unmarried patients and their partners will not complete the LMAT.

- 12.1.1 Institutions are required to provide patients with questionnaires for each protocol time point as described in Section 12.1.
- 12.1.2 Questionnaires for all time points in section 11.1 are required even if submission time points deviate from the specified intervals, i.e., the questionnaire is collected and submitted even when it is “off schedule”. Questionnaires will not be excused because of institutional error or omission. Only patient death or documented patient refusal will be an acceptable reason. Follow instructions on page 1 of the questionnaires.
- 12.2 **Quality of Life Documentation Submission**
All quality of life forms for this study are available for download from the RTOG website. **Every effort possible should be made to collect the data on time and to follow up by telephone with the patient and/or partner on any missing quality of life questionnaires.**
- 12.2.1 The quality of life questionnaires are to be mailed one week ahead or given to the patients and their partners at their scheduled visits and should be filled out before leaving the clinic.
- 12.2.2 Patients who fail to return for a scheduled visit will receive follow-up phone calls and appointment should be rescheduled as close to the original date as possible.
- 12.2.3 Patients or partners who cannot or refuse to come in for an appointment must be asked if they will accept a telephone interview; if a telephone interview is acceptable to the patient/partner, an appointment for the telephone interview should be set in advance. Telephone interviews will be conducted as follows:
- The questionnaires should be mailed to the patient and/or partner if they were unable to keep their follow-up appointment. When questionnaires have been sent home or mailed, patients should be instructed not to open the envelope until they are contacted by phone by the research assistant or nurse. Patients should have the questionnaire in front of them while they are asked which response they would choose. The research assistant then fills out the form. This assistance and the reason must be documented on the cover sheet.
- 12.2.4 The patient or partner may receive assistance filling out the questionnaire if necessary (i.e., cannot read, forgot their glasses, etc). It is, however, important to avoid influencing their response. Any assistance along with the reason for assistance must be noted on the cover form. Partners are not permitted to assist the patient filling out the questionnaire. It is preferable that partners and patients fill out the questionnaires separately.
- 12.2.5 The questionnaire must be reviewed after the patient completes the form to be sure all items are answered and that each item has only one response circled.
- 12.2.6 It is permissible to send the questionnaire home with the patient or partner in a sealed envelope with a return addressed, stamped envelope if he/she refuses to fill them out at the time of their appointment.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 *Primary Endpoint*

The primary endpoint will be improvement in the ability to obtain an erection, measured as a change from a pretreatment score on the IIEF question # 1: “How often were you able to get an erection during sexual activity?” from a response of “no sexual activity or

almost never/never” [response 0-1] or “a few times (much less than half the time) or sometimes (about half the time)” [response 2-3] to a post treatment response to this question of either 4 or 5 indicating “most times (much more than half the time) or almost always/always”.

13.1.2 Secondary Endpoints

- Overall sexual function and satisfaction
- Partner sexual satisfaction
- Patient and partner marital adjustment
- Predictors of response to ED therapy
- Treatment-induced morbidity

13.2 Sample Size

13.2.1 Stratification (11/7/03)

Patients will be stratified by history of prior use of sildenafil after RTOG 99-10 protocol treatment (No; Yes–Unsatisfactory Response; Yes–Satisfactory Response), IIEF Question #1 Score (0-1 vs. 2-3), and RTOG 99-10 treatment arm (1 vs. 2).

13.2.2 Overview

The primary hypothesis of this trial is that Sildenafil will improve a man’s ability to have an erection sufficient for sexual activity after prostate cancer therapy as prescribed in RTOG 99-10 (16 vs. 28 weeks neoadjuvant/current androgen suppression plus RT).

13.2.3 Sample Size Derivation

The sample size of RTOG 99-10 is 1540 cases accrued over four years. Accrual began in February 2000, and 595 eligible (605 total) patients were entered as of November 2001. A standard AB, BA crossover design has been selected for this study. This design will utilize a linear model for marginal logits⁵⁵ to test the null hypothesis of no difference between treatment arms. The primary endpoint will be assessed using the IIEF question on ability to obtain an erection (question #1). If the post treatment response to this question is either 4 or 5 indicating “most times (much more than half the time) or almost always/always” then the patient will be considered a responder. Any other response will be considered a non-responder. It is assumed that 20% of the patients will respond while on placebo, and 75% will respond while on sildenafil. An effect size of 0.367 has been selected for this study. A sample size of 158 patients per arm will be required for 90% statistical power and a 0.05 (two-sided) significance level. Assuming 5% of the patients are retrospectively found to be ineligible, **then 332 total patients will be randomized.**

These same assumptions are made for the treatment comparisons using the SAQ and SAQ-P. However, the clinically meaningful differences for the SAQ-based analyses are 7 points. Therefore, if the variance is less than expected and the effect size is larger, then the required sample size may produce statistically significant results that are less than clinically meaningful. A difference of less than 7 points will not be considered meaningful, even if it has statistical significance.

13.2.3.1 **(11/7/03)** In the original study design, age was one of three stratification variables (age, IIEF Question #1 Score, and RTOG 99-10 treatment arm). In the revised design, age has been replaced with history of prior use of sildenafil after radiation therapy. As noted in section 13.3.2.1, stratification will be utilized to provide balance of known prognostic factors for ED. To control for baseline imbalances for other possible prognostic variables of ED (e.g., history of prior use of sildenafil prior to RTOG 99-10 protocol treatment), these variables will be controlled for at the time of the analysis.

13.3 Analysis Plan

13.3.1 Aims and Hypotheses

13.3.1.1 The primary aim of this study is to determine if there is a significant difference in erectile function in men treated with sildenafil versus placebo after radiation therapy + antiandrogens for prostate cancer. We hypothesize, based on data from the single institution, nonrandomized radiation therapy and sildenafil series,^{36-39, 41} that approximately 75% of patients will report improved erectile function as indicated by

an increase in IIEF question # 1 score (“How often were you able to get an erection during sexual activity?”) from no sexual activity or almost never/never (response 0-1) or < half the time (response 2-3) to most times/almost always/always (response 4-5) after 12 weeks of sildenafil therapy as compared to less than 20% on placebo (based on data from Meuleman, et al.³³ in patients without prostate cancer). There is a concern that there may be either a period effect or a treatment by period interaction. The sample size is sufficient to permit tests of these effects as well as testing the log-odds ratios.

- 13.3.1.2** The second aim is to determine if there is a significant difference in overall sexual function and satisfaction between men treated with sildenafil versus placebo after radiation therapy + antiandrogens for prostate cancer.
- 13.3.1.3** The third aim is to determine if there is a significant difference in partner sexual satisfaction between the sildenafil versus placebo arms of this study.
- 13.3.1.4** The fourth aim is to determine if there is a significant difference in patient and spouse marital adjustment between the sildenafil versus placebo arms of this study.
- 13.3.1.5** The fifth aim is to assess factors that may predict response to ED therapy (for example, age, pretreatment sexual function, tobacco use, and comorbidities).
- 13.3.2** Preliminary analyses include:
- 13.3.2.1** The crossover design was selected to evaluate the primary endpoint 13.3.1.1. The primary outcome measure is the IIEF. Patients that score ability to have an erection as “most times (much more than half the time) or almost always/always” (4-5 response on question 1) will be a success. In the following table, + is a positive response.

Table 3. Crossover Design

		AB				BA	
Placebo		Viagra		Placebo		Viagra	
		Response				Response	
Response		+	-			+	-
	+	N ₁₁₁	N ₁₂₁	Response	+	N ₁₁₂	N ₁₂₂
	-	N ₂₁₁	N ₂₂₁		-	N ₂₁₂	N ₂₂₂

Based upon the log-nonlinear model,⁵⁵ the following parameters will be estimated:

$$\log(n_{1+1}/n_{2+1}) = \hat{\alpha}$$

$$\log(n_{+11}n_{2+2}/n_{+21}n_{1+2}) = \hat{\rho}_2$$

$$\log(n_{1+2}n_{2+1}/n_{2+2}n_{1+1}) = \hat{\tau}_2$$

$$\hat{\tau}_2 - \log(n_{+11}n_{+22}/n_{+21}n_{+12}) = \hat{\gamma}_2$$

$$\log[n_{111}n_{221}/(n_{121}n_{211})] = \hat{\psi}_1$$

$$\log[n_{112}n_{222}/(n_{122}n_{212})] = \hat{\psi}_2$$

The effect of sildenafil ($\hat{\tau}_2$) will be examined using the log-likelihood test.⁵⁶ There is a concern that there may be either a period effect ($\hat{\rho}_2$) or a treatment by period interaction ($\hat{\gamma}_2$). The log-odds ratios ($\hat{\psi}$) will also be tested. Stratification is utilized to provide balance of known prognostic factors for ED (age and severity of ED). Post hoc subset analyses of the treatment comparison will be performed if there are sufficient numbers of patients in the subsets.

- 13.3.2.1.1** (11/7/03) In the original study design, age was one of three stratification variables (age, IIEF Question #1 Score, and RTOG 99-10 treatment arm). In the revised design, age has been replaced with history of prior use of sildenafil after radiation therapy. As noted in Section 13.3.2.1, stratification will be utilized to provide balance of known prognostic factors for ED. To control for baseline imbalances for other possible prognostic variables of ED (e.g., history of prior use of sildenafil prior to RTOG 99-10 protocol treatment), these variables will be controlled for at the time of the analysis.
- 13.3.2.2** The endpoint in Section 13.3.1.2 will be evaluated using the SAQ. The clinically meaningful difference for the SAQ is 7.0.⁵³

Table 4. Crossover Design for Continuous Data

<u>Period</u>		Sum	Difference
1	2		
A (X_1)	B (X_2)	$T_1=X_1+X_2$	$D_1=X_1-X_2$
B (Y_1)	A (Y_2)	$T_2=Y_1+Y_2$	$D_2=Y_1-Y_2$

The change scores from baseline at period 1 and period 2 for the SAQ will be assessed. Referencing the above table, X_1 and Y_1 , and X_2 and Y_2 are the observation of the SAQ change score from baseline for periods 1 and 2, respectively. Therefore, D_1 and D_2 are the differences in the SAQ change scores. A two-sample t-test will be utilized to test whether the average D_1-D_2 is significantly different from zero. Note that in the t-test, the average values of D_1 and D_2 are used. Hence, if the difference is significantly different from zero, then the null hypothesis of no difference can be rejected. Post hoc subset analyses of the treatment comparison will be performed if there are sufficient numbers of patients in the subsets. Correlations between ED and sexual function, as measured by SAQ, will be performed using logistic regression with ED as the dependent variable.

- 13.3.2.3** The third endpoint in Section 13.3.1.3 will be evaluated using the SAQ for partners (SAQ-P). The change scores from baseline at period 1 and period 2 for the SAQ-P will be assessed. Referencing the above table, X_1 and Y_1 , and X_2 and Y_2 are the observation of the SAQ-P change score from baseline for periods 1 and 2, respectively. Therefore, D_1 and D_2 are the differences in the SAQ-P change scores. A two-sample t-test will be utilized to test whether the average D_1-D_2 is significantly different from zero. Again, if the difference is significantly different from zero, then the null hypothesis of no difference can be rejected. Post hoc subset analyses of the treatment comparison will be performed if there are sufficient numbers of partners in the subsets. Correlations between patient-ED and partner sexual function, as measured by SAQ-P, will be performed using logistic regression with ED as the dependent variable. Correlations between patient SAQ and partner SAQ-P will be performed using a linear regression with SAQ as the dependent variable.
- 13.3.2.4** The fourth endpoint in Section 13.3.1.4 will be evaluated using the LMAT. Referencing the above table, X_1 and Y_1 , and X_2 and Y_2 are the observation of the LMAT score for periods 1 and 2, respectively. Therefore, D_1 and D_2 are the differences in the LMAT scores. A two-sample t-test will be utilized to test whether the average D_1-D_2 is significantly different from zero. Note that in the t-test the average values of D_1 and D_2 are used. Hence, if the difference is significantly different from zero, then the null hypothesis of no difference can be rejected. Post hoc subset analyses of the treatment comparison will be performed if there are sufficient numbers of patients in the subsets. Correlations between patient-ED and marital adjustment, as measured by LMAT, will be performed using logistic regression with ED as the dependent variable. Correlations between patient SAQ and LMAT will be performed using a linear regression with SAQ as the dependent

variable. Correlations between partner SAQ-P and spouse LMAT will be performed using a linear regression with SAQ-P as the dependent variable.

13.3.2.5

The literature provides evidence that factors such as age, pretreatment sexual function, tobacco use, and comorbidities may be prognostic for ED or sexual adjustment. Including all of these factors into a regression analysis may result in overfitting the model.⁵⁷ To assess the last endpoint in Section 13.3.1.5, univariate linear regression analysis for ED will be performed for each factor; those factors with a p-value associated with its coefficient of less than or equal to 0.25 will be included into a final model. Linear regression is chosen because we want to determine the severity of ED associated with these factors. The same type of analysis will be utilized for sexual function (SAQ). Exploratory analyses of predictors of marital adjustment will also be performed. Additional questions from the IIEF and subscales of the SAQ and SAQ-P will be incorporated into exploratory analyses to generate new hypotheses.

13.5 Inclusion of Minorities

In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and racial/ethnic minorities in clinical research, we also considered the possible interaction between race and treatments. Based on accrual statistics from RTOG 94-13 and 94-08, we projected that 73% of men accrued to RTOG 99-10 will be white, 23% black (not of Hispanic origin), 3% Hispanic, 0.4% Asian or Pacific Islander, 0.2% American Indian or Alaskan Native, and 0.5% will be others or unknown. The following table lists the projected accrual for each racial group in the present investigation.

Planned Gender and Minority Inclusion

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	0	10		10
Not Hispanic or Latino		320		320
Unknown		2		2
Ethnic Category: Total of all subjects*	0	332		332*
Racial Category				
American Indian or Alaskan Native		1		1
Asian		2		2
Black or African American		76		76
Native Hawaiian or other Pacific Islander		0		0
White		251		251
More than one race				
Unknown		2		2
Racial Category: Total of all subjects*	0	332		332*

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APPENDIX I

RTOG 0215

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

TREATMENT OF ERECTILE DYSFUNCTION IN PATIENTS TREATED ON RTOG 99-10 FOR PROSTATE CANCER: IMPACT ON PATIENT AND PARTNER QUALITY OF LIFE

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know," is available from your doctor.

You are being asked to take part in this study because you have had prostate cancer and have difficulty getting and/or keeping an erection for sexual activity.

WHY IS THIS STUDY BEING DONE?

This study uses the drug sildenafil, better known as Viagra™, given after your radiation therapy and hormone treatments. The purpose of this study is to see if sildenafil can help you get an erection for sexual activity. This study also will try to find out more about how this drug affects your overall sexual satisfaction and your partner's satisfaction (if your partner is willing to participate in the study).

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 332 people will take part in the study.

WHAT IS INVOLVED IN THE STUDY? (11/7/03)

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. A computer will assign you to a group. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in either group.

Treatment 1

You will be given sildenafil for 12 weeks and then a placebo for another 12 weeks.

Treatment 2

You will be given a placebo for 12 weeks and then sildenafil for another 12 weeks.

The placebo is a pill that contains no active agents. It looks and tastes like sildenafil but does not produce erections. You will not know which pill you are taking during each twelve-week period. We ask that you keep a Pill Diary of when you use the pill and how many pills you use. You will need to bring the Pill Diary with you to get more pills from your doctor, if you need them.

Both Treatments (11/7/03)

For the duration of this study (25 weeks), you must agree to take only the study pills to get an erection. Also, while on this study, you must agree not to use mechanical devices (such as vacuum devices) or other topical or oral medications or herbal supplements to produce an erection.

In addition, although you can take your usual medications, you must agree not to take any organic nitrate (such as nitroglycerin) or antibiotics such as ketoconazole, itraconazole, or erythromycin while taking part in this study (for 25 weeks). If you are not sure if you are taking any of these drugs, you can talk to your doctor. If your doctor tells you that you need to take one of these drugs, you must stop taking sildenafil/placebo, and tell us immediately by calling (doctor/institution).

You and your partner (if your partner is willing to participate in this study) will be asked to fill out three questionnaires about your ability to have an erection, your overall sexual function and satisfaction, and your relationship. The questionnaires will need to be filled out at four (4) different times: a) before you start taking any pills; b) 12 weeks after you start the first pills; c) 12 weeks after you start the second pills; and d) one year after you began this study. The questionnaires will take about 30 to 45 minutes to fill out, each time you are asked to complete them. The research associate or nurse will be available to help you or answer any questions you may have. These questionnaires will not go in your medical chart. They will be kept separately and confidential in your research chart at your institution and in your research record at the headquarters of the Radiation Therapy Oncology Group (RTOG).

HOW LONG WILL I BE IN THE STUDY?

You will take sildenafil/placebo for 25 weeks. You will be seen by your physician at 12 weeks, 25 weeks, then one year after beginning the study.

Your doctor may decide to take you off this study if your doctor believes it is in your medical best interest, if funding for this study is stopped, if the drug supply is insufficient,

or your condition worsens. You may also be taken off this study if new information becomes available about how to better help you get an erection for sexual activity.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor.

Treatment for erectile dysfunction, whether given in a research study or in the ordinary practice of medicine, may have some harmful side effects. Although sildenafil has been shown to be well tolerated by most patients, there have been some mild to moderate side effects. The treatment used in this study may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

In 3,700 patients studied using sildenafil the following side effects were noted in the following percentage of patients: headache (16%), flushing (warm feeling and color rushing to your cheeks) (10%), upset stomach (7%), stuffy nose (4%), urinary infection (3%), temporary eyesight problems (color tinge or light sensitivity; 3%), diarrhea (3%), dizziness (2%), and rash (2%).

A slight drop in your blood pressure may occur; your blood pressure then returns to normal in a short time after the drug is taken. Your doctor will be checking you closely for these side effects. You should contact your doctor between visits if you have concerns or questions about possible side effects. Side effects usually disappear after the treatment is stopped. In the meantime, your doctor may prescribe medication to keep these side effects under control.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Sildenafil has been reported to improve erections in men after radiation therapy, but the benefits of this drug after treatment with hormones, as you have been given, is unknown. It is not known whether the treatment you will be given in this research study will help your condition more than another treatment for erectile dysfunction. The information from this study may help others by providing information about response to sildenafil after radiation therapy and hormone treatments for prostate cancer. A possible personal benefit of this research study may be an improvement in your ability to have an erection

for sexual activity. Another possible benefit may be improved sexual satisfaction for you and/or your partner. None of these possible benefits is certain or guaranteed.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study, and you also may choose to take sildenafil as prescribed by your doctor, independent of this study. Other treatments are available for erectile dysfunction, but only three others have been recommended by expert doctors. Other treatments that could be used for erectile dysfunction may include the following: (1) The vacuum device: this is a hollow tube placed around the penis to draw blood into the penis to make it erect; (2) Vasoactive drugs: such as papaverine and alprostadil that may cause a temporary enlargement of blood vessels in the penis and allow it to fill with blood to become erect. The medication has to be injected with a needle into the penis or inserted into the urethra (the tube that carries urine through the penis); (3) Penile prostheses: rods or cylinders are surgically placed into the penis. Some rods leave the patient with a permanent erection that is sometimes difficult to hide. Other rods use a pump system placed inside the body that can pump fluid into the rods in the penis to give you an erection; or (4) no treatment. With the last choice, you may someday be able to have an erection on your own but the chance of having an erection on your own is unknown.

Your doctor can tell you more about erectile dysfunction and the possible benefits and drawbacks of the different available treatments. You should discuss your condition and the expected outcome with your doctor. Your doctor will be available to answer any questions. You are encouraged to ask your doctor any questions you have about this research study and the choices of treatment available to you. If you have any questions at all, please ask your doctor.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI), and qualified representatives of applicable drug manufacturers.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You (and your partner, if your partner also participates in this study) will receive no payment for taking part in this study.

Sildenafil and placebo will be given to you free of charge while you are a part of this study. The use of medication to help control side effects could result in added costs.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You or your partner may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. You may seek care from a doctor of your choice at any time. If you do not take part in this study or if you withdraw from the study, you will continue to receive care.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615.

Visit the NCI's Web sites for comprehensive clinical trials information at
http://www.cancer.gov/clinical_trials or for accurate cancer information including PDQ
(Physician Data Query) visit http://www.cancer.gov/cancer_information

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).

Patient's Name

Signature

Date

Partner's Name

Signature

Date

Name of Person Obtaining Consent

Signature

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

APPENDIX III

ADVERSE EVENT REPORTING GUIDELINES

Federal Regulations require that investigators report adverse events and reactions in a timely manner. This reporting improves patient care and scientific communication by providing information to the National Cancer Institute (NCI) whereby new findings can be more widely disseminated to investigators and scientists.

A. Definitions and Terminology

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at initiation of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to commencement of treatment or an event, though present at the commencement of treatment, becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

Known/expected events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form, or noted in the drug insert.

Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

Definite:	The adverse event is <i>clearly related</i> to the treatment/procedure.
Probable:	The adverse event is <i>likely related</i> to the treatment/procedure.
Possible:	The adverse event <i>may be related</i> to the treatment/procedure.
Unlikely:	The adverse event is <i>doubtfully related</i> to the treatment/procedure.
Unrelated:	The adverse event is <i>clearly NOT related</i> to the treatment/procedure.

B. Grading of Adverse Events

Unless specified otherwise, the NCI Common Toxicity Criteria (CTC) version 2.0 is used to grade severity of adverse events. Protocols approved prior to March 1998 will use one of several different morbidity grading systems. To grade severity of adverse events in studies prior to this date, consult the protocol document for the appropriate rating system.

C. General Guidelines

In order to assure prompt and complete reporting of adverse events and toxicity, the following general guidelines must be observed. The guidelines apply to all RTOG studies. **When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supercede the General Guidelines.** A protocol may stipulate that specific grade 4 events attributable to treatment are expected and therefore may not require the standard reporting; however, exceptions to standard reporting must be specified in the text of the protocol.

1. The Principal Investigator will report to the RTOG Group Chair, to the Headquarters Data Management Staff (215/574-3214) and to the Study Chair within 24 hours of discovery, the

details of all unexpected severe, life-threatening (grade 4) and fatal (grade 5) adverse events if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.

2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require telephone notification within 24 hours of discovery.
3. A written report, including all relevant clinical information and all study forms due up to and including the date of the event, will be sent by mail or FAX (215/928-0153) to RTOG Headquarters within 10 working days of the telephone report (unless specified otherwise within the protocol). The material must be labeled: ATTENTION: Adverse Event Reporting.
 - a. The Group Chair in consultation with the Study Chair will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.
 - b. For events that require telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB), the Food and Drug Administration (FDA), to another co-operative group or to the study sponsor, the investigator may first call RTOG (as outlined above) unless this will unduly delay the required notification process.

A copy of all correspondence sent to recipients of the call, e.g. NCI, IDB, another cooperative group office (non-RTOG coordinated studies) must be submitted to RTOG Headquarters. **Copies must include the RTOG study and case numbers.**

4. When participating in non-RTOG coordinated intergroup studies or in RTOG sponsored pharmaceutical studies, the investigator must comply with the reporting specification required in the protocol.
5. Institutions must comply with their individual Institutional Review Board policy regarding submission of documentation of adverse events. All "expedited" adverse event reports should be sent to the local Institutional Review Board (IRB).
6. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.
7. When submitting reports and supporting documentation for reports to RTOG on an RTOG protocol patient, **the study number and the case number must be recorded** so that the case may be associated with the appropriate study file. This includes submission of copies of FDA Form 3500 (MedWatch).
8. All data collection forms through the date of the reported event and the applicable reporting form are submitted to RTOG Headquarters data management department (Attention: Adverse Event) **within 10 working days** of the telephone report or sooner if specified by the protocol. Documentation must include an assessment of attribution by the investigator as previously described in section A.
9. MedWatch Forms (FDA 3500) submitted on RTOG protocol patients must be signed by the Principal Investigator.
10. All neuro-toxicity (\geq grade 3) from radiosensitizer or radioprotector drugs are to be reported to RTOG Headquarters Data Management, to the Group Chair, and to the Study Chair within 10 days of discovery.

D. Adverse Event Reporting Related to Radiation Therapy

1. All fatal events resulting from protocol radiation therapy must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management department and to the radiation therapy protocol Study Chair within 24 hours of discovery.
2. All grade 4, (CTC v 2.0 and RTOG/EORTC Late Radiation Morbidity Scoring Scheme Criteria) and life-threatening events (an event, which in view of the investigator, places the patient at immediate risk of death from the reaction) and grade 4 toxicity that is related, possibly related or probably related to protocol treatment using non-standard fractionated radiation therapy, brachytherapy, radiopharmaceuticals, high LET radiation, and radiosurgery must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management and to the radiation therapy Study Chair within 24 hours of discovery. Expected grade 4 adverse events may be excluded from telephone reporting if specifically stated in the protocol.
3. All applicable data forms and if requested, a written report, must be submitted to RTOG Headquarters within 10 working days of the telephone call.

E. Adverse Event Reporting Related to Systemic Anticancer Agents

Adverse drug reactions (ADRs) are adverse events that are related to an anticancer agent and meet certain criteria: are unexpected effects of the drug or agent, or are severe (grade 3), life-threatening (grade 4), or fatal (grade 5), even if the type of event has been previously noted to have occurred with the agent.

1. Commercial Agents/Non-Investigational Agents

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE¹	Hospitalization During Treatment²	Secondary AML/MDS³
FDA Form 3500 ^{4,5} within 10 days	X	X	X	
NCI/CTEP Secondary AML/MDS Form within 30 days of diagnosis ^{4,5}				X
Call RTOG within 24 hrs of event ⁷	X ⁶			

1. Any increased incidence of a known AE.
2. Inpatient hospitalizations or prolongation of existing hospitalization for medical events equivalent to CTC Grade 3-5 which precipitated hospitalization must be reported regardless of the requirements or phase of study, expected or unexpected and attribution.
3. Reporting required during or subsequent to protocol treatment.
4. Submitted to Investigational Drug Branch, PO Box 30012, Bethesda, MD 20924-0012.
5. Copy to RTOG Data Management labeled: Attention: Adverse Event Report.
6. All grade 5 known toxicity.
7. Call RTOG Data Management (215) 574-3214. To leave a voice mail message when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number, and a telephone number where you may be contacted.

2. Investigational Agents

An investigational agent is one sponsored under an Investigational New Drug Application (IND). Reporting requirements and timing are dependent on the phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the NCI Agent Specific Expected Adverse Event List, protocol and/or Investigator's Brochure. An expedited adverse event report requires submission to CTEP via AdEERS (Adverse Event Expedited Report). See the CTEP Home Page, <http://ctep.info.nih.gov> for complete details and copies of the report forms.

a. AdEERS (Adverse Event Expedited Reporting System)

Effective January 1, 2001, the NCI Adverse Event Expedited Reporting System (AdEERS) was implemented for all protocols for which NCI is the supplier of an investigational agent.

Attribution: An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any phase of trial. An expedited report is required for unexpected Grade 2 and Grade 3 adverse events with an attribution of possible, probable or definite for any phase of trial. An expedited report is not required for unexpected or expected Grade 1 adverse events for any phase of the trial.

RTOG uses "decentralized" notification. This means that all reportable events will be directly reported to NCI, just as has been done with paper-based reporting. AdEERS is an electronic reporting system; therefore, all events that meet the criteria must be reported through the AdEERS web application. Once the report is filed with AdEERS, the institution need not send notification to RTOG, as the AdEERS system will notify the Group Office. Institutions that utilize this application are able to print the report for local distribution, i.e., IRB, etc.

For institutions without Internet access, if RTOG is the coordinating group for the study, contact RTOG Data Management (215-574-3214) to arrange for AdEERS reporting. In these instances, the appropriate Adverse Event Expedited Report template (Single or Multiple Agents) must be completed. The template must be fully completed and in compliance with the instruction manual; i.e., all mandatory sections must be completed including coding of relevant list of value (LOV) fields before sending to RTOG. Incomplete or improperly completed templates will be returned to the investigator. This will delay submission and will reflect on the timeliness of the investigators' reporting. A copy of the form sent to RTOG must be kept at the site if local distribution is required. Do not send the template without first calling the number noted above.

Templates for Single or Multiple Agents may be printed from the CTEP web page or will be supplied from the RTOG Registrar upon faxed request (FAX) (215) 574-0300.

When reporting an event on a patient in an RTOG-coordinated study, you must record the RTOG case number in the Patient ID field.

AdEERS reporting does not replace or obviate any of the required telephone reporting procedures.

Investigational Agent(s) used in a Clinical Trial Involving a Commercial Agent(s) on separate arms: **An expedited adverse event report should be submitted for an investigational agent(s) used in a clinical trial involving a commercial agent(s) on a separate arm only if the event is specifically associated with the investigational agent(s).**

Investigational Agent(s) used in a Clinical Trial in Combination with a Commercial Agent(s): **When an investigational agent(s) supplied under an NCI-sponsored IND is used in combination with a commercial agent(s), the combination should be considered investigational and reporting should follow the guidelines for investigational agents.**

a. Expedited Reporting for Phase 1 Studies

Unexpected Event		Expected Event	
Grades 2-3 Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution
Grade 2: Expedited report within 10 working days. Grade 3: Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. Grade 1: Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of last dose of treatment with an investigational agent.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of the last dose of treatment with an investigational agent.

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.
2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

c. Expedited Reporting for Phase 2 and Phase 3 Studies

Unexpected Event		Expected Event	
Grades 2-3 Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution
Expedited report within 10 working days. Grade 1: Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days.	Adverse Event Expedited Reporting NOT required.	Expedited including Grade 5 aplasia in leukemia patients within 10 working days. Grade 4 myelosuppression not to be reported, but should be submitted as part of study results. Other Grade 4 events that do not require expedited reporting would be specified in the protocol.

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.
2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

APPENDIX IV (12/5/03)

International Index of Erectile Function Questionnaire (IIEF)

Please circle the appropriate Response Option to indicate how you were feeling over the past four (4) weeks.

Question	Response Option
1: How often were you able to get an erection during sexual activity?	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
2: When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
3: When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
4: During sexual intercourse, <u>how often</u> were you able to maintain your erection after you had penetrated (entered) your partner?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
5: During sexual intercourse, <u>how difficult</u> was it to maintain your erection to completion of intercourse?	0 = Did not attempt intercourse 1 = Extremely difficult 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult

Rosen et al. *Urology*. 49: 1997

APPENDIX IV (continued) [12/5/03]

<p>6: How many times have you attempted sexual intercourse?</p>	<p>0 = No attempts 1 = One to two attempts 2 = Three to four attempts 3 = Five to six attempts 4 = Seven to ten attempts 5 = Eleven + attempts</p>
<p>7: When you attempted sexual intercourse, how often was it satisfactory for you?</p>	<p>0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always</p>
<p>8: How much have you enjoyed sexual intercourse?</p>	<p>0 = No intercourse 1 = No enjoyment 2 = Not very enjoyable 3 = Fairly enjoyable 4 = Highly enjoyable 5 = Very highly enjoyable</p>
<p>9: When you had sexual stimulation <u>or</u> intercourse, how often did you ejaculate?</p>	<p>0 = No sexual stimulation/intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always</p>
<p>10: When you had sexual stimulation <u>or</u> intercourse how often did you have the feeling of orgasm or climax?</p>	<p>0 = No sexual stimulation/intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always</p>
<p>11: How often have you felt sexual desire?</p>	<p>1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always</p>

Rosen et al. *Urology*. 49: 1997

APPENDIX IV (continued) [12/5/03]

12: How would you rate your level of sexual desire?	1 = Very low/none at all 2 = Low 3 = Moderate 4 = High 5 = Very high
13: How satisfied have you been with your overall <u>sex life</u> ?	1 = Very dissatisfied 2 = Moderately dissatisfied 3 = About equally satisfied and dissatisfied 4 = Moderately satisfied 5 = Very satisfied
14: How satisfied have you been with your <u>sexual relationship</u> with your partner?	1 = Very dissatisfied 2 = Moderately dissatisfied 3 = About equally satisfied and dissatisfied 4 = Moderately satisfied 5 = Very satisfied
15: How do you rate your <u>confidence</u> that you could get and keep an erection?	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very high

Rosen et al. *Urology*. 49: 1997

APPENDIX V (12/5/03)

Sexual Adjustment Questionnaire (SAQ)- Patient Version

Please answer each question carefully. The items deal with sensitive and personal issues but are important to our research. However, if you do not wish to complete an item, **please initial it** so we may know that you did not wish to record an answer. If possible, fill out the questions alone. We want only your answers. Please recheck to see that you have not omitted any questions.

Completion of Form: Circle the response that best describes how you feel.

PLEASE ANSWER EACH QUESTION EVEN IF YOU ARE NOT SEXUALLY ACTIVE RIGHT NOW.

1. What is the importance of sexual activity in your life right now?

Extremely Important 5	Very Important 4	Important 3	Slightly Important 2	Of No Importance 1
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2. How soon after your last cancer treatment did you resume sexual activity (alone or with another person)?

Never Stopped 5	Less than 1 month 4	1 to 3 months 3	3 to 6 months 2	Have Not Yet 1
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3. How often is sexual activity enjoyable to you now?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1
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4. Do you find that you are too tired for sexual activity?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1
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5. Do you have desire for sexual activity?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1
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6. Do you desire sexual activity more often than your partner(s)?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1
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Waterhouse J, Metcalfe M. *ONF*. 23(3): 1986.

APPENDIX V (continued) [12/5/03]

7. How soon after your last cancer treatment did you resume your previous sexual relationship(s) with another person(s)?

Never Stopped 5	Less than 1 month 4	1 to 3 months 3	3 to 6 months 2	Have Not Yet	No Partner 1
-----------------------	---------------------------	-----------------------	-----------------------	-----------------	--------------------

8. Have you been the one to initiate (start) sexual activity with your partner(s) since your last cancer treatment?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1	No Partner 0
-------------	-----------------------	----------------	----------------------	------------	--------------------

9. How often do you have sexual activity (with or without a partner)?

More than 4 times/week 5	2 to 3 times a week 4	1 time a week 3	1 to 3 times a month 2	Less than once a month 1	Not at all 0
--------------------------------	-----------------------------	-----------------------	------------------------------	--------------------------------	-----------------

10. Do you have trouble becoming sexually aroused or excited?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1	Have Not Tried 0
-------------	-----------------------	----------------	----------------------	------------	------------------------

11. When sexually excited, are you able to get an erection?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1	Have Not Tried 0
-------------	-----------------------	----------------	----------------------	------------	------------------------

12. Do you feel it takes a long time for you to get a firm erection?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1	Have Not Tried 0
-------------	-----------------------	----------------	----------------------	------------	------------------------

13. Since your cancer treatments, do you have a problem in "coming" (ejaculating) or feel that you "come" too soon?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1	Have Not Tried 0
-------------	-----------------------	----------------	----------------------	------------	------------------------

Waterhouse J, Metcalfe M. *ONF*. 23(3): 1986.

APPENDIX V (continued) [12/5/03]

14. Is it important for you to reach a climax (“come”)?

Always	Almost Always	Sometimes	Almost Never	Never
5	4	3	2	1

15. Do you feel satisfied after sexual activity?

Always	Almost Always	Sometimes	Almost Never	Never	No Sexual Activity
5	4	3	2	1	0

16. Are you satisfied with the frequency of sexual activity in your life?

Very Satisfied	Somewhat Satisfied	Neutral	Somewhat Unsatisfied	Very Unsatisfied
5	4	3	2	1

17. Do you feel tense or frustrated after a sexual experience?

Always	Almost Always	Sometimes	Almost Never	Never	No Sexual Activity
5	4	3	2	1	0

18. Has having cancer changed your sexual relationship with your partner(s)?

Very Bad Effect	Some Bad Effect	No Effect	Some Good Effect	Very Good Effect	No Partner
5	4	3	2	1	0

19. Has having cancer treatment changed your sexual relationship with your partner(s)?

Very Bad Effect	Some Bad Effect	No Effect	Some Good Effect	Very Good Effect	No Partner
5	4	3	2	1	0

20. Have you had difficulties with your sexual ability since your cancer treatment?

No Activity	Very Many Difficulties	Many Difficulties	Some Difficulties	A Few Difficulties	No Difficulties
5	4	3	2	1	0

Waterhouse J, Metcalfe M. *ONF*. 23(3): 1986.

APPENDIX V (continued) [12/5/03]

COMMENTS _____

Waterhouse J, Metcalfe M. *ONF*. 23(3): 1986.

Sample

APPENDIX VI (12/5/03)

Sexual Adjustment Questionnaire - Partner Version (SAQ-P)

We would like you to answer the questions below with your partner in mind; keep in mind changes in your partner (if any) since his cancer therapy. Please answer each question carefully. The items deal with sensitive and personal issues but are important to our research. However, if you do not wish to complete an item, **please initial it** so we may know that you did not wish to record an answer. If possible, fill out the questions alone. We want only your answers. Please recheck to see that you have not omitted any questions.

Completion of Form: Circle the response that best describes how you feel

PLEASE ANSWER EACH QUESTION EVEN IF YOU ARE NOT SEXUALLY ACTIVE.

1. What is the importance of sexual activity in your life right now?

Extremely Important 5	Very Important 4	Important 3	Slightly Important 2	Of No Importance 1
-----------------------------	------------------------	----------------	----------------------------	--------------------------

2. How often is sexual activity enjoyable to you now?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1
-------------	-----------------------	----------------	----------------------	------------

3. Do you find that you are too tired for sexual activity?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1
-------------	-----------------------	----------------	----------------------	------------

4. Do you have desire for sexual activity?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1
-------------	-----------------------	----------------	----------------------	------------

5. Do you desire sexual activity more often than your partner?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1
-------------	-----------------------	----------------	----------------------	------------

6. Are you the one who initiates (starts) sexual activity with your partner?

Always 5	Almost Always 4	Sometimes 3	Almost Never 2	Never 1	No Partner 0
-------------	-----------------------	----------------	----------------------	------------	--------------------

Adapted from Waterhouse J, Metcalfe M. *ONF*. 23(3): 1986.

APPENDIX VI (continued) [12/5/03]

7. How often do you have sexual activity (with your partner)?
- | | | | | | |
|---------------------------|------------------------|------------------|-------------------------|---------------------------|------------|
| More than 4
times/week | 2 to 3 times
a week | 1 time
a week | 1 to 3 times
a month | Less than
once a month | Not at all |
| 5 | 4 | 3 | 2 | 1 | 0 |
8. Do you have trouble becoming sexually aroused or excited?
- | | | | | | |
|--------|------------------|-----------|-----------------|-------|-------------------|
| Always | Almost
Always | Sometimes | Almost
Never | Never | Have Not
Tried |
| 5 | 4 | 3 | 2 | 1 | 0 |
9. Is it important for you to reach a climax ("come")?
- | | | | | |
|--------|------------------|-----------|-----------------|-------|
| Always | Almost
Always | Sometimes | Almost
Never | Never |
| 5 | 4 | 3 | 2 | 1 |
10. Do you feel satisfied after sexual activity?
- | | | | | | |
|--------|------------------|-----------|-----------------|-------|-----------------------|
| Always | Almost
Always | Sometimes | Almost
Never | Never | No Sexual
Activity |
| 5 | 4 | 3 | 2 | 1 | 0 |
11. Are you satisfied with the frequency of sexual activity in your life?
- | | | | | |
|-------------------|-----------------------|---------|-------------------------|---------------------|
| Very
Satisfied | Somewhat
Satisfied | Neutral | Somewhat
Unsatisfied | Very
Unsatisfied |
| 5 | 4 | 3 | 2 | 1 |
12. Do you feel tense or frustrated after a sexual experience?
- | | | | | | |
|--------|------------------|-----------|-----------------|-------|-----------------------|
| Always | Almost
Always | Sometimes | Almost
Never | Never | No Sexual
Activity |
| 5 | 4 | 3 | 2 | 1 | 0 |
13. Does your partner have trouble becoming sexually aroused or excited?
- | | | | | | |
|--------|------------------|-----------|-----------------|-------|-------------------|
| Always | Almost
Always | Sometimes | Almost
Never | Never | Have Not
Tried |
| 5 | 4 | 3 | 2 | 1 | 0 |

Adapted from Waterhouse J, Metcalfe M. *ONF*. 23(3): 1986.

APPENDIX VI (continued) [12/5/03]

14. When sexually excited, is your partner able to get an erection?
- | | | | | | |
|--------|------------------|-----------|-----------------|-------|-------------------|
| Always | Almost
Always | Sometimes | Almost
Never | Never | Have Not
Tried |
| 5 | 4 | 3 | 2 | 1 | 0 |
15. Do you feel it takes a long time for your partner to get a firm erection?
- | | | | | | |
|--------|------------------|-----------|-----------------|-------|-------------------|
| Always | Almost
Always | Sometimes | Almost
Never | Never | Have Not
Tried |
| 5 | 4 | 3 | 2 | 1 | 0 |
16. Does your partner have a problem in "coming" (ejaculating) too soon?
- | | | | | | |
|--------|------------------|-----------|-----------------|-------|-------------------|
| Always | Almost
Always | Sometimes | Almost
Never | Never | Have Not
Tried |
| 5 | 4 | 3 | 2 | 1 | 0 |
17. Has the quality of your partner's erections changed since your partner started treatment?
- | | | | | | |
|----------------|--------------------|-------------|-------------------|------------|-------------------|
| Much
Better | Somewhat
Better | Is the Same | Somewhat
Worse | Much Worse | Have Not
Tried |
| 5 | 4 | 3 | 2 | 1 | 0 |
18. Has the quality of your sex life changed since your partner started treatment?
- | | | | | | |
|----------------|--------------------|-------------|-------------------|------------|-------------------|
| Much
Better | Somewhat
Better | Is the Same | Somewhat
Worse | Much Worse | Have Not
Tried |
| 5 | 4 | 3 | 2 | 1 | 0 |

COMMENTS _____

Adapted from Waterhouse J, Metcalfe M. *ONF*. 23(3): 1986.

APPENDIX VII (12/5/03)

Locke's Marital Adjustment Test (LMAT)

All the questions can be answered by placing a check next to the appropriate answer. Please fill out all items. If you cannot give the exact answer to a question, answer the best you can. *Give the answers that best fit your marriage at the present time.* Thank you very much.

1. Have you ever wished you had not married?
 - a. Frequently_____
 - b. Occasionally_____
 - c. Rarely_____

2. If you had your life to live over again, would you:
 - a. Marry the same person_____
 - b. Marry a different person_____
 - c. Not marry at all_____

3. Do husband and wife engage in outside activities together?
 - a. All of them_____
 - b. Some of them_____
 - c. Few of them_____
 - d. None of them_____

4. In leisure time, which do you prefer?
 - a. Both husband and wife to stay at home_____
 - b. Both to be on the go_____
 - c. One to be on the go and other to stay home_____

5. Do you and your mate generally talk things over together?
 - a. Never_____
 - b. Now and then_____
 - c. Almost always_____
 - d. Always_____

6. How often do you kiss your mate?
 - a. Every day_____
 - b. Now and then_____
 - c. Almost never_____

Kimmel D, Van der Veen F. *J Marriage and the Family*. 29:1974.

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APPENDIX VII (continued) [12/5/03]

7. Check any of the following items which you think have caused serious difficulties in your marriage.

- Mates attempt to control my spending money _____
- Other difficulties over money _____
- Religious differences _____
- Different amusement interests _____
- Lack of mutual friends _____
- Constant bickering _____
- Interference of in-laws _____
- Lack of mutual affection (no longer in love) _____
- Unsatisfying sex relations _____
- Selfishness and lack of cooperation _____
- Adultery _____
- Desire to have children _____
- Sterility of husband or wife _____
- Veneral diseases _____
- Mate paid attention to (became familiar with) another person _____
- Desertion _____
- Nonsupport _____
- Drunkenness _____
- Gambling _____
- Ill health _____
- Mate sent to jail _____
- Other reasons _____

8. How many things satisfy you most about your marriage?

- a. Nothing _____
- b. One thing _____
- c. Two things _____
- d. Three or more _____

9. When disagreements arise they generally result in:

- a. Husband giving in _____
- b. Wife giving in _____
- c. Neither giving in _____
- d. Agreement by mutual give and take _____

10. What is the total number of times you left mate or mate left you because of conflict?

- a. No times _____
- b. One or more times _____

Kimmel D, Van der Veen F. *J Marriage and the Family*. 29:1974.

APPENDIX VII (continued) [12/5/03]

11. How frequently do you and your mate get on each other's nerves around the house?

- a. Never _____
- b. Occasionally _____
- c. Frequently _____
- d. Almost always _____
- e. Always _____

12. What are your feelings on sex relations between you and your mate?

- a. Very enjoyable _____
- b. Enjoyable _____
- c. Tolerable _____
- d. Disgusting _____
- e. Very disgusting _____

13. What are your mate's feelings on sex relations with you?

- a. Very enjoyable _____
- b. Enjoyable _____
- c. Tolerable _____
- d. Disgusting _____
- e. Very disgusting _____

State approximate extent of agreement or disagreement between husband and wife on the following items:

Check one Column for each item below	Always Agree	Almost Always Agree	Occasionally Disagree	Frequently Disagree	Almost Always Disagree	Always Disagree
14. Handling Family finances (ie: installment buying)						
15. Matters of recreation (ie: going dancing)						
16. Demonstration of affection (ie: frequency of kissing)						
17. Friends (ie: dislike of mate's friends)						
18. Intimate relations (ie: sex relations)						
19. Ways of dealing with in-laws						
Check one Column for each item below	Always Agree	Almost Always Agree	Occasionally Disagree	Frequently Disagree	Almost Always Disagree	Always Disagree

20. The amount of time that should be spent together						
21. Conventionality (ie: right, good, or proper conduct)						
22. Aims, goals and things believed to be important in life.						

23. On the scale on the line below, mark *which best describes the degree of happiness, everything considered, of your marriage*. The middle point, "happy" represents the degree of happiness which most people get from marriage, and the scale gradually ranges on one side to those few who experience extreme joy in marriage and on the other to those few who are very unhappy in marriage.

Very Unhappy Happy Perfectly Happy

Kimmel D, Van der Veen F. *J Marriage and the Family*. 29:1974.

APPENDIX VII (continued) [12/5/03]

Locke's Marital Adjustment Test (LMAT)

Scoring of Visual Analogue

Scoring is for research purposes only and not to be given to the patient.

Very Happy _____ Happy _____ Perfectly Happy

0 1 3 7 10 13 18

* Scoring follows procedures suggested by Locke (1951). Scores are given for husband's form and are the same for the wife's form except where the wife's score is given in parentheses.

Sample

APPENDIX VIII (12/5/03)

Sildenafil (Viagra™) Pill Diary

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each twelve-week period.
2. Record the date and number of pills used each time you use the drug.
3. Record your response on the same line.
4. Please return the form to your physician at the end of the twelve-week period along with the remaining pills.

	Date	# of pills used	Did you have an erection adequate for intercourse? (circle your response)		Date	# of pills used	Did you have an erection adequate for intercourse? (circle your response)
1	- - -	/ /	no yes		26	- - -	/ / no yes
2	- - -	/ /	no yes		27	- - -	/ / no yes
3	- - -	/ /	no yes		28	- - -	/ / no yes
4	- - -	/ /	no yes		29	- - -	/ / no yes
5	- - -	/ /	no yes		30	- - -	/ / no yes
6	- - -	/ /	no yes		31	- - -	/ / no yes
7	- - -	/ /	no yes		32	- - -	/ / no yes
8	- - -	/ /	no yes		33	- - -	/ / no yes
9	- - -	/ /	no yes		34	- - -	/ / no yes
10	- - -	/ /	no yes		35	- - -	/ / no yes
11	- - -	/ /	no yes		36	- - -	/ / no yes
12	- - -	/ /	no yes		37	- - -	/ / no yes
13	- - -	/ /	no yes		38	- - -	/ / no yes
14	- - -	/ /	no yes		39	- - -	/ / no yes
15	- - -	/ /	no yes		40	- - -	/ / no yes
16	- - -	/ /	no yes		41	- - -	/ / no yes
17	- - -	/ /	no yes		42	- - -	/ / no yes
18	- - -	/ /	no yes		43	- - -	/ / no yes
19	- - -	/ /	no yes		44	- - -	/ / no yes
20	- - -	/ /	no yes		45	- - -	/ / no yes
21	- - -	/ /	no yes		46	- - -	/ / no yes
22	- - -	/ /	no yes		47	- - -	/ / no yes
23	- - -	/ /	no yes		48	- - -	/ / no yes
24	- - -	/ /	no yes		49	- - -	/ / no yes
25	- - -	/ /	no yes		50	- - -	/ / no yes

APPENDIX IX (8/22/03)

RTOG 0215

STUDY AGENT (SILDENAFIL) SHIPMENT FORM

Sildenafil will be shipped only to institutions that have identified a single individual for receipt of shipment. Each institution must submit a Study Agent Shipment Form to the CTSU Regulatory Office (Fax 215-579-0206) as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution's first case. **Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0330).** Allow adequate processing time (7-10 days) before calling to register the first case.

SHIP TO:

Name: _____

Address: _____
(no P.O. addresses)

Telephone: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

IRB Approval Date: _____

Investigator (PI) Signature _____ Date: _____

Investigator Name (Print) _____

Investigator NCI # _____

Send Completed Form to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX 215-569-0206

RTOG Headquarters Approval _____ Date: _____