Erectile dysfunction (ED) has been estimated to affect up to 30 million American men with a two to three-fold increase in the prevalence of moderate to severe ED between the ages of 40 and 70 (Feldman, Goldstein, Hatzichristou, Crane, & McKinlay, 1994; The National Institutes of Health [NIH] Consensus Conference, 1993). Erectile dysfunction has a proven deleterious effect on quality of life (QoL) including diminished physical and emotional well-being, marital discord, and loss of self-esteem (Burnett, 1998; Laumann, Paik, & Rosen, 1999; NIH, 1993). The NIH Consensus Conference defined ED as “the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance” and recommended the development of reliable methods for assessing the symptoms of ED and evaluating treatment outcomes (NIH, 1993).

Following definitive local treatment for early-stage prostate cancer, preservation of erectile function has been assumed to be most likely following brachytherapy. However, recent studies have demonstrated that brachytherapy-related erectile dysfunction (ED) is more common than initially reported. The exacerbation of brachytherapy-related ED is closely related to several clinical, treatment, and dosimetric parameters including pre-implant erectile function and radiation dose to the proximal penis. The majority of patients with brachytherapy-induced ED respond favorably to oral erectogenic agents.

At the time of prostate cancer diagnosis, ED is present in 30% to 50% of men with a substantial number of additional men developing treatment-related ED (Karakiewicz, Aprikian, & Bazinet, 1997). Although it has been widely asserted that preservation of erectile function is more likely following brachytherapy, the incidence of brachytherapy-induced ED is substantially greater than initially reported (Merrick, Wallner, & Butler, 2003a). Subgroup analyses have demonstrated ED is present in 6% to 90% of patients undergoing brachytherapy. The wide ranges of reported ED likely reflect differences in followup, patient selection, implant technique, and the mode of data collection (Litwin, Lubeck, Henning, & Carroll, 1998; Merrick et al., 2003a). In general, those series with longest followup or the utilization of patient-administered questionnaires report lower...
rates of potency preservation (Merrick et al., 2003a). Fortunately, most patients with brachytherapy-induced ED respond favorably to oral erectogenic agents such as sildenafil citrate (Merrick et al., 1999).

Assessment of Sexual Function

The use of patient-administered validated instruments is essential for the accurate and reliable collection of QoL data (Litwin et al., 1998). In our clinic, we utilize the erectile function component of the International Index of Erectile Function (IIEF) (see Figure 1) (Merrick et al., 2002b; Rosen, Riley, & Wagner, 1997; Stipetich, Abel, & Blatt, 2002).

The IIEF has been validated as a sensitive and specific tool for evaluating male sexual function; consists of a 15-item questionnaire with domains of erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction; and requires patients to quantify erectile function (Rosen et al., 1997). We utilize the erectile function component, which comprises six questions with a total survey score ranging from 1 to 30 (see Figure 1). Erectile function scores <11 and <6 are indicative of moderate and severe ED respectively (Blander, Sanchez-Ortiz, Broderick, 1999; Rosen et al., 1997).

Following brachytherapy, the reported prevalence of ED varies considerably from study to study (Merrick et al., 2003a). These discrepancies may be attributed to differences in followup, patient selection, treatment technique, and the mode of data collection. The most accurate information is obtained by patient-administered questionnaires. To date, few institutions have used the patient-administered IIEF to evaluate brachytherapy-related ED (Merrick et al., 2002b). Following all definitive local therapies including brachytherapy, most erectile function series have focused exclusively on erectile function. However, various additional sexual symptoms have been reported (Merrick, Wallner, Butler, Lief, & Sutlief, 2001). In a prospective randomized trial, hematospermia, orgasmalgia (pain at orgasm), and alteration in the intensity of orgasm are reported in 26%, 15%, and 38% of

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**Figure 1. International Index of Erectile Function**

Please fill out this short questionnaire to help us find out more about any problems you might be having with sexual function. Answer these questions for your situation over the last month and without the assistance of Viagra or other medications or devices.

1. How often are 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 = 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

4. During sexual intercourse, how often 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, how difficult 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

6. How do you rate your confidence that you could get and keep an erection?
   - 1 = Very low
   - 2 = Low
   - 3 = Moderate
   - 4 = High
   - 5 = Very high
patients respectively (Merrick et al., 2001) (see Figure 2). For the majority of patients, these side effects were of limited duration.

Factors Affecting Potency

The mechanism of brachytherapy-induced ED has not been definitively proven; however, it likely represents a multifactorial process including neurogenic compromise, vascular insufficiency, local trauma, and psychogenic causes (Merrick et al., 2003a; Zelefsky & Eid, 1998).

Pre-implant erectile function. Pre-implant erectile function is the best clinical predictor of post-treatment ED (Merrick et al., 2002b; Stock, Kao, & Stone, 2001). In a prospective randomized trial using the IIEF questionnaire, Merrick and colleagues reported potency preservation rates of 58%, 48%, and 22% in patients with pre-implant IIEF scores of 24 to 30, 18 to 23, and 13 to 17, respectively (Merrick et al., in press) (see Figure 3).

Patient age. Patient age is related to the development of brachytherapy-induced ED. In a prospective randomized trial, Merrick and colleagues reported potency preservation rates of 61%, 49%, and 32% in patients <60, 60 to 69 and 70 years of age (Merrick et al., in press) (see Figure 4).

Supplemental therapies. Conflicting data regarding the contribution of supplemental external beam radiation therapy (XRT) and/or neoadjuvant androgen deprivation therapy (ADT) on potency preservation has been reported (Merrick et al., 2002b; Merrick et al., in press; Potters, Torre, Fearn, Leibel, & Kattan, 2001; Stock et al., 2001). In general, it appears that without conformal or intensity-modulated radiation therapy techniques, supplemental XRT increases brachytherapy-related ED (Merrick et al., 2002b; Potters et al., 2001). However, a recent study reported no correlation between the use of supplemental XRT and brachytherapy-related ED with the utilization of XRT techniques that significantly limited the dose to the proximal penis (Merrick et al., in press).

To date, three studies have failed to discern a relationship between neoadjuvant ADT and potency preservation, while a fourth study reported a strong correlation between neoadjuvant ADT and the development of brachytherapy-related ED (Merrick et al., 2002b; Merrick et al., in press; Potters et al., 2001; Stock et al., 2001).

Isotope. In both retrospective and prospective studies, isotope (Pd-103 versus I-125) has not influenced potency preservation (Merrick et al., 2002b; Merrick et al., in press).

Nocturnal erections. In patients reporting adequate pretreatment erectile function, the absence of nocturnal erections may potentially be an indicator of early vascular compromise. In a prospective randomized trial, the absence of pre-implant nocturnal erections predicted for brachytherapy-related ED (Merrick et al., in press).
Mechanism of Brachytherapy-Induced ED

Although ED is likely a multifactorial process, there is an increasing body of data implicating radiation dose to the proximal penis with brachytherapy-related ED (Merrick et al., 2003a; Merrick et al., 2002a).

The penile erectile bodies (the paired corpora cavernosa and the midline corpus spongiosum) represent potential site-specific structures for brachytherapy-related ED (see Figures 5 & 6) (Merrick et al., 2003a). Excessive radiation doses to the proximal penis have resulted in significantly increased rates of brachytherapy-related ED (Merrick et al., 2003b; Merrick et al., 2003c; Merrick et al., 2002a).

In contrast, in both retrospective and prospective studies, no correlation between radiation dose to the neurovascular bundles and brachytherapy-related ED (Merrick et al., 2001; Merrick, Butler, Dorsey, Lief, & Donzella, 2000). However, it is possible that with longer followup, neurovascular bundle doses may contribute to brachytherapy-related ED. On the basis of the available data, it is not rational to recommend neurovascular bundle-sparing brachytherapy because the neurovascular bundles are so close (approximately 2 mm) to the frequently biopsy-positive peripheral zone of the prostate.

Management of Brachytherapy-Induced ED

Radiation-related ED typically responds well to sildenafil citrate (Merrick et al., 1999). In a brachytherapy population, the 6-year actuarial rate of potency preservation was approximately 90% when potent patients were grouped with patients with ED who used sildenafil (Merrick et al., 2002b). In addition, the post-implant response to sildenafil was highly dependent on pre-implant potency (Merrick et al., 2002b). Among patients with normal pre-implant erections and suboptimal pre-implant erections, 95% and 70% of patients responded favorably to sildenafil following brachytherapy (Merrick et al., 2002b). To date, there have not been formal studies evaluating the efficacy of tadalafil or vardenafil in brachytherapy-related ED, although it is expected that both agents would have efficacy similar to sildenafil. Radiation-induced ED also normally responds to vasoactive agents and penile implants (Dubocq, Bianco, Maralani, Forman, & Dhabuwala, 1997).

Involuntary nocturnal erections represent the body’s intrinsic mechanism for maintaining function of the corpora cavernosa. Nightly inflow of blood into the penile smooth muscle provides oxygen to the tissue and appears to be essential for normal erectile function (Montorsi et al., 2000). As such, during routine telephone and office followup evaluations, the urologic oncology nurse, in conjunction with the physician, should encourage patients to develop regular erections with or without sexual relations (Merrick et al., 2003b; Mulhall, 2001). This concept is based on cavernosal oxygenation. In the absence of rou-
tine penile erections, the corpora smooth muscle experiences chronic hypoxia with resultant loss of elasticity and distensibility which may lead to a venous leak (Mulhall, 2001). On the basis of the premise that erections enhance tissue oxygenation and suppress smooth muscle fibrosis, therapy to enhance nocturnal erections (penile rehabilitation, nighttime physical therapy) might have a therapeutic benefit. Montorsi et al. (2000) demonstrated that sildenafil but not placebo taken at bedtime produced a significant improvement in nocturnal erectile activity. This concept of nighttime physical therapy could potentially reduce brachytherapy-related ED.

PDE-5 Inhibitors: Mechanism Of Action and Side Effects

Phosphodiesterase type-5 (PDE-5) inhibitors enhance the effect of nitric oxide which results in the relaxation of penile corpora cavernosa smooth muscle and vasodilation of the corpora cavernosa. These erection-producing effects are mediated by cyclic guanosine monophosphate (cGMP). The inhibition of PDE-5 results in prolongation of the effects of cGMP with subsequent increased concentrations of nitric oxide.

Oral PDE-5 inhibitors have low rates of adverse events. Although it appears that vardenafil, tadalafil, and sildenafil improve erectile function equally well, the duration of action of the three agents is significantly different. Sildenafil and vardenafil have half-lives of approximately 4 hours, while tadalafil has a half-life of 17.5 hours. Food interactions with sildenafil and vardenafil suggest dosing restrictions after a high-fat meal, while tadalafil can be administered without regard to food. Table 1 is a summary of the most common side effects attributable to the three PDE-5 inhibitors. Vardenafil is contraindicated for patients using alpha-blockers; however, tadalafil and sildenafil are not. The FDA is currently formulating new guidelines for each of the aforementioned drugs regarding concurrent use with alpha-blockers.

Approximately 40% of patients classified as sildenafil failures can be converted to responders through a re-education program (Atiemo, Szostak, & Sklar, 2003). Incorrect drug administration was the most common reason for correctable failure (81% of all failures).

In addition, Klotz, Mathers, Klotz, and Sommer (2004) noted that 31% of patients discontinued sildenafil following successful usage. The majority of these patients discontinued the medication because of the lack of opportunity or desire for sexual intercourse or that their partner showed no sexual interest.

Rehabilitation Strategies

Although there have been no formal studies evaluating the prophylactic and prolonged use of erectogenic agents in the reversal of brachytherapy-induced ED, such studies do exist for radical prostatectomy. Following radical prostatectomy, Levine, McCullough, and Padma-Nathan (2004) reported that 10 of 35 men using nightly sildenafil, and only 1 out of 19 men taking placebo, regained spontaneous erectile function. In men with erectile dysfunction unrelated to radical prostatectomy, Sommer and Engleman (2004) reported that nightly sildenafil was more effective than PRN dosing. In 76 men with ED of >6 month duration, 50 mg of nightly sildenafil for 1 year resulted in 59% of those men reporting a full return of sexual function after discontinuing the medication. Only 10% of men using sildenafil on demand had normal erectile function at 1 year. An important part of a postoperative penile rehabilitation program includes recommendation for routine penile erectile activity (three or more erections per week). This could be supported by any commonly prescribed treatment of current medical recommendation, including vacuum erection devices, prostaglandin penile injections or urethral suppositories, or PDE-5 inhibitors.

Fertility after Prostate Brachytherapy

Although it is unlikely that men remain fertile following prostate brachytherapy, post-brachytherapy fertility evaluations have occasionally revealed the absence of significant change in the semen with the subsequent

| Table 1. Side Effects Frequencies (in percent) of Three PDE-5 Inhibitors |
|---------------------------------|----------------|----------------|----------------|
| Effect                          | Sildenafil 1   | Tadalafil 2    | Vardenafil 3   |
| Headache                        | 16            | 15            | 15            |
| Flushing                        | 10            | 3             | 11            |
| Dyspepsia                       | 7             | 10            | 4             |
| Nasal Congestion/Sinusitis      | 4             | 3             | 3             |
| Abnormal Vision                 | 3             | <2            | <2            |
| Diarrhea                        | 3             | <2            | <2            |
| Dizziness                       | 2             | >2            | <2            |
| Back Pain                       | >2            | 6             | 2             |

1 Medical Economics, 2004
2 Lilly ICOS, 2003
3 Bayer HealthCare, 2003
ability to father children without deleterious consequences (Mydlo & Lebed, 2004). Although younger men choosing brachytherapy should consider sperm banking because of presumed treatment-related infertility, those with younger spouses must consider contraception to prevent the occasional unexpected pregnancy. This is not often discussed pre-operatively and may be a significant afterthought if unwanted consequences occur. Nursing management should therefore include discussion of reproductive concerns.

Conclusions
Brachytherapy-induced erectile dysfunction is more common than previously reported with the available data strongly supporting the proximal penis as an important site-specific structure. Fortunately, brachytherapy-related ED responds well to oral erectile agents. However, if oral erectile agents are ineffective, multiple other options exist including vacuum devices, injectable therapies, and penile prostheses. The stimulation of nightly nocturnal erections may improve long-term erectile function. Refinements in implant techniques should result in lower radiation doses to the proximal penis with expected improvements in potency preservation.

References