



*Several potentially effective therapeutic options are available to manage erectile dysfunction resulting from treatment for prostate cancer.*

Tina Sotis. *The Summer House* ©2001. Oil on canvas, 24" × 30".

# Management of Erectile Dysfunction Secondary to Treatment for Localized Prostate Cancer

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**Background:** Management options for localized prostate cancer include radical prostatectomy, external radiation therapy, brachytherapy, and watchful waiting. Improvements in treatment techniques have resulted in fewer side effects. Nevertheless, long-term complications such as erectile dysfunction (ED) continue to affect a significant percentage of men treated for prostate cancer and can have a distressing and debilitating effect on the patient's quality of life.

**Methods:** The author reviews both the prevalence and the current options for the management of ED secondary to treatment for clinically localized prostate cancer.

**Results:** The ability to preserve potency after prostate cancer treatment is controversial, with reports ranging from 10%-90%. For patients complaining of impotence, efficacious alternatives are available such as oral drugs, intraurethral alprostadil, vacuum devices, intracavernous injections, and penile prostheses.

**Conclusions:** Sexual function is an integral part of patient satisfaction and quality of life. Although ED is a frequent complication of definitive treatment of localized prostate cancer, a variety of treatment options are now available to maximize quality of life despite age and other comorbidities.

## Introduction

Advances in the early detection and management of prostate cancer have improved the chance for survival in many patients. Current treatment options for localized prostate cancer include radical prostatectomy, external-beam radiotherapy, and brachytherapy. These treatments are effective, but they also produce deleterious effects on patient quality of life, including erectile dysfunction (ED). ED is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse.<sup>1</sup>

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Submitted: July 1, 2001; accepted: October 16, 2001.

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ED is a common side effect in men treated for prostate cancer, but its prevalence does not seem more or less likely in patients presenting with prostate cancer compared with normal population studies. Sexual function in patients who have been treated for localized prostate cancer has multiple determinants, including age (patients with prostate cancer are often in late middle age, when sexual performance may be diminished), diabetes, hypertension, hypercholesterolemia, pelvic trauma, clinical treatments for hypertension, depression, obesity, smoking, sleep disorders, and inactivity. Nevertheless, the factor found to have the most significant effect on potency in univariate and multivariate analyses was pretreatment erectile function.<sup>2</sup>

Patients with other factors contributing to ED are less likely to preserve potency after definitive treatment for prostate cancer. Likewise, treatment modalities are likely to be less effective.

Obtaining a detailed erectile function assessment before any therapy is initiated provides patients with a more realistic probability of potency preservation following prostate cancer treatment. Improvements in the management of localized prostate cancer have produced a corresponding increase in the need to consider physiological and psychosocial correlates, particularly in relation to sexual function.

## Pathophysiology of Erectile Dysfunction

Penile erection is a neurovascular event modulated by neurotransmitters and hormonal status. The penis is

innervated by autonomic and somatic nerves. In the pelvis, the sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa to regulate blood flow during erection and detumescence. The parasympathetic visceral efferent fibers arise from sacral roots 2-4 to supply the pelvic plexus located on the lateral wall of the rectum. The cavernous nerves leave the pelvic plexus and travel in the lateral pelvic fascia on the posterolateral surface of the prostate gland to supply the corpora cavernosa of the penis.

The somatic component, the pudendal nerve, is responsible for penile sensation. Autonomic denervation followed by blunt pelvic or perineal trauma, radical pelvic surgeries (eg, for colon or prostate cancer) affect poor smooth muscle relaxation, arterial insufficiency, and venous abnormalities, thus preventing adequate erection.<sup>3</sup> Both surgery and radiation therapy appear to affect this mechanism.

## Radiation Therapy

### *External-Beam Radiation Therapy*

Radiation is thought to produce ED by accelerating microvascular angiopathy causing cavernosal fibrosis or stenosis of the pelvic arteries and by accelerating existing arteriosclerosis, leading to vascular impotence.<sup>4</sup> Years may elapse before clinically significant ED occurs.

Siegel and colleagues<sup>5</sup> found no significant difference in posttreatment erectile function in patients treat-

Table 1. — Erectile Dysfunction Following Radiation Therapy for Localized Prostate Cancer

Author	No. of Patients	Follow-up (mo)	ED Following External-Beam Radiotherapy (%)	ED Following Interstitial Radiotherapy (%)
Sanchez-Ortiz et al <sup>6</sup>	171	23		51
Matzkin et al <sup>7</sup>	63	15		30
Stock et al <sup>8</sup>		72		42
Merrick et al <sup>9</sup>	34	13		35
Potters et al <sup>14</sup>	482	60		52.7
Turner et al <sup>10</sup>	146	24	60	
Zelevsky et al <sup>11</sup>	50	60	68	53
Wilder et al <sup>12</sup>	51	15	63	
al-Abany et al <sup>13</sup>	31	9-18	45	
Siegel et al <sup>5</sup>	315		85.4	
Madalinska et al <sup>15</sup>	278	12	41-55	

ed with radical prostatectomy compared with those treated with external-beam radiation. However, the overall incidence of ED following external-beam radiation ranges from 41%-85% (Table 1)<sup>5-15</sup> and is dose- and age-dependent.<sup>4</sup>

Three-dimensional conformal therapy (3D-CRT) may enhance the chance of preservation of erectile function sufficient for vaginal penetration the majority of patients. In 2000, Wilder et al<sup>12</sup> reported their preliminary results on potency preservation following 3D-CRT for prostate cancer. In their study of 51 evaluable patients with a median follow-up of 15 months, 35 (69%) were potent. Further follow-up is needed to assess long-term potency with 3D-CRT.

### Brachytherapy (Radioactive Seed Implantation)

Few studies have evaluated the effect of interstitial radiation therapy on erectile function, particularly at 5 years or more after treatment. Pretreatment ED and higher implant radiation dose are associated with greater impotency rates.<sup>8</sup> ED rates after seed implantation range from 30%-53% (Table 1), and potency rates after brachytherapy compare favorably to those following external-beam irradiation.<sup>5</sup>

### Cryotherapy

The incidence of impotence after cryotherapy for prostate cancer is 100%. Onik<sup>16</sup> has reported on a few

patients treated with “nerve-sparing” cryotherapy with retention of potency, but these data need confirmation.

### Radical Prostatectomy

Radical prostatectomy is one of the standard treatments for organ-confined prostate cancer. Radical prostatectomy causes ED due to intraoperative damage to the neurovascular mechanisms that initiate erections. ED develops immediately after surgery, with variable return of function.

Criteria that influence recovery of erections after surgery include younger patient age, stronger erections before operation, preservation of the neurovascular bundles, and attention to fine details in the surgical technique. Recovery of erections occurs in 68% of preoperatively potent men treated with bilateral nerve-sparing surgery and in 47% of those treated with unilateral nerve-sparing surgery.<sup>17</sup>

A controversial issue associated with ED after radical prostatectomy is the wide discrepancy in the potency rates reported in the literature. Several variables are involved that impede a helpful comparison among reported series. According to McCammon et al,<sup>18</sup> preservation of sexual function was disappointingly low among patients who underwent nerve-sparing surgery. On the other hand, Walsh<sup>19</sup> suggests that by meticulous preservation of the nerves, erections can resume in the majority of patients who were previously potent. The reason for the discrepancy in results is unclear and may

Table 2. — Incidence of Erectile Dysfunction Following Radical Retropubic Prostatectomy

Author	No. of Patients	Follow-up (mo)	Non-Nerve-Sparing Surgery (%)	Bilateral Nerve-Sparing Surgery (%)	Unilateral Nerve-Sparing Surgery (%)	Not Stratified for Sparing Surgery (%)
Gralnek et al <sup>20</sup>	163	12	83	50		
Madalinska et al <sup>15</sup>	63	12				80-91
Walsh et al <sup>21</sup> *	62	18		14		
Catalona et al <sup>17</sup>	798	18		32	53	
Kawanishi et al <sup>22</sup>	126			57		
Stanford et al <sup>23</sup>	1,291	18	65.6	56	58.6	
Kao et al <sup>24</sup>	1,069					88.4
Valdivia et al <sup>25</sup>	204					90.8
Rabbani et al <sup>26</sup>	314	36	75			
Formenti et al <sup>27</sup>	94	36		60		
Siegel et al <sup>5</sup>	392					90

\* 1/3 using sildenafil intermittently

be related to surgical volume and experience or the selection of younger, healthier patients for surgery.

Following bilateral nerve-sparing radical retropubic prostatectomy, incidence rates of ED range from 14%-60% (Table 2). Full erection recovery is significantly reduced if either one or both bundles are resected.<sup>5,15,17,20-27</sup>

Radical prostatectomy is still associated with significant morbidity. However, further refinements in surgical technique (eg, perioperative testing of the cavernosal nerves, videotape) will pave the way for minimal side effects while preserving efficacy of therapy. Although radical prostatectomy morbidity affects self-reported quality of life, most patients would elect surgery again as therapy for localized prostate cancer.<sup>24</sup>

## Treatment

Patients undergoing radical prostatectomy or radiation therapy all showed comparable improvement in sexual function during the first year after treatment for early-stage prostate cancer.<sup>28</sup>

There is no "gold standard" algorithm to treat impotence following adequate treatment in patients with ED due to localized prostate cancer. Success or failure of a treatment is dependent on the severity of ED. Guide-

lines for the management of patients with ED include three lines of therapy (1999 WHO First International Consultation on ED).<sup>29</sup> First-line treatment includes oral pharmacotherapy, which is considered the first option, or vacuum devices. Second-line therapy includes intracavernous injection (ICI) or medicated urethral system for erection (MUSE). Third-line therapy includes surgical treatment (penile prosthesis) for those who do not respond to less invasive forms of treatment.

### Oral Pharmacology Options

Sildenafil citrate (Viagra) was the first effective oral drug. It is a potent inhibitor of phosphodiesterase type 5, which is the predominant phosphodiesterase isozyme in the corpus cavernosum. Inhibition of phosphodiesterase type 5 causes increased concentrations of cyclic GMP that in turn enhance smooth muscle relaxation and hence the erectile response. Sildenafil citrate is effective in clinical practice in patients with psychogenic and vascular etiologies. In contrast, patients with ED following radical prostatectomy or with neurological etiology had the lowest satisfaction rate.<sup>30</sup> This observation provides some insight into the mechanism of action of the drug, which appears to be dependent on adequate nerve supply to the corpora cavernosa. Sildenafil improves erectile function of patients with ED following radiotherapy from 70% to 80.6% (Table 3)<sup>30-37</sup> and appears less effective after radical prostatectomy.<sup>34</sup> Success with sildenafil in improving erectile function is enhanced if bilateral nerve-sparing surgery can be per-

Table 3. — Efficacy of Sildenafil in Erectile Dysfunction After Local Treatment for Prostate Cancer

Procedure	Author	No. of Patients	Mean Age	Improvement %
Radical Retropubic Prostatectomy	Jarow et al <sup>30</sup>	77	61	35
	Vale <sup>32</sup>			43
	Zippe et al <sup>34</sup>	91		71 <sup>a</sup>
				50 <sup>b</sup>
				15 <sup>c</sup>
	Baniel et al <sup>31</sup>	85	59.5	20
Radiotherapy	Vale <sup>32</sup>			70
	Zelefsky et al <sup>33</sup>	50	68	74
	Weber et al <sup>35</sup>	35		77
	Merrick et al <sup>36</sup>	62		80.6
	Kedia et al <sup>37</sup>	21		71

<sup>a</sup> = bilateral nerve-sparing surgery  
<sup>b</sup> = unilateral nerve-sparing surgery  
<sup>c</sup> = non-nerve-sparing surgery

formed. Sublingual apomorphine, a dopaminergic agonist, has been launched but its efficacy in ED following prostate cancer treatment is unknown. Clinical studies are under way in these patients. Other oral 5-phosphodiesterase inhibitors such as vardenafil (Nuviva) and IC-351 (Cialis) will be available soon.<sup>38</sup>

### Other Approaches

For those who do not respond to oral drugs, other options are available, including medicated urethral system for erection (MUSE), vacuum devices, or intracavernous injection (ICI). Oral drugs are sometimes used together with ICI.

A significant percentage of patients will respond to a vacuum erection device to give an erection sufficient for vaginal penetration. This is relatively simple to use, but the erection produced is unlike a physiologic erection. Some patients consider it unappealing; in a report by Baniel et al,<sup>31</sup> only 11 (14%) of 78 patients who responded to the vacuum erection device agreed to continue with it. For patients who failed either sildenafil or MUSE therapy and do not want to use ICI or penile prostheses, a combination of MUSE and sildenafil may allow erections sufficient for penetration.<sup>39</sup>

ICI is considered the best nonsurgical option because it is efficacious, but needle phobia, painful erection, loss of efficacy, loss of interest, and the presence of fibrotic nodules in the penis cause patient dropouts. ICI can be used as one, two, three or four drugs (prostaglandin E1, phentolamine, papaverine, and chlorpromazine, respectively). Montorsi et al<sup>40</sup> have reported some success with alprostadil.

The poor acceptability and compliance to invasive ICI appear to be less important factors in patients in whom ICI was previously integrated into the global management of their prostate cancer.<sup>41</sup> Because of the widespread use of oral drugs, however, ICI has become second-line therapy, to be used when oral drugs are not effective or are contraindicated. After 1 year of follow-up, ICI was described as the most effective alternative for ED after radical retropubic prostatectomy.<sup>31</sup>

Kim and colleagues<sup>42</sup> have described some recovery of erectile function in men who underwent bilateral sural nerve graft placement during radical retropubic prostatectomy where both cavernous nerves were deliberately resected. Other authors remain skeptical about the value of nerve grafts in restoring sexual function in men undergoing radical surgery.<sup>19</sup>

For those who failed noninvasive options, penile prostheses have been implanted with satisfaction rates

of approximately 85%.<sup>43</sup> Patient expectations, however, were met in only 74%.<sup>44</sup>

## Conclusions

Despite significant advances in the management of localized prostate cancer, ED remains a common problem. However, several therapies are available. For every patient complaining of ED after being treated for clinically localized cancer prostate there is at least one potentially efficacious therapeutic alternative. Treatment should begin with oral drugs or intraurethral drug administration. Additional options include vacuum erection devices and intracavernous injection. Combinations of oral with intraurethral and/or intracavernous injections also may be effective.

Interventions to address treatment-induced impotence should start as early as possible to minimize anxiety and depression, which are common symptoms in patients with prostate cancer. It is likely that early introduction of medical therapy, particularly intracorporal injections, has resulted in a higher incidence of spontaneous return of erections.

The ideal pharmacotherapeutic agent is not yet available. Such a drug should be able to produce recovery of the endothelial and neurogenic potential to produce nitric oxide and thus erection and should provide on demand a sustained and reproducible penile erection with minimal side effects.

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