12

Medical and Psychosocial Issues in Prostate Cancer Survivors

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Of the more than 200,000 men diagnosed each year with prostate cancer in the United States,[1] most live with their disease or the effects of treatment for many years.[2] Although many men remain asymptomatic throughout their lives, others face a multitude of physical and psychosocial challenges. Because the duration of survival is typically long, patients and their families are particularly interested in optimizing their quality of life. At the generic level, health-related quality of life (HRQOL) encompasses an individual's perceptions of his or her own health and ability to function in the physical, emotional, and social domains.[3,4] In prostate cancer survivors, the medical outcomes of urinary, bowel, and sexual impairments that result from treatment will influence the rest of the patient's life. The psychosocial aspects of HRQOL are impacted by the intimate nature of these medical side effects. Urinary leakage and erectile dysfunction may cause both private and public social embarrassment. In addition, such treatment-related complications may be compounded by the additional stressors associated with aging, such as retirement or death of peers.[5] Nearly one-third of men diagnosed with prostate cancer in a genitourinary clinic had levels of psychologic distress that met criteria for anxiety disorder.[6]

This chapter examines the medical and psychosocial issues impacting men with early- and late-stage prostate cancer. Late-stage patients are included because the course of prostate cancer recurrence is often indolent. Therefore, men with prostate cancer typically "survive" to require secondary treatments that compound existing medical problems. For men with early-stage tumors, the focus is on the repercussions of treatment decision on medical outcomes, the partner, decisional regret, and fear of recurrence. For men with advanced disease, the focus is on these issues with the addition of end-of-life decisions. The chapter concludes with emerging research challenges.

Early-Stage Medical Issues

Survivor Demographics

The strongest risk factors for prostate cancer are age and positive family history.[7,8] When survival rates are compared without controlling for stage, Caucasian men have improved survival rate compared to African-American, Hispanic, and American Indian men.[9–11] Survival rates are favorably influenced by higher socioeconomic status and the presence of a spouse or partner.[12,13] African American and Hispanic men bear a disproportionately high prostate cancer burden when compared to Caucasians.[14] Numerous studies have confirmed that both African-American and Hispanic men present with more-advanced [higher initial prostate-specific antigen (PSA) and T stage] prostate cancer than do non-Hispanic white men.[1,10,15–17] Debate exists as to whether this is a function of underlying differences in biology or disparities in access to health care. Ross et al.[18] found African-American men to have testosterone levels that were 15% higher than white men, suggesting a possible endocrine explanation for their increased risk. Because access to the healthcare system is influenced by socioeconomic parameters such as income and insurance status, African-American and Hispanic men often lack consistent high-quality medical care.[19,20]

Treatment Decision Making and the Effect on Survivorship

The impact of treatment effects on HRQOL is the major issue affecting posttreatment psychosocial quality of survivorship. Since the advent of prostate-specific antigen (PSA) screening in the early 1990s, most men present with early-stage disease, leading them to consider a variety of issues related to treatment. Those diagnosed with early-stage prostate cancer are

challenged to choose among several treatment options (radical prostatectomy, radiation therapy, or watchful waiting) because studies have not yet proven an overall survival benefit of one treatment option over another.[21,22] The cure rates, defined as no evidence of biochemical (PSA) recurrence, for early-stage disease following radiation therapy or surgery range from 70% to 94%.[23–26] However, the medical outcomes do differ among these treatment options.

Medical Outcomes

Prostate cancer survivors face three long-term medical problems following primary treatment: incontinence, erectile dysfunction, and recurrence. The likelihood of these side effects will vary depending on the primary treatment chosen, stage of disease, and need for additional treatments. However, to date, no randomized controlled trials evaluating brachytherapy versus prostatectomy have been performed. The American College of Surgeons Oncology Group initiated such a trial but it was closed in 2004 for lack of enrollment. Cancer control outcomes and complication rates are inferred from predominantly retrospective, single-institution studies using different endpoints.

Postsurgical Incontinence

Even with improved surgical technique, urinary leakage after operative intervention persists (Table 12.1). Centers of excellence often report high rates of continence and potency whereas community-based outcomes may be different.[27–30] Causative factors for disparate outcomes include differences in patient selection, surgical volume, surgical skill, and definitions used for particular outcomes.[30–34] Further, the reporting of symptoms has been shown to be most accurate when elicited with written, confidential surveys that are self-administered and submitted to third parties, rather than by physician assessment.[35,36]

Time to recovery varies for each condition and may continue for at least 2 years after therapy.[37–39] Talcott et al.[40–42] reported that 12 months after prostatectomy 35% of patients were wearing pads, whereas Walsh et al.[40–42] reported this rate to be only 7%, despite using what appears to be the same definition and time point. These differences could be due to surgical technique, but the disparity is striking. Using yet another definition, Catalona and colleagues[43] also reported at 12 months that 45% of men under 70 years old claimed total urinary continence. Indeed, several authors have found that the definition itself influences continence rates. Wei[41] reported continence rates that varied from 43% to 84% depending on whether the definition was total urinary control or zero to one pad per day. Similarly, Krupski et al. found that among men claiming total urinary control, 98% also claimed no pads; however, among those reporting no pads, only 47% reported total control. Hence, total control is the stricter definition.[44] By 2 years postsurgery, further improvement in urinary control is unlikely. Therefore, men must learn to adapt with any residual incontinence for the rest of their lives. Table 12.1 depicts surgical rates of incontinence.

Management

Posttreatment incontinence may be secondary to bladder dysfunction or sphincteric insufficiency.[45] The former of these is treated with anticholinergic therapy, timed voiding, and fluid restriction in the evening.[46] If the etiology of the incontinence is from an incompetent sphincter, bulking agents may be attempted, although long-term results have been mixed at best. Collagen and Durasphere are agents that, if injected in the periuretheral space, will increase sphincter competence.[47] Smith et al.[48] treated 62 postprostatectomy patients with multiple collagen injections, and one-third achieved social continence. Patients experiencing minimal incontinence (fewer than three pads/day) have the greatest chance of benefiting from a bulking agent.[49] The definitive therapy for patients with severe incontinence is an artificial urinary sphincter (AUS). After placement of an AUS, 76% were dry.[50] Appropriate patient selection is important, as mechanical failure, infection, and erosion are known complications.[51]

Postsurgical Potency

All surgical series have demonstrated that men undergoing radical prostatectomy have more sexual impairment than do age-matched controls.[43,52,53] The spectrum of reported potency using a similar definition, erections sufficient for intercourse, ranges from 87% to 21% to 14%[40,54,55] (Table 12.2).

Because the cavernosal nerves provide the innervation required for erections, the logical assumption would be that preservation of both sets of nerves would lead to higher potency rates. As familiarity and acceptance of nerve-sparing techniques developed, potency rates increased. A community-based urologist employed chart review techniques and reported 71% potency rates after bilateral nerve-sparing

TABLE 12.1. Postsurgical continence.

	N	*Definition of incontinence*	*% incontinent*	*Time from procedure*
Assessment of treating physician				
Zincke et al. 1994[128]	1,728	Uses three or more pads/day	5	5 years
Eastham et al. 1996[28]	581	Leaks with moderate activity	9	2 years
Murphy et al. 1994[176]	1,796	Requires a pad	19	
		Complete incontinence	4	
Survey data				
Talcott et al. 1998[177]	279	Wears an absorptive pad	35	1 year
Stanford et al. 2000[178]	1,291	Requires a pad	21	1.5 years
		Severe leaking	8.4	1.5 years
Smith et al. 2000[43]	941	Less than total urinary control	65	1 year
		Occasional dribbling	14	1 year
Walsh et al. 2000[40]	64	Using pads	7	1.5 years
Potosky et al. 2000[115]	1,156	Wearing a pad	9	2 years

TABLE 12.2. Postsurgical potency.

	N	*Definition of potency*	*% potent*	*Time from procedure*
Cohn et al. 2002[a] [55]	199	Erections rigid enough for vaginal penetration	71	1.5 years
Murphy et al. 1994[a] [176]	1059	Capable of full erection	35	1 year
Smith et al. 2000[43]	941	Sufficient for intercourse, <70 years old	25	1 year
Walsh et al. 2000[40]	64	Unassisted intercourse ± phosphodiesterase (PDE) inhibitor	86	1.5 years
Moul et al. 1998[54]	374	Full erections when stimulated	13	10 months
Potosky et al. 2000[115]	1156	Erection sufficient for intercourse	20	2 years

[a]Assessment by treating physician.

prostatectomy, which is similar to the 86% reported by centers of excellence.[40,55]

Management

The treatment of erectile dysfunction consists of a stepwise approach beginning with the least invasive therapies progressing to surgical options. The type 5 phosphodiesterase inhibitors (PDEs) constitute the first line of therapy because they are an oral medication. The largest body of evidence surrounds sildenafil, as it has been marketed the longest, and suggests that PDEs increase penile nitric oxide, leading to cavernosal smooth muscle dilation and engorgement.[56] Younger men who have undergone unilateral or bilateral nerve sparing appear to benefit the most.[57] Zagaja et al.[58] found that postprostatectomy patients enjoyed an increasing response rate with highest satisfaction 18 to 24 months after surgery. Local medical therapies require an intraurethral suppository or needle injection into the cavernosal bodies (ICI). The success rate of the intraurethral suppository as measured by successful intercourse at home is reported at 40%.[59] ICI in postsurgical patients results in 60% to 90% of men developing an erection, but many patients conceptually have difficulty undertaking this therapy.[60,61] Third-line therapy is a vacuum device; an external vacuum device generates negative pressure, leading to penile engorgement. Soderdahl et al.[62] randomized groups of men to ICI or an external vacuum device and found a statistical difference in preference for ICI (50%) compared to the vacuum device (27%). Last, a penile prosthesis can result in an active sex life. Although no data specifically relate to postsurgical patients, general function and satisfaction have been reported as around 85%.[63] An industry-sponsored multicenter trial demonstrated 5- and 10-year reliability rates of 85% and 71%, respectively.[64]

Urethral Stricture

Anastomotic stricture has been reported in 0.5% to 10% of patients following surgical treatment of prostate cancer.[65] Patients will typically present with a decreased force of urinary stream. If left untreated, urinary obstruction and urinary retention may result. Gentle dilation in the clinic is often sufficient, but for more-severe strictures an endoscopic operative procedure is necessary.[66]

External-Beam Radiation

For prostate cancer, the traditional target radiation dose with a four-field box is 70 Gy. The advent of three-dimensional (3-D) conformal therapy allowed radiation oncologists to increase the dose to 78 Gy. However, several studies documented that morbidity is both dose- and volume dependent.[67] Although the higher dose results in improved biochemical recurrence for men with high-risk disease, increased complications are also seen.[67,68] The late complications (2–5 years postprocedure) associated with such dosing follow: persistent incontinence, 29%; grade 2 to 3 bladder toxicity, 9% to 20%; grade 2 or higher rectal toxicity, 14% to 26%; and only 51% retained erections adequate for intercourse.[67,69,70] Ensuring that less than 25% of the rectum receives the higher dose minimizes these complications. Fowler et al.[30] assessed complication rates in Medicare beneficiaries treated with external-beam radiation and compared these rates to a previously published sample of Medicare surgery patients. They noted that radiation patients experienced less incontinence (7% versus 32%), more erections (77% versus 44%), and greater bowel dysfunction (10% versus 4%). Tables 12.3 through 12.5 summarize the complication rates by radiation type. An additional side effect of external radiation not seen with

TABLE 12.3. Postradiation bladder complications.

	N	*Definition of bladder symptom*	*% affected*	*Time from procedure*
Brachytherapy				
Wallner et al. 2002[73]	380	Grade 1–2 toxicity	19	1 year
Talcott et al. 2001[93]	105	Daily leakage	11	5 years
		Wearing a pad	16	
External beam				
Fowler et al. 1996[30]	621	Pads for wetness	7	5 years
Potosky et al. 2000[115]	435	Wearing a pad	3	2 years
Storey et al. 2000[70] (70 Gy vs. 78 Gy)	189	Grade 2 or higher	20 and 9	5 years
External beam + brachytherapy				
Ghaly et al. 2003[94]	51	Grade 1–2	7	6 months
Zeitlin et al. 1998[86]	212	Any leakage of urine	4	2 years

TABLE 12.4. Postradiation potency.

	N	*Definition of potency*	*% potent*	*Time from procedure*
Brachytherapy				
Stutz et al. 2003[83]	148	Score of 22 on Sexual Health Inventory	69	2 years
Raina et al. 2003[85]	79	Erections sufficient for vaginal penetration – PDE	29	4 years
		Erections sufficient for vaginal penetration + PDE	70	
Potters et al. 2001[82]	482	Erection suitable for intercourse + PDE	76	3 years
External beam				
Fowler et al. 1996[30]	621	Ability to achieve erection	77	5 years
Potosky et al. 2000[115]	435	Erection sufficient for intercourse	39	2 years
External beam + brachytherapy				
Potters et al. 2001[82]	482	Erection suitable for intercourse + PDE	56	3 years
Zeitlin et al. 1998[86]	212	Ability to have satisfactory vaginal intercourse	62	2 years

surgery is fatigue. Immediately after initiation of radiotherapy, patients experience increasing symptoms of fatigue. Longer follow-up reveals the fatigue is temporary, with most men returning to baseline by 6 months.[71,72]

Brachytherapy

Brachytherapy (BT) is touted as having a very low rate of acute or long-term complications. In the initial 6 months all patients suffer from obstructive or irritative symptoms as a consequence of the radiation prostatitis. A randomized prospective comparison of iodine-125 (^{125}I) and palladium-103 (^{103}Pd) found that American Urologic Association symptom scores (now called the International Prostate Symptom Score, IPSS) peaked at 1 month and were generally higher in the ^{125}I patients. ^{125}I patients also experienced slightly higher grade 1 and grade 2 urinary and rectal morbidity.[73] The literature, in general, suggests that 2% to 18% of patients experience grade 2 or 3 urinary or rectal morbidity. Examples of such complications include stricture, urethritis, cystitis, proctitis, and rectal ulceration.[74–79] Urinary retention has been reported at 10% and incontinence was as high as 6% in the Medicare population.[80,81] Potency with implants alone is 69% to 76% at 1 to 3 years after implantation.[82,83] Because even the longest modern BT series span only 12 to 15 years, very little literature exists on long-term complications from BT. Merrick et al. commented that long-term urinary morbidity is restricted to patients having a prior transurethral resection of the prostate. Long-term erectile dysfunction ranges from as low as 29% without use of a phosphodiesterase inhibitor to as high as 70% at 5 years. The most serious and difficult to treat of the reported complications is a prostatourethral–rectal fistula.[84–88]

External-Beam Therapy Combined with Brachytherapy

Controversy still exists over the role for combined radiotherapy in prostate cancer.[76] Patients at low risk for extracapsular disease (Gleason less than 7, PSA less than 10 ng/dL, clinical stage less than T2b) are excellent candidates for brachytherapy monotherapy.[89,90] However, patients at intermediate or high risk for extracapsular disease may be better served by combined radiotherapy or either form of radiotherapy with the addition of androgen ablation.[24,91,92] The Radiation Therapy Oncology Group has initiated trial P-0232 [external-beam radiation therapy (EBRT) + BT versus BT] to assess these issues.[93,94]

Management

Following EBRT or BT, patients are started prophylactically on alpha-blockers to decrease the expected side effects of dysuria and frequency that result from radiation prostatitis. Select patients may stay on the alpha-blocker for 6 to 12 months. Nonsteroidals and antiinflammatory suppositories are used to treat proctitis. For a patient with a large prostate gland (more than 50 mm^3), androgen deprivation therapy is

TABLE 12.5. Postradiation bowel complications.

	N	*Definition of bowel toxicity*	*% affected*	*Time from procedure*
Brachytherapy				
Wallner et al. 2002[73]	380	Grade 1	20	1 year
Talcott et al. 2001[93]	105	Diarrhea or watery stool several times/week	6	
External beam				
Potosky et al. 2000[115]	435	Bowel urgency	36	2 years
Storey et al. 2000[70] (70 Gy vs. 78 Gy)	189	Grade 2 or 3	14 and 21	5 years
Kuban et al. 2003[67] (70 Gy vs. 78 Gy)	1,087	Grade 2 or 3	12 and 26	5 years
External beam + brachytherapy				
Zeitlin et al. 1998[86]	212	Blood per rectum (proctitis)	21	2 years

employed to "downsize" the prostate, facilitating BT.[95] The added benefit of androgen deprivation therapy is to decrease the risk of postoperative urinary retention. Sacco et al. have also demonstrated that dexamethasone (4 mg twice daily for 1 week then 2 mg twice daily) instead of androgen ablation also decreases the risk of retention in these patients.[96] Erectile dysfunction is treated in the same manner as for post-surgical patients as already described.

Prostate-Specific Health-Related Quality of Life

Several cross-sectional surveys have compared health-related quality of life outcomes after brachytherapy, external-beam radiation, and radical prostatectomy. Two studies reported that overall HRQOL was similar between brachytherapy and radical prostatectomy patients, with those undergoing brachytherapy having better urinary control but similar bother.[97,98] However, in a study of 1,400 patients, Wei et al.[99] found that men receiving brachytherapy experienced worse outcomes in the areas of urinary, bowel, and sexual HRQOL than did those undergoing either of the other two treatments. This finding contrasts with that of Eton et al.,[100] who reported that brachytherapy patients had the least sexual dysfunction and the best physical functioning of all treatment groups, and with that of Davis et al.[101] who reported that bowel bother was worst after external-beam therapy. Direct comparison of such studies is difficult because demographic characteristics, clinical factors, and measurement instruments vary from one investigator to another. Van Andel et al.[102] reported that radiation patients, on average, are 7.9 years older, have lower socioeconomic status, and more often have a higher tumor stage. They also found that radiation patients reported more pain and fatigue, lower overall HRQOL, and worse sexual function than men undergoing surgery.

Early-Stage Psychosocial Issues

Partners

Cancer affects family members as well as patients. Prostate cancer, more so than other malignancies, has been labeled a "relationship disease" because it so profoundly impacts both partners.[103,104] In fact, studies have found that psychologic distress is equivalent in the prostate cancer patient and his partner.[105] Clearly, once the cancer is discovered, both partners experience increased levels of anxiety compared with healthy couples.[106]

Although there is evidence that marital status impacts prostate cancer outcomes, the direction of the effect is mixed. The diagnosis of prostate cancer may evoke anxiety or depression in both partners. The response to this stress can nurture or undermine the relationship. A good relationship can foster healthy coping skills, alleviate distress, and encourage optimism. Increased optimism has been shown to correlate with improved cancer outcomes and survival.[107]

Depression/Distress

Being diagnosed with cancer naturally evokes a sense of sadness.[108] The difficulty is to distinguish the normal response from a clinical disorder. Symptoms indicative of a clinical disorder include a sense of failure, social withdrawal, suicidal ideation, and indecision.[109–111] Few studies have examined depression in patients with early-stage disease. Kornblith et al. studied 163 men with localized prostate cancer and found that 29% reported "worry" and 21% complained of depression. Patients and spouses both had frequent intrusive thoughts and images.[112]

Psychologic distress is complicated in prostate cancer because of the dual implications of treatment and distress. Prostate cancer treatment may itself induce sexual dysfunction, which adds further to such distress. Studying traumatic distress in men newly diagnosed with early-stage disease, Bisson et al.[113] found very few depressive symptoms. Instead, patients demonstrated higher anxiety and traumatic stress symptoms. The authors postulated that older men may be more likely to use denial as a defense mechanism. A more-holistic approach by the physician, incorporating attention to both psychologic and physical needs, benefits the patient and his spouse. Emotional support allows both members of the couple to target their energies on preparing for the treatment process.

Regret

Decisional regret relates to the notion that another treatment might have been preferable. Davison et al.[114] undertook a study to assess how factors such as HRQOL and level of patient involvement in medical decision making impact decisional regret. Higher regret scores did correlate with poorer emotional and urinary function. Although not a direct measure of decisional regret, the Prostate Cancer Outcomes Study that found 92% of patients who chose surgery or radiation would do so again.[115] In contrast, Hu et al.[116] used the two-item Clark regret scale[117,118] and discerned that 16% of men with localized prostate cancer experienced decisional regret. College education and worse HRQOL appeared to foster regret, but treatment type did not have an effect.

Fear of Recurrence

Using the CaPSURE database, Mehta et al.[119] identified more than 500 men with pre- and posttreatment questionnaires to measure fear of recurrence. All patients, regardless of treatment type, reported the most severe fear of recurrence before treatment. Their levels of fear improved after treatment and remained constant over the next 2 years. Another study utilized the Profile of Mood States (POMS)[120] in men with and without biochemical recurrence. Urinary tract symptoms were associated with increased cancer fear, but biochemical recurrence alone was not associated. However, men with both urinary tract symptoms and biochemical recurrence reported the highest level of cancer fear.[121] In an attempt to elucidate better the problems faced by men with prostate cancer, Roth et al. developed a new scale to measure anxiety in prostate cancer patients. The Memorial Anxiety Scale for Prostate Cancer (MAX-PC)[122] comprises three subsections including a prostate cancer anxiety scale, PSA anxiety scale, and fear of recurrence scale. The authors identify the prostate cancer anxiety subscale as being most specific to cancer anxiety while the fear of recurrence captures general distress. Loneliness and general uncertainty about the future heighten

anxiety in prostate cancer survivors. Men who have elected to undergo no treatment (watchful waiting) also experience PSA anxiety. Wallace[123] identified 19 men on watchful waiting and found they experienced heightened uncertainty, leading to a higher perception of danger, which impaired their quality of life. Discussions with other men facing similar clinical scenarios promote positive coping skill and diminish anxiety. National and local support groups can help meet the emotional and educational needs of patients concerned with facing a recurrence.[124,125]

Late-Stage Medical Issues

Demographics

African-American men have a significantly higher mortality rate from prostate cancer than do non-Hispanic white men.[126] However, the traditional 5-year survival rates are almost irrelevant to men with prostate cancer, given that this rate approaches 100%, regardless of treatment.[2] This figure includes the 15% to 35% of men who will experience biochemical progression within 10 years of treatment.[25,127,128] The natural history of disease recurrence following radical prostatectomy was characterized by Pound et al.,[23] who showed that the median time to development of metastatic disease was 8 years and death followed at a median of 5 additional years. The risk factors for progression were time to biochemical progression, Gleason score, and PSA doubling time. The earlier the PSA recurrence, the higher the Gleason score, and the faster the doubling time, the worse the prognosis. No patients placed on early hormone ablation were included in the study.

Definition of Recurrence

After a radical retropubic prostatectomy, PSA levels should be undetectable. Original assays utilized a threshold level of 0.2 ng/dL, and values less than this constituted freedom from disease. Although more-recent assays have lowered this threshold, the PSA should still be undetectable. A detectable PSA preceded clinical recurrence by 6 to 8 years.[129,130] The definition of recurrence after radiation therapy is three successive rises in PSA based on American Society for Therapeutic Radiology and Oncology (ASTRO) criteria.[131] However, because recurrent patients after either treatment will survive for many years, secondary treatment in the form of hormonal therapy results in additional medical problems.

Androgen Ablation

Medical induction of castration can be obtained through drugs affecting the production of luteinizing hormone-releasing hormone (LHRH), blocking the peripheral effects of androgens (steroidal and nonsteroidal antiandrogens), eliminating all steroid hormone production, and estrogens. The luteinizing hormone-releasing hormone agonists (which paradoxically lower LHRH levels) are typically administered by injection every 3 to 4 months whereas peripheral blocking agents are taken orally every day. However, once androgens are ablated, the prostate cancer begins an inexorable change to hormone independence.[132] Once a hormone refractory state has developed, few effective treatment options exist. Therefore, questions arise regarding the timing of androgen ablation and which agents to use.

Hormonal Complications

The predominant treatments are LHRH agonists and nonsteroidal antiandrogens, but these are not without side effects. LHRH agonists cause hot flashes, loss of libido and potency, anemia, fatigue, weight gain, depression, and decreased bone mineral density.[133,134] Antiandrogens maintain potency in a subset of patients but lead to gynecomastia and nipple tenderness.[135] Controversy remains over whether these agents are as effective when used alone as when used in combination with LHRH agonists. Two large trials demonstrated prolonged time to progression (by 2 months) in patients with modest disease; however, meta-analysis and other small studies have failed to demonstrate a significant advantage to combined androgen blockade.[136–138] Once metastatic bone deposits develop, LHRH agonists appear to be the most cost-effective, efficacious treatment.[139] However, men with high-risk disease or rising PSA are often started on hormone ablation.[140,141] To decrease the side effects, intermittent hormone ablation is increasingly being utilized.

Bone Complications

Hypogonadal men are at risk for potentially debilitating bone complications such as osteoporosis and hip fractures.[142,143] In patients with prostate cancer on androgen ablation, Hatano et al. reported a 6% nonpathologic fracture rate while Townsend et al. found a 9% overall fracture rate.[144,145] A smaller retrospective studies found even higher fracture rates of 40% after 15 years in 161 men after bilateral orchiectomy.[146] Daniell analyzed 59 men who had undergone bilateral orchiectomy for prostate cancer and found 8 (13.6%) with osteoporotic fractures of the femur or vertebra. However, when he analyzed the 17 patients still alive 5 to 12 years later, he noted that 38% had had one or more osteoporotic fractures.[147]

According to the World Health Organization, osteopenia denotes a bone mineral density between 1.0 and 2.5 standard deviations below the mean for young adults and osteoporosis is greater than 2.5 standard deviations below the mean.[148] Using this definition, Finkelstein et al. documented cortical bone density loss at least 2 standard deviations below normal in men with isolated gonadotropin-releasing hormone deficiency.[149] These changes in bone mineral density have been confirmed in men with therapeutic hypogonadism from prostate cancer treatment.[150,151] Smith et al. reported that trabecular bone mineral density of the spine decreased by 8.6% during the first year of androgen-deprivation therapy (ADT) for nonmetastatic prostate cancer.[151] With aging itself leading to decreased bone mineral density, the addition of ADT further places these men at risk.[152,153]

Management

The agents used in the treatment of osteoporosis and osteopenia depend on whether the etiology of the bone loss is from a benign or malignant process. Disease of benign etiology has been successfully treated with calcitonin, oral bisphosphonates, and a combination of vitamin D and calcium.[154,155]

However, the bone loss associated with prostate cancer and androgen deprivation therapy is accelerated, requiring additional therapeutic options.[153,156,157] A prospective randomized controlled trial revealed that intravenous bisphosphonate was effective in increasing bone mineral density in men on androgen deprivation therapy for prostate cancer.[158] Therefore, men with D0 disease as well as metastatic prostate cancer on ADT are candidates for intravenous bisphosphonates.

Fatigue

Throughout the disease trajectory, cancer patients experience fatigue, which is recognized to have a significant impact on quality of life.[159] Indeed, clinical experience with fatigue in hypogonadal men indicates that androgen deprivation therapy should lead to some degree of fatigue.[160] Stone et al.[161] used the Fatigue Severity Scale[162] to follow patients before and after treatment with goserelin and cyproterone. Fatigue worsened in 66% of patients after 3 months of androgen deprivation therapy. All patients responded to the therapy with decreasing PSA levels, eliminating disease progression as a possible source of fatigue. On multivariate analysis, only depression remained a significant predictor of fatigue.[163] The depression literature supports this association.[164] This study did not find any association with anemia, but others suggest that fatigue in prostate cancer patients on androgen deprivation therapy may be because of anemia, a well-known side effect of therapeutic hypogonadism.[165] Patients on androgen deprivation therapy experience not only the expected physical side effects such as hot flashes, loss of libido and potency, weight gain, and anemia but also the psychosocial changes of depression and fatigue. Close monitoring of all these parameters is critical.

Health-Related Quality of Life

The clinical rationale for selecting the method and agent for androgen ablation is controversial. Therefore, the physician must engage the patient in a discussion to decide what balance of side effects, cost, and risk of progression is optimal. Because the patient will likely survive for many years before developing bone metastasis or other evidence of clinical progression, the potential cost in quality of life may be great. Additionally, when the physical side effects of fatigue, sexual dysfunction, and weight are considered, deferment of this potentially emotionally debilitating therapy may promote HRQOL in men living daily with prostate cancer.

Late-Stage Psychosocial Issues

Partners

Researchers have used focus groups to describe the impact of prostate cancer on the couple as a unit. Both patients and partners feel unprepared to manage treatment- and prostate-related changes as they arise. The spousal role is increasingly difficult as the cancer progresses. Often the role shifts to that of a caregiver focusing on three major areas of concern. Caregivers contend with fear of cancer and its spread, helping patients respond to the emotional ramifications of the disease, and managing the disruptions caused by cancer.[166] For survivors of prostate cancer with late-stage disease, uncertainty prevails. Men with partners may benefit from physical assistance from their partner but bear additional emotional weight from their sense of being a burden. Men without partners experience more of a physical decline and loneliness.[166–168]

Depression

The concept that depression is linked to testosterone has been explored in the psychiatric literature. Studies have examined the treatment of elderly males with major depressive disorders with testosterone replacement. The therapy appears to be effective in men with late-onset depression.[169] Therefore, older men receiving androgen deprivation therapy for prostate cancer are an at-risk population. Among 45 men receiving androgen deprivation therapy (ADT) as prostate cancer treatment, the prevalence of major depressive disorder was eight times the national rate.[170] Although cancer progression was not the primary cause of the depression, history of depression was a strong risk factor. Involving experts in depression and palliative care can provide social support and help patients confront end-of-life issues.

Regret

Regret has been evaluated in men who developed metastasis and had initiated androgen deprivation therapy. Almost one-fourth of these men expressed regret. The demographics and time since diagnosis with metastatic disease were similar between men who were and were not regretful; however, men who had undergone orchiectomy were more likely to express regret.[119] Clark et al.[118] did find that men expressing regret were more likely to have poorer quality of life, particularly in the role and emotional limitations subscales. These men did not have more treatment-induced side effects, yet they perceived themselves as having worse functional status.

End of Life

Quality of life steadily descends in the final months of life.[171] Marriage appears to protect men from rapid decline in the physical domains but surprisingly does not offer protection in the emotional domains. Single men may feel the persistent effects of loneliness, while married men may sense being a burden. Higher socioeconomic status has been associated with a slower decline in physical domains but a more acute decline in the emotional domains.[172] Other studies in terminally ill cancer patients have found accelerated HRQOL declines at 1 to 3 weeks before death.[173] Because prostate cancer death can be so delayed, patients, family, and physicians often neglect to address end-of-life planning issues. Steinhauser et al.[174] evaluated factors considered important for a "good death," emphasizing that this is highly idiosyncratic. Control of symptoms, preparation for death, opportunity for closure, and good relationship with healthcare professionals were factors considered crucial to easing the end-of-life transition for patients and families. One responsibility of the physician is to consider what the patient and caregiver need emotionally and psychologically. This need includes assessing what interventions might be used for long-

or short-term gain or discussing transfer to a hospice or palliative care program. When these issues are adequately addressed, terminally ill patients feel more prepared for death and are better able to live to the fullest degree possible.[175]

Conclusion

The high prevalence of prostate cancer and the impact on the partner make the psychosocial aspects of prostate cancer particularly relevant to long-term survivorship. A man's masculinity is intricately intertwined with his personal identity. Therefore, the intimate nature of the treatment-related side effects of early- or late-stage prostate cancer may have far-reaching emotional consequences for these men. They are at risk for anxiety, depression, distress, fatigue, and bone complications at many stages of the disease trajectory. The most effective tool against these sequelae is awareness on the part of physicians and other health professionals in identifying psychosocial needs and directing patients to the appropriate resources.

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