Sexual dysfunction in cancer patients: a review

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Summary
Cancer is a life-threatening disease despite the advanced therapeutic strategies now available. A common problem is that physicians and patients tend to concentrate on intensive medical treatment options and underestimate the treatment-related adverse effects. In this review, we summarize one of these adverse effects in cancer patients; sexual dysfunction (SD). In addition, current therapeutic choices with optimal doses and patient selection strategies are defined. All patients should be informed about problems associated with therapy-related SD and must be guided toward the most appropriate therapeutic options before starting treatment.

Key words: cancer, chemotherapy, radiotherapy, sexual dysfunction, surgery

Introduction
Various biological and physiological factors affect sexual perception in cancer patients. Alterations in body image due to cancer surgery, chemotherapy-related menopause, and hair loss along with the emotional stress due to struggling with a serious illness make the patients more vulnerable to sexual problems.

Diagnosis of life-threatening cancer leads to intensification in medical treatment options on the part of both physicians and patients, and social and sexual problems are frequently underestimated [1]. Chemotherapy- and radiotherapy-related SD generally ends after the completion of therapeutic manipulations, whereas anatomical defects due to surgery might have a long-lasting effect on the patients’ sexuality.

In this review, we discuss separately the various types of SD from breast and gynecological cancers for women and prostate cancer for men and provide medical advice from the point of view of medical oncologists in order to help patients cope with these problems.

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A. Possible types of dysfunction according to treatment options

1. Dysfunction resulting from surgery

With the introduction of new therapeutic modalities, cancer has become a chronic form of disease in recent years. Nevertheless, surgery is still the primary treatment option for cancer, especially for the early stages, but surgery may be associated with some disadvantages; for example, gynecological cancers that require the resection of reproductive organs can cause physiological difficulties in female patients attempting to have sexual intercourse. In cervix cancers, a classical radical hysterectomy generally includes an upper vaginal excision which may cause dyspareunia and some innervational problems [2].

Moreover, vulvar and vaginal cancer surgery with large excisional procedures can lead to difficulties in penile-vaginal intercourse. Anatomically, the thoracic and sacral plexus innervate the pelvic organs, and some types of procedures related to cancer may lead to these nerves being cut or damaged during surgery. When a radical hysterectomy is performed, paraaortic lymph node and uterosacral ligament excision can result in superior hypogastric plexus and hypogastric

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nerve damage, respectively [3]. Thus, nerve injuries can hinder sexual arousal and cause orgasmic disorders.

In addition, an oophorectomy will result in iatrogenic menopause in premenopausal patients, a serious problem in and of itself, by means of early hormonal withdrawal in young patients. Postmenopausal patients may also suffer from sexual arousal problems due to ovarian testosterone loss.

2. Dysfunction resulting from radiotherapy

Radiotherapy is one of the main therapeutic modalities in cancer treatment. In gynecological cancers, this is the primary therapeutic option for early stage cervix and endometrial cancer. During radiotherapy, nerve damage, vaginal atrophy, and fibrosis can occur in the genital area which was exposed to radiation. In the literature, some local methods have been advised to prevent these complications, and these will be discussed later in the treatment section of the article.

3. Dysfunction resulting from hormonotherapy

In hormone receptor positive breast cancer patients, selective estrogen receptor modulators (SERMs), such as tamoxifen and aromatase inhibitors (AIs) that decrease the exposure of breast tissue to estrogen are widely being used for the prevention of local and distant recurrences. Tamoxifen has a partial agonistic effect on the female genital tract, but during the estrogen blockage on the breast tissue, it has a minimal estrogenic effect on the vaginal mucosa. Furthermore, AIs have a stronger effect on hormone depletion in breast tissue and a pure antagonistic effect on the genital tract. Vaginal dryness, pruritus, and dyspareunia are seen more frequently in this group of patients [4]. The quality of life evaluation of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial showed that the incidence of vaginal dryness and dyspareunia along with a decrease in sexual desire was more prevalent in the AI group, whereas the Intergroup Exemestane Study (IES) showed no difference between the exemestane and tamoxifen group regarding SD [5,6]. Although AIs are more frequently related to vulvar and vaginal symptoms, they are the first hormonal treatment option, particularly for postmenopausal women.

4. Dysfunction resulting from chemotherapy

Chemotherapy can cause ovarian dysfunction due to the age of the patient, type of the agent used, and treatment duration. Various agents are related to ovarian failure, the most well-known being alkylating agents and taxanes. Amenorrhea can be permanent or transient as a result of therapy. Women who became postmenopausal after chemotherapy develop more sexual problems [7]. Since chemotherapy inhibits the maturation of the primordial follicles in a dose- and drug-dependent manner, younger patients who have more follicles have a better chance of regaining their ovarian functions after chemotherapy [8]. Besides these permanent repercussions, the chemotherapeutic agents can also lead to temporary adverse reactions such as nausea/vomiting, hair loss, and disturbances in body perception that might decrease the patients’ sexual desire.

B. Medical advice to overcome treatment-related sexual dysfunction in female cancer survivors

Diseases related to social and physiological issues as well as sexual problems are often underestimated by physicians during cancer chemotherapy. Nevertheless, for any disease, therapeutic choices that do not seriously restrict the quality of life of the patients but help them adapt to the therapy are much better. By managing therapy-related complications properly, doctors can provide more comfortable treatment duration for the patients.

1. Vaginal atrophy treatment

Vaginal dryness and dyspareunia are important predictors of SD in women with cancer [9,10]. Regular usages of vaginal moisturizers can relieve the symptoms. These moisturizers, frequently consisting of ingredients such as purified water, glycerin, and mineral oil, adhere to the vaginal epithelium and form a thin layer on the vaginal tissue. It is recommended that patients use these moisturizers regularly every two to three days. Vaginal lubricants, not to be confused with vaginal moisturizers, should be used before sexual intercourse. These are generally inserted into the vagina by applicators and should be used at least 15 minutes before intercourse.

Vaginal moisturizers and lubricants only provide relief from symptoms, but vaginal estrogen preparations have therapeutic effects on vaginal atrophy. Both systemic and local estrogens are efficacious, but local forms are preferable since they have a minimal effect on systemic estrogen exposure. Although some authors claim that more systemic estrogen absorption occurs in the atrophic epithelium, this hypothesis has not yet been proven [11]. Vaginal estrogen comes in cream, tablet, or ring form. The efficacy is similar for each group. Vaginal rings contain estradiol...
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ol and release 6-9 mcg daily over a three-month period. This level of estradiol is similar to that of a postmenopausal woman receiving hormone therapy. The rings are generally well tolerated. They are replaced every three months and do not cause discomfort during sexual intercourse. Vaginal tablets also contain estradiol or estriol and are used once daily for the first two weeks and twice a week afterwards as maintenance dose. The tablets are inserted by applicators. Vaginal creams also can be used daily for the first three weeks and twice a week afterwards for maintenance. Although vaginal estrogen has dominant local effects, studies have shown minimal systemic effects. In one study conducted with low dose local estrogen therapy, the decline in bone resorption raised the probability of systemic absorption [12]. In another study, breast cancer patients being treated with AIs in combination with these vaginal preparations demonstrated increased serum estrogen levels in the early stages of therapy [13]. Therefore, based on these results, forms of vaginal estrogen do not seem to be safe in hormone responsive malignancies. If they have to be used because of severe symptoms, then using vaginal preparations containing estriol is preferable to estradiol since estriol can not be turned into estradiol at the steroid pathway.

2. Testosterone for sexual desire

In women, half of the circulating testosterone is produced from the ovaries. Even in postmenopausal women, a bilateral oophorectomy can cause sexual desire disorder due to the decrease in serum testosterone levels [14]. To our knowledge, concomitant testosterone patches and estrogen usage augment the sexual desire. Since some studies have shown a relationship between increased estrogen and androgen levels and breast cancer development in postmenopausal women, the role of testosterone in carcinogenesis has not been elucidated clearly [15,16]. Thus, the use of testosterone remains controversial.

3. Sildenafil

Sildenafil didn’t demonstrate any benefit in a study in female patients and standard usage in women is not yet recommended [17].

4. Vaginal dilators to prevent vaginal fibrosis

Pelvic radiotherapy may cause vaginal fibrosis. Some studies have suggested that having sexual intercourse three to four times a week for sexually active patients and using vaginal dilators three times a week for at least 10 minutes for sexually inactive patients might prevent vaginal fibrosis due to radiotherapy. Although vaginal dilators have become an established practice in the United Kingdom, they pose a small but serious risk for vaginal rupture. A recent Cochrane review concluded that there was insufficient data to confer benefit and did not recommend routine regular use of vaginal dilators [18].

In conclusion, some women become postmenopausal during chemotherapy and never recover ovarian function. When patients experience postmenopausal symptoms, vaginal atrophy and dyspareunia can be coped with local vaginal treatment procedures. Our experience has shown that systemic estrogen and testosterone treatment are not options for hormone-responsive tumors. Breast cancer patients who will receive adjuvant hormonotherapy, especially AIs, should be carefully instructed regarding the possible adverse effects which may occur and should be given advice on how to cope with them.

Sexual dysfunction in male cancer survivors

Sexual function contributes to quality of life. Cancer-related surgery and androgen deprivation therapy (ADT) for prostate cancer can lead to SD in men. Radical prostatectomy, genitourinary cancer, and rectal cancer operations are some of the primary causes. Preoperative erectile function (EF) and nerve-sparing status are critical predictors of erectile dysfunction (ED) [19]. The main causes and therapeutic alternatives for SD are discussed below.

A. Possible types of the dysfunction according to treatment options

1. Dysfunction resulting from surgery

Male genitourinary cancer can result in ED and orgasmic problems. Prostate cancer is the most common type encountered in men, and prostatectomy is one of the main treatment options in the early stages. Prostate operations, even if nerve-sparing procedures are performed, can result in ED [20]. The cavernous bodies of the penis are innervated from the cavernosal nerves that originate from the pelvic plexus. This plexus is localized at the upper part of the seminal vesicles and anterolateral wall of the rectum. As a consequence of this anatomic closeness, besides prostate surgery, low anterior resection of rectal tumors and bladder cancer surgery can also cause ED. Even if nerve-sparing techniques are used,
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2. Dysfunction resulting from androgen deprivation therapy

Gonadal testosterone is the main source of androgen. In the prostate, testosterone is converted by the 5α-reductase to dihydrotestosterone, which has a more potent androgenic activity. The goal of ADT is to lower the testosterone levels by either medical luteinizing hormone-release hormone (LHRH) agonists or surgical procedures (bilateral orchiectomy) in order to treat the prostate cancer. There is no difference in the efficacy with regard to testosterone levels in either of these methods, and combining them has shown no proven benefits [22]. Although ADT appears to have advantages for locally advanced and metastatic prostate cancer, its impact on quality of life remains controversial. Hormone deprivation may result in a decrease in the size of the penis and testicles, loss of libido, and a decrease in intrapenile nitric oxide synthase levels, which are essential for having an erection [23]. Although some patients might not experience loss of EF or arousal despite the testosterone deprivation, these problems are not rare. Before being treated, the adverse effects of ADT should be discussed, and during follow-up, the patients who develop ED should be warned that after the cessation of ADT, some time may pass before they recover EFs.

3. Dysfunction resulting from radiotherapy

External beam radiation therapy is one of the principle treatment options for localized prostate cancer and has similar progression free survival rates as surgery,[22]. During this therapy, the radiation dose is delivered to the bulb of the penis. Corporal bodies seem to be associated with radiation-induced impotence due to penile strictures [24]. Although some data has claimed that radiotherapy provides more benefits than surgery, it is believed that surgery causes ED more frequently within the first two years, whereas fibrosis after radiotherapy occurs nearly three years after this treatment. Overall, at the five-year follow-up, the results of EF are similar in the surgical and radiation groups [25].

B. Medical advice to overcome treatment-related sexual dysfunction in male cancer survivors

In prostate cancer patients, whether the therapeutic choice is radiation therapy or surgery, the use of erectogenic agents is referred to as penile rehabilitation. This therapy does not only support the patients’ ability to achieve erection but also aims to preserve EF for cavernosal oxygenation.

1. Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 (PDE5) inhibitors are the first choice of treatment for male SD. During sexual stimulation, nitric oxide is released from the cavernous bodies of the penis, and this activates the guanylate cyclase enzyme. This results in an increase in cyclic guanosine monophosphate (cGMP) levels. cGMP relaxes the smooth muscle of the cavernous bodies and provides blood flow to the cavernosal tissues. In turn, these perform an erection. The guanylate cyclase enzyme is specific for cGMP degradation. Through the inhibition of PDE5, cGMP degradation is prevented. Since the primary erectile problems after surgery are related to hypoxia due to innervation or ischemia, penile tissue oxygenation might be maintained by sustained erections. Various studies have been conducted to support this hypothesis, and they have shown that spontaneous EF is recovered earlier via the use of PDE5 inhibitors [26,27].

Both routine and on-demand usage seem to be effective in the studies, and past comparisons did not confirm the superiority of one method or the other [28]. There are three forms of PDE5 inhibitors: sildenafil, vardenafil, and tadalafil. The efficacies of these drugs are similar, but the duration effect is nearly four hours for sildenafil and vardenafil but up to 36 hours for tadalafil. The optimal timing for usage is one hour before sexual intercourse. It is important to note that these agents can cause severe hypotension and syncope if used with nitrates. Thus, PDE5 inhibitors are not recommended for patients on nitrate treatment [29]. Sildenafil is recommended at doses of 50 mg; however, if well tolerated, this may be elevated to 100 mg in order to achieve sufficient results. The recommended starting dose for tadalafil is 10 mg, and this should be adapted according to the patient’s response. Vardenafil is available in 5,10, and 20 mg forms. It is generally advised to start
with 10 mg and increase the amount if necessary [30]. In the past, these agents were believed to cause myocardial infarction and sudden death; however, study results never confirm this connection. The deaths could have been related directly to the act of sexual intercourse itself [31,32]. To our knowledge, these drugs do not have a negative effect on coronary hemodynamics and can be used by patients who have stable coronary artery disease and are not using nitrate medication.

2. Urethral suppositories and penile self-injection agents

Alprostadil (PGE1) is another medical option for cavernosal nerve damage and is administered to patients so as to increase corporal oxygenation by increasing blood flow. Intracavernosal injections and intraurethral suppository forms (MUSE®) are available. Studies have shown the efficacy of intraurethral alprostadil in postprostatectomy patients [33,34]. These patients should be adequately informed and instructed before performing self-injections as these injections could often result to priapism when compared with intraurethral applications. Studies which compared the effectiveness of PDE5 inhibitors with alprostadil revealed comparable results with a higher dropout rate in the alprostadil group [35]. Although the application of alprostadil causes more discomfort than PDE5 inhibitors, it has no systemic consequences due to localized therapy and might be a satisfactory option for patients to avoid cardiac toxicity.

3. Vacuum constriction devices

Vacuum constriction devices (VCDs) have a partial vacuum effect on the penis via an elastic ring that is located at the base of the penis to maintain the erection. The ring should be removed within 30 minutes to avoid hypoxic injury of the penis. However, VCDs can also result in an ejaculation due to urethral constriction. The complication rate is low, and there is no clear contraindication except for bleeding disorders. Recent studies have shown positive results regarding the early use of VCDs for penile rehabilitation; thus they are becoming recognized as an acceptable option for cancer patients experiencing SD [36,37]. In the early postprostatectomy period, for some patients with severe neural or hypoxic injuries, initiating erections might be impossible. We believe that this group of patients could benefit from the use of VCDs.

These three treatment options mentioned above have proven to be effective for male cancer survivors suffering from SD. Most clinicians prefer to begin treatment with PDE5 inhibitors and then move to alprostadil and VCDs for patients who are not suitable for PDE5 inhibitor. Combinations of VCDs and PDE5 inhibitors can be used for selected populations to achieve a rapid return of sexual function [38,39]. Patients who do not respond to these medical options should be referred to an experienced urologist for a penile prosthesis to maintain sexual function.

Conclusions

Cancer treatment has multiple and variable adverse effects. Sexual dysfunction from various surgical and medical approaches is often underestimated by physicians and may lower the quality of life and break down the main treatment unison. All patients should be informed in detail about treatment-related adverse effects and must be guided through the therapeutic options in order to choose the best mode of action.

References

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