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Review Article

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Ways to Improve Radiation-Induced Sexual Toxicity in Gynecologic Cancer

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Abstract

Radiotherapy plays a critical role in gynaecologic cancer treatment. Despite the improvement of modern radiation techniquesin healthy tissue protection, patients still experience significant treatment related effects. We aim to assesstherapeutic management of radiation-related sexual adverse events for early or locally advanced-staged carcinomas.

A literature search was performed up to March 2021. The management of patients with radiation-induced sexual toxicity involves multidisciplinary care coordination. Clinicians must be aware of the long-term adverse reactions associated with radiotherapy to ensure prompt diagnosis and appropriate management.

Key words: Gynecologic cancers; Radiotherapy; Side effects; Quality of Life; Treatment.

Introduction

Gynecological cancer involves primarily cervix uteri, endometrium, ovaries, vulva, vagina and rarely fallopian tubes. Uterine cancer (corpus and cervix) is the most diagnosed among them while ovarian cancer is the fifth leading cause of cancer death [1]. Approximately 89,000 women were diagnosed with gynecological cancer in the USA in 2018 with 29,000 of them having died [1].

Radiotherapy (RT) plays a significant role in the therapeutic management of gynecological malignancies; 60% of cervical, 45% of endometrial, 35% of vulvar and 100% of vaginalcancer patients undergo RT as radical or adjuvant treatment [2]. RT can be administered to these patients as external beam radiotherapy of the pelvis (EBRT) and/or vaginal brachytherapy (VBT) [2].

Technical EBRT developments enabled improved target conformity and allowed reduction of safety delineation margins. Modern RT methods (i.e. IMRT, VMAT) can avoid unexpected dosimetricinaccuracies, control patient setup errors, and weight changes or internal organ deformations. Although there has been RT improvement in surrounding healthy tissues' sparing patients still experience RT-induced late adverse effects [3]. Since RT-related cancer treatment methods are in a continuous evolution process, cancer survival rates are rising and life expectancy is longer. Sexual symptoms such as:a)impaired vaginal lubrication, b)reduced vaginal sensitivity and elasticity, c)vaginal narrowing, stenosis and shortening, d)decreased sexual desire, e)lower intensity of orgasm, and f) dyspareunia may have a remarkably negative impact on patients' well-being. We summarize the current therapeutic management of RT-induced toxicityin order to ameliorate cancer survivors' quality of life (QoL).

Materials and Methods

Every publication offering any data concerning the RT sexual side effects in gynecologic malignancies and strategies for managing them was included. Electronic databases were searched using the following terms: 'gynecologic cancers', 'radiotherapy', 'radiation', 'side effects', 'treatment', 'quality of life'. PubMed and Cochrane Database of Controlled Trials were searched up to March 2021. Cross references from the included studies were hand-searched. We used papers only in the English language.

Results

Both sexual and everyday lives are affected. Specifically, radiation therapy induces changes in vaginal epithelium as well as in urinary and gastrointestinal system. These changes can be on short- or long-term basis and for this reason the effects are divided into acute and late adverse effects. However, long-term symptoms are those which mostly concern patients, since these effects may compromise their quality of life. Major treatment related side effects are relatively rare. Comorbidities play an important role in the risk of radiation-induced adverse effects.

The combination of treatments such as surgery, chemotherapy and RT (EBRT ± IVB) may cause dyspareunia, decreased sexual activity and enjoyment in survivors. Patients who underwent surgery and received pelvic RT, experienced more severe sexual symptoms and worse body image than women who underwent surgery alone [4]. The quality of life in those is also affected by lower limbs' lymphedema onset or exacerbation when lymphonodal dissection has been performed.

Despite the positive effect of RT on loco-regional control and survival rates, it can also induce vaginal epithelium lesions, which, as aforementioned, may be a long-term effect, having an impact on patients' quality of life. The RT technique can also affect the symptoms severity. EBRT compared to BRT may induce higher gastro-intestinal toxicity rates. Sexual functioning and symptoms do not differ between the two methods at a median follow- up of 2 years [5].

Radiation Sexual adverse reactions

Survivors of gynecologic cancer experience a broad range of sexual concerns after diagnosis and treatment [6,7]. Vagina is mostly affected by RT since in most cases it is close to the primaryneoplasm or in some cases the tumor is located to the vagina.

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The RT acute vaginal effects include erythema, moist desquamation, confluent mucositis and hyperemia. These symptoms usually subside overtime. The RT late adverse effects are the following: fibrosis,dryness and atrophy of the vaginal epithelium, intravaginal and perinealpain. Symptoms severity varies depending on radiation dose, comorbidities, patient age, and anatomical treated site. Older and overweighed patients have a slower tissue damage recovery, mainly due to underlying diseases (i.e. hypertension and heart disease) and reduced physical activity. They may have a poorer body image, so, it is more difficult to improve their sexual life [8,9].

The incidence of vaginal stenosis (VS) ranges from 20 to 88% [10-13]. Some studies have demonstrated that patients who undergo surgery and receive IVB alone,have an incidence of VS from as low as 2.5%. The lowest rates are reported in those who receive low-dose-per-fraction IVB, to as high as 54% with the use of tandem [13,14]. The distal vaginal mucosa has smaller radiation tolerance than the mucosa in the upper region, and vagina may shorten during RT [15]. A randomized trial showed that higher rates of VS are related to higher IVB doses [16]. RT doses >80 Gy have been related to a 10 to 15% increased risk of vaginal toxicity, including VS [17]. Vaginal stenosis is most likely to occur within the first year of treatment, but it has been observed to expand in as short a time as 26 days and as far out as 5.5 years from RT [11,18]. Vaginal atrophy is also a problem for patients caused not only because of RT but chemotherapy and hormonotherapy as well [18].

Treatment

The vaginal dilator use usually starts within 4 weeks after RT end, for at least 3 years and 3 times per week [6,19,21]. In a systematic review by Miles et al, there was shown no strong evidence that regular VD use during RT prevented VS or improved QoL [20]. Evaluated 56 patients and found that the VD use did not prevent sexual impairment and VS [21]. Due to dilation of irradiated and fibrotic tissues, there was a risk of fistula formation [21].

There are different formulations of low-dose vaginal estrogen treatment, including vaginal (topical) oestrogen with minimal systemic absorption;intravaginal ring; intravaginal insert; topical lubricants [22,23]. They can be taken approximately 3-5 times per week,at bedtime,and may help with vaginal dryness and dyspareunia.

Pelvic floor rehabilitation program (PFRP) may improve vulvo-vaginal atrophy symptoms, pelvic floor dysfunction and QoL of gynecological cancer patients [24-26]. Yang et al investigated the effect of PFRP on pelvic floor function and quality of life, in twenty four gynecologic cancer survivors suffering from pelvic floor dysfunction [24]. The investigators found an improvement in pelvic floor strength, sexual functioning, and quality of life [24].

Patients who experienced wound dehiscence or late radionecrosis -including soft tissue fibrosis, epithelial ulceration, skin atrophy, skin necrosis, major vessel rupture, fistula formation- can be treated with hyperbaric oxygen therapy (HBO) [27,28]. HBO in radiation-damaged tissue induces angiogenesis, fibroblast proliferation and collagen formation [29]. It can potentially boost wound healing. Higher oxygen delivery can enhance leukocyte function and bacterial infection reduction. Collagen formation can allow for a boost in wound healing potential [30-35].

Reconstructive surgery and replacement of the damaged tissue with distant healthy tissue in the form of a musculocutaneous, fasciocutaneous, or free flap represents a therapeutic choice [27,29]. The technique outcome depends on tissues vascularity and local blood flow. Due to radiation there is a replacement of healthy tissues with dense fibrotic tissue. There is a risk of wound infection, dehiscence and disfiguration because of the endothelial cells, arteriolesand dermal fibrosis, elastin fibers fragmentation and increased propensity for small vessels to form microthrombi [27-35].

Pelvic EBRT, as a gonadotoxictreatment,induces ovarian insufficiency and iatrogenic premature menopause [36]. Long term consequences such as a) bone mineral density (BMD), b) neurocognitive dysfunction, c) cardiovascular disease and d) vasomotor symptoms (e.g. hot flashes,vaginal dryness) should be minimized in particular in young survivors and can be managed with oral progesterone and estrogen [36].

Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are effective non-hormonal alternatives for vasomotor symptoms [37] and can be considered in order to reduce morbidity and enhance quality of life. Among SSRIs, sertraline, paroxetine, citalopram, escitalopram and fluoxetine and SNRIs such as venlafaxine, desvenlafaxine and duloxetine have shown benefits to menopausal symptoms, such as hot flashes [38]. Anticonvulsant drugs such as gabapentin and pregabalin [39,40], as well as clonidine as an anti-hypertensive alpha-adrenergic agonist, have also shown a beneficial effect in menopausal symptom control [41].

Weight-loss intervention has been associated with improvement in endometrial cancer-specific survival [42]. Maintaining healthy body weight and regular physical activitycan help in controlling menopausal symptoms [43]. In addition to its weight loss-inducing effect, a selective serotonin receptor agonist (5-HT2C) modulation may positively affect vasomotor symptoms as well [44].

Lower limb radiation-related lymphedema follows dysfunction in the pelvic and inguinal lymphonodes. It is a debilitating condition that adversely influences sexual function [45]. Manual lymphatic drainage, instrumental lymphatic drainage, vascular gymnastics (with loaded external compression), multilayer bandage, hydrotherapy, may provide some benefit, but there are no randomized clinical trials regarding their use in gynecologic cancer [46,47].

mHealth interventions such as a) physical activity/fitness (i.e. pelvic floor muscle core exercises or yoga and pelvic floor muscle training with counseling), b) cognitive behavioral therapy and mindfulness/ stress management, may be beneficial in improving sexual function, vasomotor symptoms and optimizing health-related quality of life in gynecological cancer survivors [48,49].

In a meta-analysis there was revealed a statistically significant reduction in frequency and severity of vasomotor symptoms, with the application of acupuncture [38,50,51]. There are not sufficient data to conduct meta-analyses examining the effect of hypnosis and various mindfulness and relaxation methods in the treatment of vasomotor symptoms [52,53].

An oncosexology interdisciplinary professionals' team (physicians,

psychologists, social workers, oncology nurses etc), can help providing cancer patients and their partners with information and adequate treatments focusing on their sexual and relational needs [54,55].

Conclusion

Although there have been improvements in advanced RT methods that protect the healthy tissues around the malignancy, administering EBRT ± BRT results in potential toxicities. Modern RT techniques may reduce this risk in some instances. Major treatment related side effects are relatively rare. Both during and after RT, careful management and long-term monitoring of patients who are treated for gynecologic malignancies are necessary in ensuring the best quality of life.

Future diagnostic testing may aid in determining which patients have the greatest risk for toxicity. Early intervention could also be helpful.

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