Journal of Womens Health, Issues and Care

Research Article A SCITECHNOL JOURNAL

Ways to Improve Radiation-Induced Sexual Toxicity in Gynecologic Cancer

Eftychia Chounta[1], Angeliki Skoutari[1], Athina Samara[1], Chrysostomos Antoniades[2], Davide Mauri[3], Nikolaos Tsoukalas[4],Nikolaos Charalampakis[5] and Maria Tolia[2*]

[1]Faculty of Medicine, School of Health Sciences, University of Thessaly, Biopolis, Larisa, Greece

[2]Radiotherapy Department, University Hospital Heraklion, University of Crete Medical School, Heraklion, Greece

[3]Department of Medical Oncology, University Hospital of Ioannina, Ioannina, Greece

[4]Department of Medical Oncology, 401 Military Hospital, Athens, Greece

[5]Department of Medical Oncology, Metaxa Cancer Hospital, 185 37 Athens, Greece

[*]Corresponding author: Tolia M, Radiotherapy Department, University Hospital Heraklion, University of Crete Medical School, Heraklion, Greece, E-mail: mariatolia@uoc.gr

Received date: July 01, 2021; **Accepted date**: July 15, 2021; **Published date:** July 22, 2021

Abstract

Radiotherapy plays a critical role in gynaecologic cancer treatment. Despite the improvement of modern radiation techniques in healthy tissue protection, patients still experience significant treatment related effects. We aim to assess therapeutic 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.

Keywords: 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].

Radio Therapy (RT) plays a significant role in the therapeutic management of gynecological malignancies; 60% of cervical, 45% of endometrial, 35% of vulvar and 100% of vaginal cancer 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 Brachy Therapy (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 dosimetric in accuracies, 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 toxicity in 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, and 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.

S.No	Pharmaceutical treatment
1	Low-dose vaginal estrogen treatment [22,23] •Topical oestrogen with minimal systemic absorption •Intravaginal ring •Intravaginal insert •Topical lubricants
2	Pelvic floor rehabilitation program [24-26]
3	Hyperbaric Oxygen Therapy [27-35]
4	Reconstructive surgery [27-29]
5	Oral progesterone and/or estrogen for premature menopause [36]
6	For vasomotor symptoms •Selective serotonin reuptake inhibitors-SSRIs (sertraline, paroxetine, citalopram, escitalopram, fluoxetine) [38] •Selective serotonin-norepinephrine reuptake inhibitors-SNRIs (venlafaxine, desvenlafaxine, duloxetine)[38] •Anticonvulsant (gabapentin, pregabalin) [39,40] •Anti-hypertensive alpha-adrenergic agonist (clonidine) [41]

Table 1: Pharmaceutical treatments that can improve sexual toxicity.

S.No	Non pharmaceutical method
1	Maintaining healthy body weight [43,44]
2	Regular physical activity [43,44]
3	•Manual lymphatic drainage •Instrumental lymphatic drainage •Vascular gymnastics (with loaded external compression) •Vascular gymnastics (with loaded external compression) •Multilayer bandage Hydrotherapy
4	Pelvic floor muscle core exercises •Pelvic floor muscle training with counseling •Yoga [48,49]
5	Cognitive Behavioral Therapy Mindfulness/stress management [48,49]
6	Acupuncture [38,50,51]
7	Onco-sexology intervention team support •Medical Doctors •Psychologists •Social Workers •Oncology Nurses

Table 2: Non pharmaceutical methods to improve sexual activity.

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 primary neoplasm or in some cases the tumor is located to the vagina (Tables 1 and 2).

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 perineal pain. 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 then 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 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]. Akbaba et al. 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 (Table 1).

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 radio necrosis - 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, arterioles and dermal fibrosis, elastin fibers fragmentation and increased propensity for small vessels to form microthrombi [27-35].

Pelvic EBRT, as a gonadotoxic treatment, 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/or 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 activity can 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].

Discussion

Health 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 [54-56].

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.

Acknowledgments

None

References

1. Ledford LRC, Lockwood S (2019) Scope and Epidemiology of Gynecologic Cancers: An Overview. Sem Oncol Nur 2: 147-150.
2. Zwaans BMM, Lamb LE, Bartolone S, Nicolai HE, Chancellor MB, et al. (2018) Cancer survivorship issues with radiation and hemorrhagic cystitis in gynecological malignancies. Int Urol Nephrol 50: 1745-1751.
3. Utena Y, Takatsu J, Sugimoto S, Sasai K (2021) Trajectory log analysis and cone-beam CT-based daily dose calculation to investigate the dosimetric accuracy of intensity-modulated radiotherapy for gynecologic cancer. J Appl Clin Med Phys.
4. Korfage IJ, Essink-Bot ML, Mols F, van de Poll-Franse L, Kruitwagen R, et al. (2009) Health-related quality of life in cervical cancer survivors: a population-based survey. Int J Radia Oncol Biol Phys 73: 1501-1509.
5. Karabuga H, Gultekin M, Tulunay G (2015) Assessing the Quality of Life in Patients With Endometrial Cancer Treated With Adjuvant Radiotherapy. Int J Gynecol Cancer 25: 1526-1533.
6. Foerster R, Schnetzke L, Bruckner T (2016) Prognostic factors for long-term quality of life after adjuvant radiotherapy in women with endometrial cancer. Strah lenther Onkol 192: 895–904.
7. Abbott-Anderson K, Kwekkeboom KL (2012) A systematic review of sexual concerns reported by gynecological cancer survivors. Gynecol Oncol 124: 477-489.
8. Pisani C, Deantonio L, Surico D, Brambilla M, Galla A, et al. (2016) Quality of life in patients treated by adjuvant radiotherapy for endometrial and cervical cancers: correlation with dose-volume parameters. Clin Transl Oncol 18: 901-908.
9. Sung UkL, Young K, Young-Ho Y, Yeon-Joo K, Myong CL, et al. (2017) General health status of long-term cervical cancer survivors after radiotherapy. Strah lenther Onkol 193: 543-551.
10. Flay LD, Matthews JH (1995) The effects of radiotherapy and surgery on the sexual function of women treated for cervical cancer. Int J Radia Oncol Biol Phys 31: 399-404.

11. Damast S, Jeffery DD, Son CH, Hasan Y, Carter J, et al. (2019) Literature Review of Vaginal Stenosis and Dilator Use in Radiation Oncology. Pract Radiat Oncol 9: 479-491.
12. Saibishkumar EP, Patel FD, Sharma SC (2006) Evaluation of late toxicities of patients with carcinoma of the cervix treated with radical radiotherapy: an audit from India. Clin Oncol 18: 30-37.
13. Nori D, Merimsky O, Batata M, Caputo T (1994) Postoperative high dose-rate intravaginal brachytherapy combined with external irradiation for early stage endometrial cancer: a long-term follow-up. Int J Radiat Oncol Biol Phys 30: 831-837.
14. Townamchai K, Lee L, Viswanathan AN (2012) A novel low dose fractionation regimen for adjuvant vaginal brachytherapy in early stage endometrioid endometrial cancer. Gynecol Oncol 127: 351-355.
15. Katz A, Njuguna E, Rakowsky E, Sulkes A, Sulkes J, et al. (2001) Early development of vaginal shortening during radiation therapy for endometrial or cervical cancer. Int J Gynecol Cancer 11: 234-235.
16. Sorbe B, Straumits A, Karlsson L (2005) Intravaginal high-dose-rate brachytherapy for stage I endometrial cancer: a randomized study of 2 dose-per-fraction levels. Int J Radiat Oncol Biol Phys 62: 1385-1389.
17. Perez CA, Breaux S, Bedwinek JM, Madoc-Jones H, Camel HM, et al. (1984) Radiation therapy alone in the treatment of carcinoma of the uterine cervix. II. Analysis of complications. Cancer 54: 235-246.
18. Kirchheiner K, Nout RA, Tanderup K, Lindegaard JC, Westerveld H, et al. (2014) Manifestation pattern of early-late vaginal morbidity after definitive radiation (chemo) therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study. Int J Radiat Oncol Biol Phys 89: 88-95.
19. Charatsi D, Tolia M (2019) Vaginal stenosis after radiation therapy for pelvic cancer: prevention and treatment options: A review of the current literature. Euro J Gyn Oncol 40: 185-189.
20. Miles T, Johnson N (2014) Vaginal dilator therapy for women receiving pelvic radiotherapy. Cochrane Database Syst Rev 8: CD00-7291.
21. Akbaba S, Oelmann-Avendano JT (2019) The impact of vaginal dilator use on vaginal stenosis and sexual quality of life in women treated with adjuvant radiotherapy for endometrial cancer. Strahlenther Onkol 195: 902-912.
22. Crandall CJ, Hovey KM, Andrews CA, Chlebowski RT, Stefanick ML, et al. (2018) Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. Menopause 25: 11-20.
23. Lethaby A, Ayeleke RO, Roberts H (2016) Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 8: CD001-500.
24. Yang EJ, Lim JY, Rah UW, Kim YB (2012) Effect of a pelvic floor muscle training program on gynecologic cancer survivors with pelvic floor dysfunction: a randomized controlled trial. Gynecol Oncol 125: 705-711.
25. Dumoulin C, PazzotoCacciari L, Mercier J (2019) Keeping the pelvic floor healthy. Climacteric 22: 257-262.
26. Grimes WR, Stratton M (2020) Pelvic Floor Dysfunction. In Stat Pearl Treasure Island.
27. Borab Z, Mirmanesh MD, Gantz M, Cusano A, Pu LL (2017) Systematic review of hyperbaric oxygen therapy for the treatment of radiation-induced skin necrosis. J Plast Reconstr Aesthet Surg 70: 529-538.
28. Griffiths C, Howell RS, Boinpally H, Jimenez E, Chalas E, et al. (2018) Using advanced wound care and hyperbaric oxygen to manage wound complications following treatment of vulvovaginal carcinoma. Gynecol Oncol Rep 24: 90-93.
29. Marx RE, Ehler WJ, Tayapongsak P, Pierce LW (1990) Relationship of oxygen dose to angiogenesis induction in irradiated tissue. Am J Surg 160: 519-524.
30. Bennett MH, Feldmeier J, Hampson NB, Smee R, Milross C (2016) Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database Syst Rev 4: CD00-5005.
31. Feldmeier JJ, Heimbach RD, Davolt DA (1996) Hyperbaric oxygen an adjunctive treatment for delayed radiation injuries of the abdomen and pelvis. Undersea Hyperb Med 23: 205-213.
32. Hampson NB, Holm JR, Wreford-Brown CE, Feldmeier J (2012) Prospective assessment of outcomes in 411 patients treated with hyperbaric oxygen for chronic radiation tissue injury. Cancer 118: 3860-3868.
33. Korpinar S, Cimsit M, Cimsit B, Bugra D, Buyukbabani N (2006) Adjunctive hyperbaric oxygen therapy in radiation-induced non-healing wound. J Dermatol 33: 496-497.
34. Niezgoda JA, Serena TE, Carter MJ (2016) Outcomes of Radiation Injuries Using Hyperbaric Oxygen Therapy: An Observational Cohort Study. Adv Skin Wound Car 29: 12-19.
35. Uzun G, Candas F, Mutluoglu M, Ay H (2013) Successful treatment of soft tissue radionecrosis injury with hyperbaric oxygen therapy. BMJ Case Rep.
36. Condemi L, Giuseppe J, DelliCarpini G, Garoia F, Frega A, et al. (2018) Vaginal natural oxygenation device (VNOD) for concomitant administration of hyaluronic acid and topical hyperbaric oxygen to treat vulvo-vaginal atrophy: A pilot study. Eur Rev Med Pharmacol Sci 22: 8480-8486.
37. Vargiu V, Amar ID, Rosati A, Dinoi G, Turco LC, et al. (2021) Hormone replacement therapy and cervical cancer: a systematic review of the literature. Climacteric 24: 120-127.
38. Marino JL, McNamara HC, Hickey M (2018) Managing menopausal symptoms after cancer: an evidence-based approach for primary care. Med J Aust 208: 127-132.
39. Biglia N, Bounous VE, Seta F, Lello S, Nappi RE, et al. (2019) Non-hormonal strategies for managing menopausal symptoms in cancer survivors: an update. Ecancer Med Science 13: 909-918.
40. Orleans RJ, Li L, Kim MJ, Guo J, Sobhan M, et al. (2014) FDA approval of paroxetine for menopausal hot flushes. N Engl J Med 370: 1777-1779.
41. Baber RJ, Panay N, Fenton A (2016) IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric 19: 109-150.
42. Sassarini J, Fox H, Ferrell W, Sattar N, Lumsden M (2012) Hot flushes, vascular reactivity and the role of the α-adrenergic system. Climacteric 15: 332-338.
43. Kitson S, Ryan N, MacKintosh ML, Edmondson R, Duffy JM, et al. (2018) Interventions for weight reduction in obesity to improve survival in women with endometrial cancer. Coch Database Syst Rev 2: CD012-513.

44. Thurston RC, Ewing LJ, Low CA, Christie AJ, Levine MD (2015) Behavioral weight loss for the management of menopausal hot flashes: a pilot study. Menopause 22: 59-65.
45. Kapoor E, Faubion S, Hurt RT, Fischer K, Schroeder D, et al. (2020) A selective serotonin receptor agonist for weight loss and management of menopausal vasomotor symptoms in overweight midlife women: a pilot study. Menopause 27: 1228-1235.
46. Hayes SC, Janda M, Ward LC, Reul-Hirche H, Steele ML, et al. (2017) Lymphedema following gynecological cancer: Results from a prospective, longitudinal cohort study on prevalence, incidence and risk factors. Gynecol Oncol 146: 623-629.
47. Iwersen LF, Sperandio F, Toriy AM, Palú M, Medeiros C (2017) Evidence-based practice in the management of lower limb lymphedema after gynecological cancer. Physiother Theory Pract 33: 1-8.
48. Kendrová L, Mikuľáková W, Urbanová K, Andraščíková Š, Žultáková S, et al. (2020) Comprehensive Decongestive Therapy as a Treatment for Secondary Lymphedema of the Lower Extremity and Quality of Life of Women after Gynecological Cancer Surgery. Med Sci Monit 26: e924-071.
49. Brennen R, Lin KY, Denehy L, Frawley HC (2020) The Effect of Pelvic Floor Muscle Interventions on Pelvic Floor Dysfunction After Gynecological Cancer Treatment: A Systematic Review. Phys Ther 100: 1357-1371.
50. Buneviciene I, Mekary RA, Smith TR, Onnela JP, Bunevicius A (2021) Can Health interventions improve quality of life of cancer patients? A systematic review and meta-analysis. Crit Rev Oncol Hematol 157:103-123.
51. Befus D, Coeytaux RR, Goldstein KM, McDuffie JR, Shepherd BM (2018) Management of Menopause Symptoms with Acupuncture: An Umbrella Systematic Review and Meta-Analysis. J Altern Complement Med 24: 314-323.
52. Mokhatri HP, Montazeri A (2020) Health-related quality of life in breast cancer patients: review of reviews from 2008 to 2018. Health Qual Life Out 18: 338-340.
53. Goldstein KM, Shepherd BM, Coeytaux RR, McDuffie JR, Adam S, et al. (2017) Use of mindfulness, meditation and relaxation to treat vasomotor symptoms. Climacteric 20: 178-182.
54. Gressel RO, Samuels N, Levy M, Leviov M, Lavie O, et al. (2020) Association Between Physical Activity and Use of Complementary Medicine by Female Oncology Patients in an Integrative Palliative Care Setting. J Altern Complement Med 26: 721-728.
55. Krychman ML, Pereira L, Carter J, Amsterdam A (2006) Sexual oncology: sexual health issues in women with cancer. Oncology 71: 18-25.
56. Falk SJ, Dizon DS (2013) Sexual dysfunction in women with cancer. Fertil Steril 100: 916-921.