Supportive therapy as prevention for iatrogenic sexual dysfunction following vaginal Brachytherapy (BRT)

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ABSTRACT — OBJECTIVE: *Endometrial cancer (EC) is the most common gynaecological cancer in postmenopausal women. Early stage diagnoses of EC have led to improved cancer-related survival increasing the onset of adverse events, which often negatively affect patient's quality of life. In this regard, frequently, women treated with radiotherapy refer a sexual desire reduction and a decreased sexual intercourse frequency. In this regard, recent studies, on supportive therapies applied in association with radiotherapy in gynaecology, have reported the capability of Low-Molecular Weight Hyaluronic Acid (LMWHA) to improve patient quality of life. For this reason, a LMWHA based treatment was used in association to standard therapies, to counteract the onset of adverse events in irradiated tissues.*

PATIENTS AND METHODS: *199 patients with EC at stage IB were enrolled, surgically treated and subsequently exposed to brachytherapy (BRT) with vaginal cylinder customized in length and diameter. Simultaneously with BRT, patients were divided in two groups and daily treated with chlorhexidine lavenders and LMWHA suppositories (Supportive therapy - SuBRT) or only with chlorhexidine lavenders (Control group – CBRT), in both cases for 15 days. To evaluate treatment effects an interview to all patients was performed by a psychologist.*

RESULTS: *After the treatment, 71% of patients decided to be interviewed. In SuBRT group an evident improvement of patients' quality of life was reported thanks to limiting radiotherapy impact on sexual activity, social activities and emotional state. In this regard, an important difference about the percentages of patients reporting significant and serious effects was reported comparing SuBRT and CBRT groups (respectively 40% and 78%) in relation to sexual activity.*

CONCLUSIONS: *As reported in this paper, thanks to LMWHA treatment, an overall improvement of patient's QoL can be reached reducing radiotherapy impact on sexual and social life of these women.*

KEYWORDS
Endometrial cancer, Quality of Life, Low-Molecular Weight Hyaluronic Acid, Brachytherapy.

INTRODUCTION

In developed countries, Endometrial cancer (EC) is undoubtedly the most common gynaecological cancer in postmenopausal women. Age, white race, factors related to an excess of oestrogen exposure, diabetes, hypertension or high socioeconomic status represent the main risk factors for EC development[1]. At an early stage, standard treatment for EC is total abdominal hysterectomy with bilateral oophorectomy (TAH-BSO), with or without lymph node dissection, associated with post-surgery external beam radiotherapy (EBRT) and/or with endovaginal brachytherapy (BRT) [1-4]. This therapeutic approach is based on several data that demonstrate a statistically significant reduction of recurrences and/or me-

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tastasis onset thanks to post-operative or adjuvant radiotherapy[4]. Recently, in light of PORTEC-2 study results, showing the equivalence of efficacy between BRT and EBRT as prevention by local vaginal recurrences and/or of distant metastases, the use of post-operative BRT is significantly increased due to the demonstrated less onset of gastrointestinal iatrogenic effects[5-7]. Equally to EBRT, BRT treatment can induce sexual dysfunction as permanent toxic effect due to the vaginal shortening and shrinkage caused by fibrosis and post-treatment stenosis[8-10]. In this regard, frequently, women treated with radiotherapy refer a sexual desire reduction (37% of patients) and a decreased sexual intercourse frequency (22% of patients)[10]. Nowadays, there is no agreement among the scientific community about the BRT impact on patient's life. Some authors have tried to evaluate the effects of BRT and surgery combined treatment comparing to surgery alone. However, considering the intrinsic limits of these studies (difficulty to address an issue such delicate, to perform studies with a considerable sample size in numerosity or willingness in filling out the self-assessment questionnaire on sexual dysfunction), unambiguous data on this topic is not available yet[11-13]. Obviously, a quality of life (QoL) improvement for these patients should favour a greater predisposition for the evaluation of adverse events related to oncological therapies.

In this regard, recent studies, on supportive therapies applied in association with radiotherapy in gynaecology[14-18], have reported the effect of hyaluronic acid in improving patients QoL. For this reason, in this study, a Low-Molecular Weight Hyaluronic Acid (LMWHA) based treatment was used in association to standard therapies, to counteract the onset of adverse events in irradiated tissues with the aim to obtain a better QoL of these patients. Particularly, the primary outcome of this study is to reduce the impairment of sexual activity due to radiotherapy.

Moreover, relatively to patient self-evaluation, in order to overcome the reticence in sharing intimate information, a suitable evaluation system was developed and applied to this study. A self-evaluation questionnaire was proposed to the patients by a psychologist with the aim to evaluate the impact of adjuvant treatment impact in association to BRT and, eventually, to adopt this new psycho-oncological evaluation system.

PATIENTS AND METHODS

Study Population and Treatments Specification

Two-hundred patients with EC, afferent to the Department of Oncology, Azienda Ospedaliera Cosenza, from January 2010 to September 2017, were enrolled. As inclusion criteria, all patients, classified histologically, according to the International Federation of Gynaecology and Obstetrics, stages IB (IB: Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2; IIA: Tumour without parametrial invasion)[19], before, were undergone to Total Abdominal Hysterectomy - Bilateral Salpingo-Oophorectomy (TAH-BSO) with or without lymph node dissection and, subsequently, were treated with exclusive BRT, performed using vaginal cylinder customized in length and diameter. BRT treatment provided a total dosage of 30 Gy with a daily fractioning of 6 Gy, to sterilize vaginal vault by irradiation of dome and terminal section of vagina, 4 cm in total, in accordance to international guidelines[20]. Exclusions criteria were no compliance to the treatment, genital abnormalities, positive Pap-test within last three months, vaginal infections, contact allergy in vulvovaginal zone, use of drugs for vaginal administration in last 15 days before the beginning of study, alcohol or drugs abuse, taking part to other studies in the month before the recruitment. Patients enrolled were divided in two groups based on treatment. Patients of treated group (SuBRT) have carried out a daily treatment with vaginal suppositories containing LMWHA, Vitamin A and Vitamin E (Santes® vaginal suppository, Lo.Li. Pharma, Rome, Italy), administered 12 hours after a chlorhexidine lavender while patients of control group (CBRT), in addition to surgery and radiation therapy, have used only daily vaginal chlorhexidine lavender, according to standard treatments. Treatments with chlorhexidine lavenders (CBRT) and with chlorhexidine lavenders and LMWHA suppositories (SuBRT) were started simultaneously with BRT for 15 days. Every patient was subjected to two gynaecological evaluations, before the initiation of radiotherapy and at the end of all treatments. A questionnaire developed for the psycho-oncological evaluation was used to report QoL improvements of these patients. A psychologist has performed evaluation interviews approaching to the patients with a short initial conversation to favour a good predisposition to share intimate information centred on health conditions and oncological treatments course. Subsequently, patients have answered questions about their sexual life and an evaluation of their sexual dysfunction grade was performed. In particular, the questionnaire was structured in 4 areas (1. Social relationship and personal feelings 2. Couple intimacy and sexuality 3. Treatment impact on sexuality 4. Doctor-patient relationship before BRT) for a total of 10 questions: 3 multiple choice questions (no effect, minor effect, significant effect, serious effect) and 7 binomial answer (yes or no). The interviews were performed at the end of all treatments. The primary outcome of this study is the reduce sexual activity impairment induced by radiotherapy by treatment with LMWHA. Moreover, the

reduction of radiation impact on social activities and emotional state of these patients was considered as secondary outcome.

All subjects involved provided written Informed Consent Form before participation. The study was conducted following the Ethical principles of the Declaration of Helsinki and the national laws.

Statistical Analysis

To evaluate if differences between SuBRT and CBRT were statistically significant, Pearson's chi-square test was performed to compare percentages obtained. An overall *p*-value of less than 0.05 was considered statistically significant.

RESULTS

In this comparative study 199 patients (average age 62.33 ± 8.51) have completed correctly all treatments, with an average follow-up of 44 months (44.21 ± 9.14), while a patient was excluded to the study for an incomplete compliance to the therapy. All tumours resulted, at TNM Classification (Tumour-node-metastasis staging system of malignant tumours), pT1B at histological level (5 squamous and 194 adenocarcinomas), grading G1 for 15%, G2 for 65% and G3 for 20% of cases. Lymph nodes were not involved (N0) in 149 cases (75%) while in other 50 cases the lymph node involvement (NX) was not be evaluable (25%). Diameter of cylinder used was 3-4 cm in 168 patients (84%) and 1-2 cm in the remaining 31 cases (26%). Only in 3 cases a tumour progression was reported (1.5%) in CBRT. 142 patients participated to psychological evaluation (median age 61.81 ± 7.44), about 71% of cases, while the remaining 57 patients were not interested because not sexually active.

The two groups evaluated were composed respectively by 69 patients CBRT and by 73 patients SuBRT. All baseline characteristics of these two groups are reported in Table 1. Data obtained from this study show clearly different results between two groups. Indeed, when compared, patients of SuBRT group have reported better results about sexual activity (Figure 1), social activities (Figure 2) and emotional state (Figure 3), relatable to the combination chlorhexidine + LMWHA, than patients of CBRT group. Particularly, an important difference about the percentages of patients reporting significant and serious effects was reported comparing SuBRT and CBRT groups (respectively 40% and 78%) in relation to sexual activity (Figure 1). Similar results were reported also analysing the differences shown by SuBRT and CBRT groups in relation to social activities and emotional state (respectively 48% vs 72% for social activities and 43% vs 76% for emotional state).

Table I. Baseline characteristics of patients involved in the study.

BASELINE PATIENTS DATA	
Patients evaluated	199
Median Age (years ± DS)	62.33 ± 8.51
Follow-up (months ± DS)	44.21 ± 29.14
Histological evaluation:	
Cases of adenocarcinoma (N - %)	194 - 97.49
Cases of squamous cell carcinoma (N - %)	5 - 2.51
Patients classified as:	
pT1bN0 (N - %)	149 - 74.87
pT1bNX (N - %)	50 - 25.13
Sexually active patients (N - %)	142 - 71.35
CBRT (N - %)	69 - 34.67
SuBRT (N - %)	73 - 36.68

pT1bN0: FIGO Tumour Classification – p(pathological) T1b (Tumour > 5 mm but ≤ 10 mm in greatest dimension) N0 (No regional lymph node metastases); pT1bNX: FIGO Tumour Classification – p(pathological) T1b (Tumour > 5 mm but ≤ 10 mm in greatest dimension) NX (Regional lymph nodes cannot be assessed (for example, previously removed); CBRT: Control group; SuBRT: Treated group.

Moreover, as reported in Figure 4, in the SuBRT group in comparison to CBRT group, there is a higher percentage of patients which referred no impact of BRT on their intimacy (51% vs 29% respectively) or on sexual desire (52% vs 19% respectively) and which reported absence of pain during sexual intercourse (52% vs 27% respectively). Interestingly, 13% CBRT vs 1% SuBRT of patients explicitly requested psychological support, an important aspect considering sexual dysfunction impact in women affected by EC. All differences reported in this paper between CBRT and SuBRT were resulted statistically significant ($p \leq 0.05$).

DISCUSSION

Early stage diagnoses of EC have led to improved cancer-related survival increasing the onset of adverse events, which often negatively affect patients QoL[21,22]. Nowadays, surgery represents the mainstay treatment of EC but recently several studies have evaluated also the results obtained with intravaginal BRT as adjuvant treatment in intermediate-risk disease (stage IB G1-2 disease, stage IA G3 disease, and stage IC G1-2 disease), reporting great results in terms of local control and toxicity[5,23-30]. Nevertheless, BRT may cause acute and long-term side effects and there are different grading systems for the assessment of clinical vaginal toxicity[31-34]. Frequently, vaginal side effects are a consequence of vaginal mucosa damage, the connective tissues and the small blood vessels. One of the most common acute toxicities is vaginal inflammation, which can be manifested by redness, oedema, pain and sexual dysfunction[4].

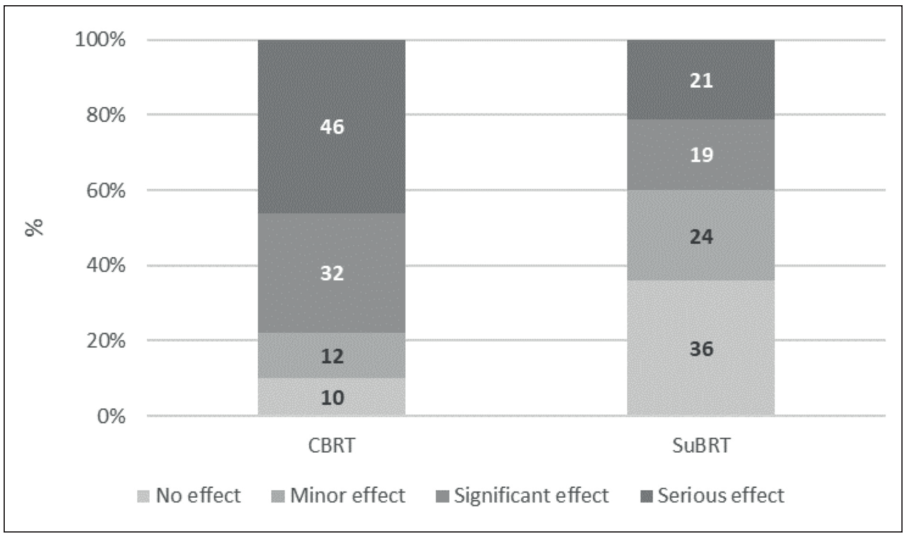

Figure 1. Percentage distribution of BRT impact on sexual activity perceived by the patients. (SuBRT: Supportive Brachytherapy; CBRT: Control Brachytherapy. The distribution (%) about the impact on sexual activity was statistical different between CBRT and SuBRT. Statistical analysis was performed using the Pearson's chi-square test. Significance was $p<0.001$).

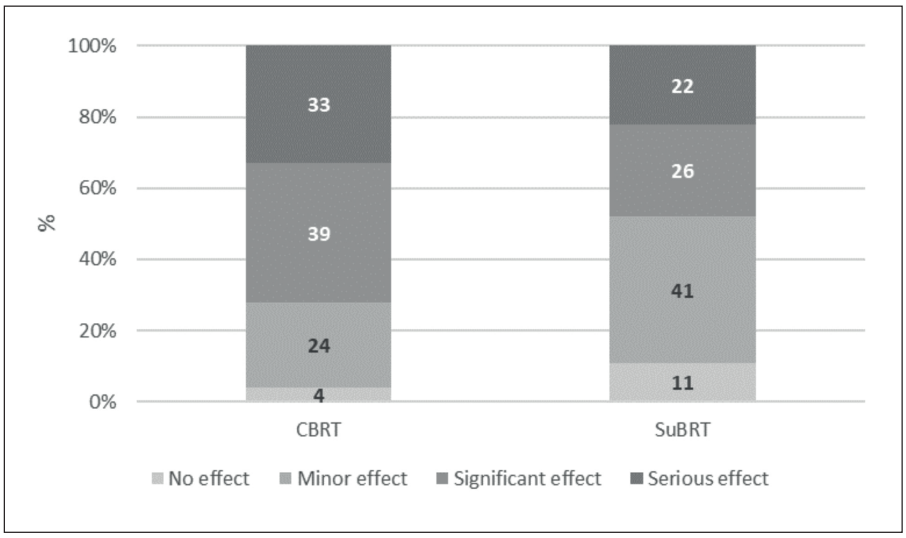

Figure 2. Percentage distribution of BRT impact on social activities (family, friends, colleagues) perceived by the patients. (SuBRT: Supportive Brachytherapy; CBRT: Control Brachytherapy. The distribution (%) about the impact on social activities was statistical different between CBRT and SuBRT. Statistical analysis was performed using the Pearson's chi-square test. Significance was $p<0.05$).

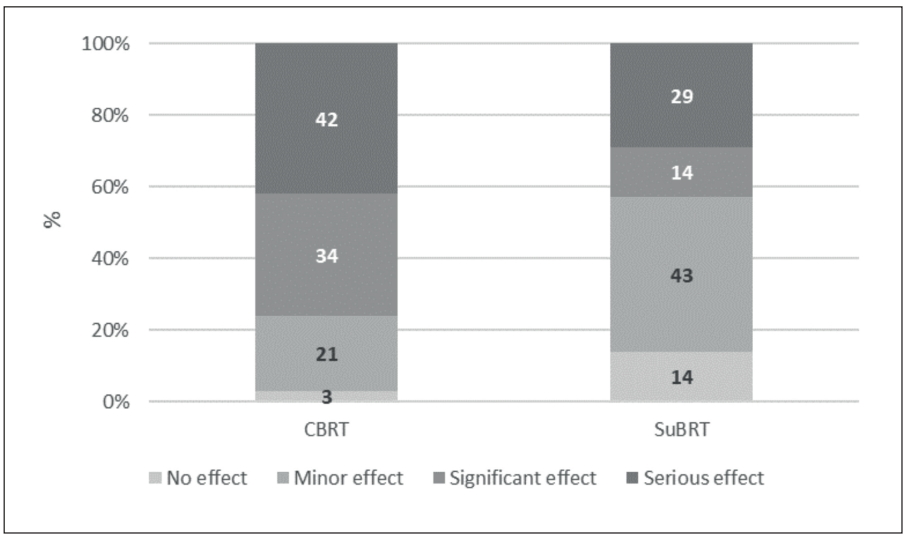

Figure 3. Percentage distribution of BRT impact on the emotional state perceived by the patients. (SuBRT: Supportive Brachytherapy; CBRT: Control Brachytherapy. The distribution (%) about the impact on emotional state was statistical different between CBRT and SuBRT. Statistical analysis was performed using the Pearson's chi-square test. Significance was $p<0.001$).

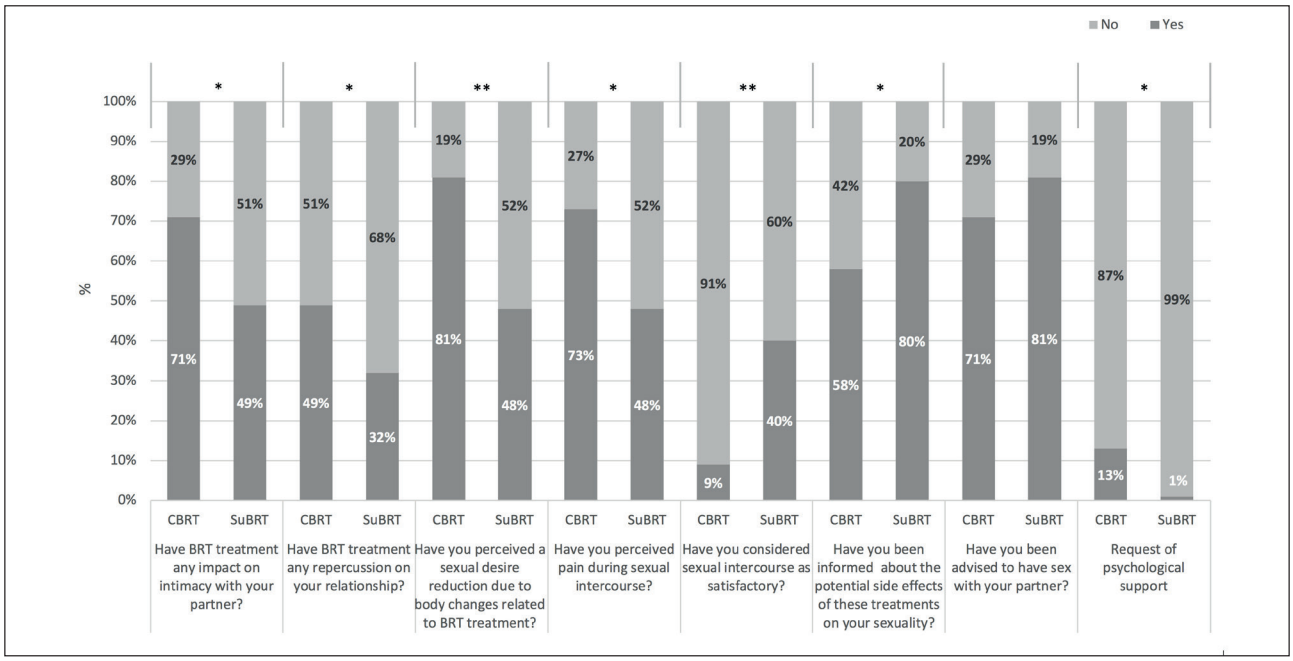

Figure 4. Patients' evaluation of BRT impact on social, emotional and sexual life. (SuBRT: Supportive Brachytherapy; CBRT: Control Brachytherapy. The distribution (%) about the impact of BRT on social, emotional and sexual life was statistical different between CBRT and SuBRT. Statistical analysis was performed using the Pearson's chi-square test. *p<0.05; ** p<0.001).

Thanks to the improvements of diagnosis techniques, the average age of EC patients has dropped. Considering also that women sexual life, nowadays, is being extended, adverse events, as sexual dysfunction, in young women can affect more their QoL, conditioning their social relationship and their confidence. Chronic toxicity impairs the image of himself, bringing the patient to feel not cured from cancer. The treatment of this toxicity, lasting over time, is problematic since the only available therapy consists in the use of vaginal dilators. Their use is debated both in terms of efficacy and patient compliance, since it is a long-lasting therapy, not always effective and difficult to accept[35-39]. For this reason, new treatments to counteract the onset of these side effects were developed. Thanks to its immunoregulatory and re-hydrating activities, the clinical use of hyaluronic acid (HA) represents one of the most interesting approach to help patients subjected to BRT. HA is a carbohydrate, more specifically a mucopolysaccharide, occurring naturally in all living organisms and consisting of a linear and energetically very stable polyanion formed by 3-D-glucuronic acid and D-N-acetylglucosamine units linked together by alternating β-1,4 and β-1,3 glycosidic bonds. The number of repeat disaccharides in a completed hyaluronan molecule can reach 10.000 or more, with a molecular mass of ~4 million Da and a total extension up to more than 10 μm[40]. The relatively simple structure of HA is conserved throughout all mammals, suggesting that HA is a biomolecule of considerable importance. In the body, HA occurs in the salt form, hyaluronate, and is found in high concentrations in several soft connective tissues and it is the principal glycosaminoglycan in the body fluids such as synovial fluid, the vitreous humour, and Wharton's jelly of the umbilical cord as well as in skin and mucous membranes[41]. Its biological functions include maintenance of the elastoviscosity of liquid connective tissues, control of tissue hydration and water transport, supramolecular assembly of proteoglycans in the extracellular matrix, and numerous receptor-mediated roles in cell detachment, mitosis, migration, tumour development and metastasis, and inflammation. HA plays several important roles in the organization of extracellular matrix by binding with cells and other components through specific and nonspecific interactions[42]. Despite the numerous functions in which HA is naturally involved, due to its high molecular mass, it is not absorbed once applied to the skin or mucosa, forming a thin, light permeable, invisible, viscoelastic surface film[14]. On the contrary, when HA is LMWHA, this can be absorbed, interacting with several cells involved in proliferation processes[43] and immunity system as osteoclasts, dendritic cells and macrophages[44-46].

In this regard, LMWHA seems to be very effective in reducing inflammation and gynaecological side effects due to radiation therapy as reported in several studies[14-16]. However, the main limit of these new treatments is the reticence of patients to report sexual dysfunctions to their physicians, delaying their application. For this reason, in this study, to evaluate the LMWHA on sexual dysfunction, a questionnaire

for the psycho-oncological evaluation was developed and used to report QoL improvements of these patients. Moreover, to overcome patience reticence the evaluation interviews were performed by a psychologist. Interestingly the percentage of participation by the patients was very high, about 71%, confirming the functionality of this kind of interview. As previously reported, data obtained from patient perception is an overall improvement of their QoL when treated with LMWHA thanks to a limited radiotherapy impact on sexual activity and social activities. The improvement of vaginal inflammation perceived by the patients and showed by the psychological interviews was also confirmed by the physicians after their gynaecological control at the end of treatments if compared to CBRT group, treated only with chlorhexidine.

Finally, a relevant aspect, particularly in this context, is the doctor-patient relationship. If we believe that correct information before treatment is important first of all to respect the patient's right to information, we cannot accept that in CBRT group only 58% declare to have been informed about the consequences on the sexual function of a BRT treatment, or that only 71% have received advice (having sexual intercourse also for therapeutic purposes). Doctors, who perform the first evaluation visit, not only should follow the guidelines for the possible prescription or not of the treatment, but also should be as much as possible detailed to explain any acute and chronic collateral effects due to the treatment proposed, avoiding underestimation of the problems reported by the patient. Physicians who ignore this principle of their relationship with patients are responsible of violation of the most important ethical principle of Medicine that is to cure sick persons minimizing the physical and psychological damage due to the treatment as reported by World Health Organization (WHO): "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[47].

CONCLUSIONS

As clearly reported in this paper, an improvement of QoL in patients undergone radiotherapy for EC is possible employing a local treatment with LMWHA. Thanks to its chemo-physical properties, this molecule resulted useful to limit radiation impact on several aspects of patient life as sexual activity, social activities and emotional state. For these reasons, the administration of vaginal suppositories of LMWHA in patients treated with radiotherapy for EC represents an interesting opportunity. Moreover, a good doctor-patient relationship is fundamental to improve compliance to the treatments. Considering the limited number of patients involved in this study, further confirmations are needed to support completely this adjuvant treatment.

Conflicts of interest:
The authors report no conflict of interest

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