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Clinical Trial Protocol

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A multimodal intervention program to improve sexual health and self-perceived quality of life in patients treated for cervical cancer: a randomized prospective study (PROVIDENCE trial)

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ABSTRACT

Background: Patients with cervical cancer treatment experience an impairment of sexual function and quality of life. This issue is usually underreported and undertreated, and evidence-based interventions are lacking. Prevention of sexual dysfunction is a crucial pillar in improving the quality of life of these patients. The primary objective of this trial is to evaluate the impact of a multimodal intervention, encompassing prevention of vaginal dysfunction and patient education, on sexual function and quality of life in cervical cancer survivors utilizing patient-reported outcome measurements.
Methods: Multi-institutional, randomized clinical trial where patients will be randomized 1:2 at diagnosis of initial or locally advanced cervical cancer to control arm or intervention arm. After treatment, control arm patients will undergo standard follow-up by their referring physician. The multimodal intervention for patients in the intervention group includes application of vaginal estrogens plus hyaluronic-acid cream along with use of vaginal vibrator, systematic evaluation of the need of systemic hormone replacement therapy and treatment if needed, and access to online content about sexuality, nutrition, sports and lifestyle habits. Through 4 appointments (at diagnosis, 1, 6, and 12 months after treatment), sexual health, vaginal trophism and self-perceived quality of life of patients in both arms will be assessed with validated questionnaires as female sexual function index (FSFI), European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30, and Cx-24, Cervantes Scale, vaginal health index and vaginal thickness assessed by ultrasound. The major inclusion criteria will be patients aged ≥18 years with the International Federation of Gynecology and Obstetrics stage I–III cervical cancer treated with surgery and/or radiotherapy. The primary endpoint will be FSFI score 12 months after treatment, which will be compared between groups. Uni- and multivariate analysis will be performed to identify factors influencing sexual function recovery after treatment. The sample size will be of 120 eligible patients, who will

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: G.I.B., D.F.B.; Formal analysis: G.I.B., C.D.N.; Funding acquisition: C.D.N., D.F.B.; Investigation: G.I.B., C.D.N., O.P.R., D.F.B.; Methodology: G.I.B., C.D.N., L.G., O.P.R., C.B.C., M.T., T.A.[1], T.A.[2], D.F.B.; Project administration: D.F.B.; Resources: G.I.B., C.D.N.; Supervision: L.G., D.F.B.; Writing - original draft: G.I.B., C.D.N., S.H.B., C.N.B.; Writing - review & editing: G.I.B., D.F.B. T.A.[1], Alvaro Tejerizo; T.A.[2], Aureli Torné.

be randomized to detect an improvement of 5.2 points in FSFI score. Complete accrual is estimated in March 2026. To date, the present study has no external funding.

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Keywords: Cervical Cancer; Sexual Health; Quality of Life; Patient Reported Outcome Measures

INTRODUCTION

Cervical cancer is the third most common tumor in women worldwide, whose main pillars of treatment are radical hysterectomy in early stage cases and radio-chemotherapy in locally advanced cases [1]. Cervical cancer treatment, both radical surgery and/or radio-chemotherapy, can impair all scopes of daily life and, beyond the physical changes caused by treatment, has psychological and social implications that influence health-related quality of life (HR-QoL). Patients undergoing treatment for cervical cancer have shown to score less in self-perceived quality of life scales compared to healthy women [2].

A patient reported outcome measure (PROM) is any direct report of the patients' health status, free from interpretation or interference by a healthcare practitioner. PROMs are assessed using validated questionnaires, serving as a reliable tool to comprehend patients' perceptions of their quality of life, thus enhancing healthcare by implementing strategies with measurable outcomes. Currently, the "European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire" (EORTC QLQ-C30) questionnaire stands as the most widely used in clinical trials across Europe for oncology patients. Comprising 30 items, it evaluates the quality of life concerning physical, emotional, social aspects, and overall functionality of cancer patients [3]. Additionally, the EORTC offers a specific module questionnaire for cervical cancer (Cx-24), which assesses symptoms related to the biology and treatment of this type of tumor [4]. On the other hand, there are few questionnaires that specifically assess the quality of life in menopausal patients. In 2004, the Cervantes Scale was developed, a 31-item questionnaire (divided into the domains of health, psychological well-being, sexuality, and partner relationships) validated in Spanish females to assess the impact of climacteric symptoms on quality of life [5]. Subsequently, in 2015, the original questionnaire was reduced to 16 items (Cervantes short form–SF), preserving its original structure in 4 main domains [6,7].

Sexual health in patients treated for cervical cancer deserves to be given special attention. More than half of women with gynecological cancer experience sexual dysfunction, especially those affected by cervical cancer. Radical hysterectomy for cervical cancer treatment has been associated with sexual impairment, as well as bladder and gastrointestinal dysfunction [8-10]. On the other hand, radiotherapy has also shown a negative impact on sexual, bladder, and gastrointestinal function in patients treated for cervical cancer [11-13]. Despite ovarian preservation in many patients with early cervical cancer, this group of patients experiences a deterioration of sexual function without differences between surgical treatment modalities [14]. Vaginal trophism is commonly affected in patients undergoing treatment for cervical cancer, who often suffer from vaginal dryness, lack of lubrication, dyspareunia fibrosis, and vaginal obliteration. The diagnosis of vaginal atrophy relies on clinical examination, although the correlation between signs and symptoms perceived by the patients has shown to be limited [15], and there is a lack of consensus in the literature regarding how to evaluate this condition [16]. The vaginal health index (VHI) evaluates vaginal elasticity, secretion, pH,

the presence of petechiae on the mucosa, and hydration, with a cutoff point of <15 for the diagnosis of vaginal atrophy [17]. Other studies have shown that ultrasound can also be useful for the diagnosis of vaginal atrophy by assessing the thickness of the vaginal wall [18].

The morbidity in the sexual sphere resulting from cervical cancer treatment significantly impacts the quality of life, underscoring the importance of preventing and treating sexual dysfunction to enhance patients' HR-QoL [19]. Sexual function is challenging to measure due to the influence of various factors [20]. Despite being an integral part of quality of life questionnaires, it is often studied separately through questionnaires that focus on different aspects. The female sexual function index (FSFI) is a validated, brief, and multidimensional questionnaire that allows for the evaluation of female sexual function across a broad age range and conditions [21].

The recently published 2023 the European Society of Gynaecological Oncology/the European SocieTy for Radiotherapy and Oncology/the European Society of Pathology (ESGO/ESTRO/ESP) guidelines on the management of cervical cancer recommend the promotion of sexual health, along with the early use of vaginal dilators concurrently with vaginal hydration and topical application of estrogens [1]. Additionally, the authors suggest that hormone replacement therapy in patients treated for cervical cancer should be considered [1]. However, these recommendations are overly generic and the quality of the evidence supporting them is low. Besides, observational studies indicate that the percentage of cervical cancer patients receiving information and treatment for early menopause and sexual dysfunction, especially regarding hormone replacement therapy, does not exceed 50% [22-24]. Protective factors that decrease sexual morbidity have been studied, such as adequate information provided by the clinician, symptom prevention, psychosocial support, and rediscovery of sexuality [25]. The new 2023 ESGO/ESTRO/ESP guidelines also propose making changes in physical activity and lifestyle [1]. Nonetheless, there are studies concluding that psychosocial interventions or lifestyle changes alone have a limited impact on the quality of life of cancer patients [26]. This highlights the importance of implementing a multifactorial approach to improve the sexual health of patients treated for cervical cancer.

The main hypothesis of this study is that a systematic assessment of sexual health and quality of life through PROMs and a specific multimodal intervention focused on improving sexual health, as opposed to the general recommendations outlined in current clinical guidelines, can improve sexual function and self-perceived quality of life in patients treated for early and locally advanced cervical cancer. These changes in women's sexual health correlate with vaginal trophism, which can be objectively measurable through VHI and vaginal thickness assessed by ultrasound.

MATERIALS AND METHODS

1. Objectives

The main objective of the present trial to provide high-quality scientific evidence supporting:

1) The systematic assessment of sexual health and quality of life using PROMs in all patients treated for cervical cancer.
2) The implementation of a multimodal and standardized intervention focused on improving sexual health and quality of life, as opposed to the general recommendations outlined in current clinical guidelines.

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The secondary objectives include:

1) To evaluate sexual function (FSFI questionnaire) in women treated for cervical cancer after completion of treatment and its evolution over 1 year.
2) To evaluate self-perceived quality-of-life (EORTC QLQ-C30 and Cx-24 questionnaires, Cervantes Scale) in women treated for cervical cancer after completion of treatment and its evolution over 1 year.
3) To identify the needs of women treated for cervical cancer (through the completion of PROMs) that can lead to the development of strategies to enhance their sexual health and quality of life
4) To objectively evaluate vaginal trophism through VHI and vaginal thickness assessed by ultrasound in women treated for cervical cancer, after completion of treatment and its evolution over 1 year.
5) To evaluate feasibility and adherence to multimodal intervention and the eventual reported adverse outcomes.

2. Trial design

The PROVIDENCE trial is a multi-institutional, randomized clinical trial which aims to demonstrate that a multimodal intervention including patient education on sexuality and healthy habits and the prevention of vaginal dysfunction reduces sexual dysfunction and HR-QoL impairment in patients treated for cervical cancer. The recruitment period is scheduled from June 2024 to March 2026 and will be held in Gynecology Oncology Units of 5 referral hospitals in Spain.

Patients will be randomized 1:2 at diagnosis of cervical cancer to control arm or intervention arm.

After treatment for cervical cancer, patients in the control arm will undergo the standard follow-up according to the general recommendations outlined in clinical guidelines and treatment of post-treatment morbidity will be performed following the standard procedures as determined by their referring physician. Patients in the control group have the option to receive treatment (hormone replacement therapy, vaginal estrogens and/or vaginal moisturizers) “on demand,” based on the criteria set by their referring physician and on the symptoms they report.

The proposed multimodal intervention for patients in the intervention group consists of the following interventions:

- Application of topical vaginal estrogens
- Systematic evaluation of the need of systemic hormone replacement therapy (and treatment if needed)
- Application of hormone-free vaginal-vulvar moisturizing cream containing hyaluronic acid
- Use of a vaginal vibrator twice a week for 5 to 10 minutes each time with the help of intimate lubricant
- Access to online informational content about sexuality, nutrition, sports and lifestyle habits

Patients in the intervention group will receive all the interventions simultaneously and will be encouraged to follow all the items that make up the multimodal intervention plan.

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The following appointments will take place during the study period (**Fig. 1**).

· First appointment: at the time of diagnosis of cervical cancer, all patients fulfilling the inclusion criteria will be proposed to participate in the study, those willing to participate will sign informed consent and will be asked to complete FSFI, EORTC QLQ-C30,

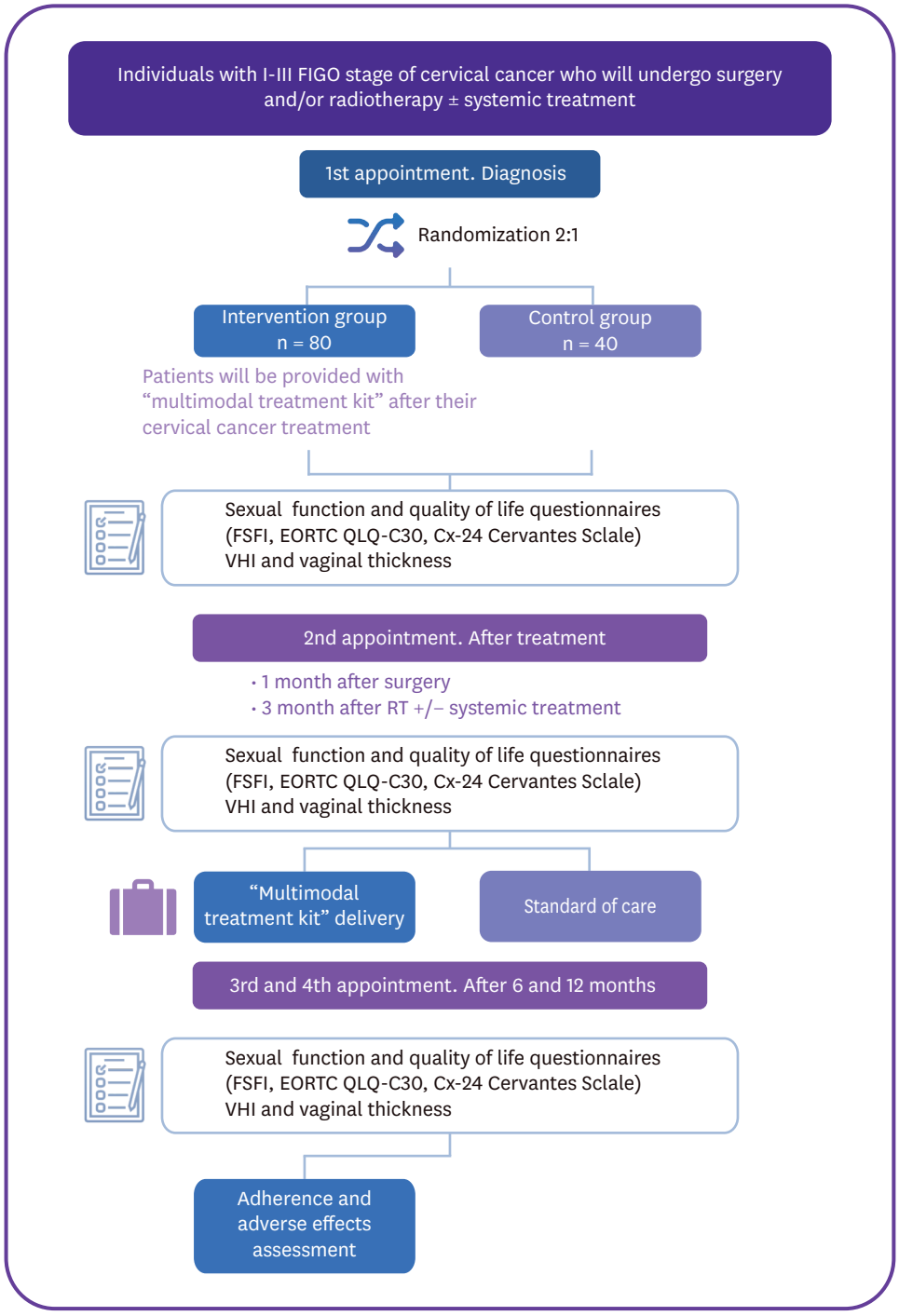

Fig. 1. Flowchart of the PROVIDENCE trial protocol.
FIGO, the International Federation of Gynecology and Obstetrics; FSFI, female sexual function index; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30; VHI, vaginal health index.

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Cx-24 and Cervantes questionnaires. Additionally, VHI [8] and vaginal thickness by transvaginal ultrasound will be evaluated. At this point, the patients will be randomized to control arm or intervention arm.

- Second appointment: 1 month after surgery (in patients treated exclusively with surgery) or 3 months after radiotherapy ± systemic treatment, the patients will be asked to complete FSFI, EORTC QLQ-C30, Cx-24, and Cervantes questionnaires. VHI and vaginal thickness by ultrasound will be evaluated. Patients in the intervention arm will be given a "multimodal treatment kit," containing hormone-free vaginal and vulvar moisturizing creams, topical vaginal estrogens with their dosage instructions, the vaginal vibrator, and access to the informational content. The need of hormone replacement therapy will be systematically evaluated in the patients of the intervention arm and will be prescribed if needed (see "8. Treatment" section). The purpose of the vaginal vibrator is to gently and progressively dilate the introitus and vaginal walls and stimulate the patient's sexual self-awareness. The initiation of its use will be delayed until 3 months after surgery. Patients will receive instructions on its use from the study physician and through the informational content on sexuality, and a guide on the vibrator usage.
- Third and fourth appointment: 6 and 12 months after the second appointment, the patients will be asked to complete FSFI, EORTC QLQ-C30, Cx-24, and Cervantes questionnaires and VHI and vaginal thickness will be assessed. Adherence to multimodal intervention items will be evaluated, as well as possible adverse effects of vaginal estrogens or hormone replacement therapy.

The data collected will be entered into the Research Electronic Data Capture software via a secure webpage interface.

Fig. 1 provides a flowchart of the trial design.

3. Primary and secondary endpoints

The primary endpoint will be improvement of sexual health assessed by FSFI twelve months after treatment, with respect to baseline determination.

Secondary endpoints include:

- FSFI score, score in quality-of-life questionnaires (EORTC QLQ-C30, Cx-24, Cervantes Scale) and measurements of vaginal trophism (VHI, vaginal thickness assessed by ultrasound) at baseline (defined as one month after treatment in case of surgery and 3 months after treatment in case of radiotherapy ± systemic treatment), 6 months after treatment and twelve months after treatment.
- Adherence to multimodal intervention in the intervention arm, is defined as the percentage of patients in the intervention arm who have completed each of the items included in multimodal intervention.
- Adverse outcomes associated with the treatments in the intervention arm: number, grading, and type.

4. Eligibility criteria

Inclusion criteria are defined as follows

- Women older that 18 years, with initial or locally advanced primary cervical cancer
- Squamous, adenocarcinoma or adenosquamous histology
- Stage the International Federation of Gynecology and Obstetrics I–III cervical cancer treated with surgery and/or radiotherapy ± systemic treatment in Gynecology Oncology

Units of referral hospitals in Spain
· Signed informed consent by the patient or legal guardian

Exclusion criteria are defined as follows
· Pregnancy or breastfeeding
· Metastatic tumor in the cervix uteri or primary tumor with atypical histology
· Inability to complete the questionnaires included in the study protocol
· Contraindications for the use of topical vaginal estrogens
· Patients undergoing fertility-preservation treatment (conization or trachelectomy)
· Patients undergoing palliative treatment

5. Sample size

Given that the objective of the study is to standardize and systematize a management protocol for patients with cervical cancer after treatment, a sample calculation has been conducted based on factibility. The study is multicentric and will involve at least 5 national reference units in oncological gynecology, each of which manages an average of 25 cervical cancer patients annually, thus it is considered feasible to achieve the goal of including 120 patients during a 22-month recruitment period.

Assuming a 5% bilateral type I error and an 80% power, this sample would allow to detect differences in FSFI scale of 5.5 points with 10 points of standard deviation. Thus 120 patients will be included during a 22-month recruiting period.

6. Randomization and blinding

Patients will be randomized 1:2 at diagnosis of cervical cancer to the control arm (40) or intervention arm (80) using the software Stata version 15.1 (StataCorp, College Station, TX, USA). Given the nature of the study, blinding is not feasible.

7. Statistical methods

Statistical analysis will be performed using Stata software version 15.1 (StataCorp). Statistical analysis will be made on the intention-to-treat population. A secondary analysis of the per-protocol population will be performed to generate new hypotheses for further studies. Numerical variables, including primary endpoint, will be reported in terms of mean and standard deviation, while categorical variables will be reported as proportion and interquartile range. The variables will be compared between study groups according to the type of variable (numerical or categorical) and their distribution (normal or non normal), using χ^2 or t-student/Mann-Whitney U tests. We will perform univariate and multivariate analysis with linear regression to assess the impact of the intervention and possible confounding factors. The p-values lower than 0.05 will be considered as statistically significant. We will perform a sub-analysis according to the modality of treatment (surgery or radiotherapy ± systemic treatment).

8. Treatment

The indications for systemic hormone replacement therapy in the intervention group will be as follows:
· Premenopausal women with iatrogenic menopause (<45 years) caused by oncologic treatment
· Postmenopausal or perimenopausal women (>45 years) with climacteric symptoms after oncologic treatment affecting their quality-of-life.

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Systemic hormone replacement therapy will be based on the indications of The European Menopause and Andropause Society and the Spanish Menopause Society (AEEM Asociación Española para el Estudio de la Menopausia) and will be administered orally or transdermally. In hysterectomized patients, various estrogen replacement options are available (oral estradiol valerate, transdermal 17-beta-estradiol patches, percutaneous estradiol spray, and estradiol gel). Regimens combining estrogen with progestogens are recommended for patients retaining the uterus, with continuous regimens preferred to prevent deprivation bleeding. These regimens may involve combining estrogen with progesterone. Combined preparations such as micronized estradiol/progesterone, estradiol/norethisterone acetate, or estradiol/cyproterone acetate are also available. Additional options for hormone therapy include tibolone. Despite the existence of other treatments for estrogen such as TSEC (tissue selective estrogenic compounds) the aforementioned drugs has been chosen to limit the intervention arm's treatment to ensure homogeneous patient management.

Vaginal estrogen therapy in the intervention arm can be administered in various formats, including vaginal creams (promestriene 10 mg/g), vaginal tablets (estradiol 10 mcg), vaginal gels (estriol 50 mcg/g), and vaginal rings (hemihydrate estradiol 7.5 mcg). These treatments are used daily for a specified period (2–3 weeks, 3 months for vaginal rings), followed by maintenance doses every 3–4 days to sustain therapeutic effects. Although ospemifene is also a first-line drug for genitourinary syndrome of menopause, it has not been included as a treatment option in the intervention arm. This decision is due to its oral administration, and the study has opted for vaginal cream application due to the local effects it generates, considering the nature of vaginal dysfunction in cervical cancer. As for prasterone, which is also a first-line treatment for genitourinary syndrome of menopause, the scarcity of studies in patients with cervical cancer and its dosing in ovules have led to its exclusion from the intervention arm treatments. This exclusion of alternative treatments has also been done to maintain homogeneity in the intervention treatment, thus allowing for a more consistent evaluation of study results.

Although ospemifene and prasterone are also considered as first-line drugs for genitourinary syndrome of menopause, both they have not been included as a treatment option in the intervention arm. This decision is due to its the scarcity of studies in patients with cervical cancer. This exclusion of alternative treatments has also been done to maintain homogeneity in the intervention treatment, thus allowing for a more consistent evaluation of study results.

The expected duration of the multimodal intervention is 1 year from the completion of onco-specific treatment (surgery and/or radiotherapy ± systemic treatment), defined as the baseline level. Once the study period has ended, patients will be advised to maintain habits related to nutrition, exercise, sexuality, and lifestyle, as well as the use of vaginal vibrators and non-hormonal vaginal and vulvar creams, always at the discretion of the treating physician. Treatment with vaginal estrogens may be continued at the discretion of the treating physician as long as there are no contraindications for its use during follow-up. Regarding the use of hormone replacement therapy in patients for whom it has been prescribed, following the recommendations of the European Menopause and Andropause Society, it will be maintained (if there are no contraindications) until the age of physiological menopause in women with early menopause or for a maximum of 5 years in patients over 40 years old.

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9. Ethics

The protocol has been approved by the Ethics Committee of the University Hospital 12 de Octubre (Nº 22/552) and was prepared following the Standard Protocol Items: Recommendations for Interventional Trials guidelines. The study has no external funding. The trial was registered at the Clinical Trials (NCT06031493).

DISCUSSION

Cervical cancer treatment has a negative impact on sexual function and self-perceived quality of life [1]. However, this issue has shown to be underestimated and underreported by clinicians [27,28]. The use of strategies to improve the sexual function of patients treated for cervical cancer, whether they involve lifestyle interventions, psychosocial support, sexology, or the use of hormone replacement therapy, is not systematically established in daily clinical practice [23] and recommendations in clinical guidelines are generic and lack high level scientific evidence [1]. The worsening in self-perceived quality of life and, especially, the sexual function of patients with cervical cancer has a complex origin that involves physical, psychological, and social factors [20]. Therefore, it is logical to think that their treatment requires a multimodal approach. The main hypothesis of this study is that a systematic evaluation of sexual health and quality of life through PROMs and a specific multimodal intervention focused on improving sexual health, can improve sexual function and therefore self-perceived quality of life in patients treated for early and locally advanced cervical cancer.

With the present study we expect to highlight the importance of systematically evaluating sexual function and self-perceived quality of life of the patients treated for cervical cancer with the use of PROMs to correctly identify their needs and implement measures to enhance their well-being after treatment. Secondly, and most important, we expect to demonstrate that a systematic multimodal intervention including patient education on healthy habits and the prevention of vaginal dysfunction using vaginal moisturizers and topical estrogens (and a thorough evaluation of the need of hormone replacement treatment) is a useful tool to improve sexual function and quality of life of these patients. It is important to emphasize that the intervention we seek to evaluate has a systematic and multimodal nature, compared to the opportunistic and broader approach currently used in clinical practice. Given that the vast majority of studies on sexual health in cervical cancer survivors are merely observational, this study might provide solid scientific evidence on specific recommendations to enhance the sexual health and quality of life of patients treated for cervical cancer.

The present study has some limitations. The use of FSFI score comes with its constraints, such as the ongoing debate surrounding the cutoff point for considering sexual dysfunction, its fluctuating scores in sexually inactive women, and its inherent bias towards heterosexual activity [29]. Nonetheless, we deem it the most suitable tool available for assessing sexual function. This study adopts an exploratory nature aiming to assess the impact of systematic reporting of sexual dysfunction and quality of life, alongside multimodal intervention, compared to opportunistic diagnosis and treatment thereof (as opposed to a non-treatment approach, which would be unethical). This design stems from clinical observation, recognizing the limitations of guideline recommendations and the underreportment and undertreatment of sexual dysfunction in routine clinical practice. A sample size estimation has been conducted for this design, based on the primary objective. However, the power of the study may be limited to specifically evaluate the impact of multimodal intervention

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within each oncologic treatment subgroup. Adherence to the multimodal intervention is another potential limitation of the study. Based on our experience from previous studies, we know that patient adherence is adequate but does not reach 100% [30]. The goal of this study is to assess the implementation (and limitations) of this type of intervention in real clinical practice, measuring its effect under real-world conditions.

In conclusion, this study aims to justify the need for a systematic multimodal intervention in patients treated for cervical cancer, with the goal of improving their sexual function and quality of life, which have a complex and multifactorial origin. Additionally, it aims to enhance the diagnosis of sexual dysfunction and impairment of quality of life through PROMs.

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