



# The effects of various therapies on vulvovaginal atrophy and quality of life in gynecological cancer patients: a systematic review

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## Abstract

**Purpose** Tumors affecting the female genital tract and their treatments have the potential to induce adverse modifications in vaginal health and impact personal aspects of patient's lives. Vulvovaginal atrophy is one of the morphological changes observed in individuals with a history of gynecological cancer, influenced both by the biological environment of tumors and the main therapeutic modalities employed. Therefore, the purpose of this study was to identify approaches to treat vulvovaginal atrophy while assessing the impact on the emotional and sexual health of women diagnosed with gynecological cancers.

**Methods** To achieve this goal, a systematic review was conducted following the methodological guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The databases used for literature research were PubMed and Web of Science.

**Results** Initially, 886 articles were obtained. After eliminating duplicates and applying inclusion/exclusion criteria, seven articles were selected for analysis. The period of highest publication activity spanned from 2017 to 2020, with the majority conducted in Italy. Five treatment modalities were identified and categorized as vaginal suppository, oral medication, surgical procedure, CO2 laser therapy, and vaginal dilator. Twenty-four outcomes related to vaginal health and 30 outcomes related to overall, sexual, and emotional quality of life were analyzed.

**Conclusion** In general, all interventions demonstrated the ability to improve vaginal health or, at the very least, the sexual health of patients. Thus, despite limitations, all treatments have the potential to address vulvovaginal atrophy in patients with a history of gynecological cancer.

**Keywords** Vaginal atrophy · Gynecological cancer · Treatments · Systematic review · Vaginal health · Sexual health

## Introduction

Vulvovaginal Atrophy (VVA), also known as vulvovaginal atrophy, genitourinary atrophy, or atrophic vaginitis, is caused by decreased estrogen and is often associated with vulvovaginal discomfort (e.g., vaginal dryness, burning, vulvar and vaginal irritation, lack of lubrication, dyspareunia),

and less commonly, urgency and increased urinary frequency, dysuria, and recurrent urinary tract infections [1]. Moreover, it affects over 50% of postmenopausal women and is more prevalent in women with cancer [2–4]. In 2014, the International Society for the Study of Women's Sexual Health and the North American Menopause Society introduced the new term Genitourinary Syndrome of Menopause (GSM) [5]. The term encompasses all atrophy symptoms a patient may experience in the vulvovaginal and vesicourethral regions due to estrogen loss during menopause [6].

The prevalence of GSM confirmed by physical examination or pH measurement has been described as ranging from 69 to 98% in postmenopausal women [7, 8], but it is even more frequent in young patients who have received antiestrogenic or antineoplastic drugs for breast and gynecological cancers [9]. Symptoms associated with GSM are often underdiagnosed and undertreated due to underreporting by

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patients and limited awareness among healthcare professionals [10]. In the literature, most studies focus on describing GSM cases related to breast cancer patients, while few have focused on cases of gynecological cancers, especially those who have undergone pelvic radiotherapy.

In this context, women with gynecological cancers, particularly those treated with radiation, have a high incidence of dyspareunia, vaginal dryness, and sexual dysfunction [11]. Vaginal moisturizers and lubricants are typically recommended for symptom control, but unfortunately, these topical agents do not treat the underlying problem of GSM [12, 13]. Although a low dose of vaginal estrogen can help alleviate signs and symptoms, adherence to treatment is low, symptoms may return after discontinuation, and insufficient improvement has been reported with systemic and vaginal estrogen therapy [14–16]. Additionally, the use of vaginal estrogens is controversial for some women with gynecological cancer [17], and doctors often hesitate to prescribe vaginal estrogens to this population [18]. Thus, there is a need for alternatives for GSM treatment to increase efficiency in impacting overall and sexual quality of life. Therefore, the aim of this review is to explore existing treatments in the literature for GSM and evaluate the impact of each on the overall and sexual quality of life of gynecological cancer patients who have undergone oncological treatment.

## Methodology

### Protocol and registration

This systematic review was conducted following the methodological guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19]. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number: CRD42023412409.

### Eligibility criteria

The guiding question for the selection of articles for analysis was: which therapies improve vaginal atrophy and quality of life in survivors of gynecological cancer? The question was divided according to the PICO model (Population, Intervention, Comparator, and Outcome). Therefore, studies were included that involved the population (P) of women with a previous diagnosis of gynecological cancer who developed vulvovaginal atrophy, underwent some form of intervention (I), compared to a group without treatment or other treatments (C), and that may or may not have a positive effect on vaginal atrophy (O).

On the other hand, reasons for excluding articles were: studies that included women without gynecological cancer

with vaginal atrophy; studies that included only women with breast cancer with vaginal atrophy; studies without any form of treatment for vaginal atrophy in women with gynecological cancer; studies that lacked a control group without intervention or with another type of intervention for comparison; works that were not original articles, such as editorials, conference documents, comments, expert opinions, systematic reviews, or any other type of review, and book chapters; articles not in Spanish, Portuguese, or English.

### Information sources and search

The databases used for literature research were PubMed and Web of Science (Supplementary Material 1–S1). Additionally, other investigations were conducted, such as manual searches in the reference lists of included studies. After the official search in the mentioned databases, the articles were transferred to the RAYYAN application. Subsequently, duplicate articles were removed using the tools provided by the application, followed by confirmation by the evaluators. The search strategy was developed according to the Peer Review of Electronic Search Strategies (PRESS) [20]. The strategy developed for the PubMed database was considered the standard, with no restriction on the search by year of publication and language.

This was slightly modified according to the criteria of each database. Below is the standard search tool used: Search: (Vaginal Atrophy) AND (cancer) AND (treatment): (“vagina”[MeSH Terms] OR “vagina”[All Fields] OR “vaginal”[All Fields] OR “vaginally”[All Fields] OR “vaginals”[All Fields] OR “vaginitis”[MeSH Terms] OR “vaginitis”[All Fields] OR “vaginitides”[All Fields]) AND (“atrophie”[All Fields] OR “atrophy”[MeSH Terms] OR “atrophy”[All Fields] OR “atrophied”[All Fields] OR “atrophies”[All Fields] OR “atrophying”[All Fields]) AND (“cancer s”[All Fields] OR “cancerated”[All Fields] OR “canceration”[All Fields] OR “cancerization”[All Fields] OR “cancerized”[All Fields] OR “cancerous”[All Fields] OR “neoplasms”[MeSH Terms] OR “neoplasms”[All Fields] OR “cancer”[All Fields] OR “cancers”[All Fields]) AND (“therapeutics”[MeSH Terms] OR “therapeutics”[All Fields] OR “treatments”[All Fields] OR “therapy”[MeSH Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR “treatment s”[All Fields]).

### Study selection and data extraction

The selection was performed in two stages, blindly and separately by two evaluators. Initially, the reviewers examined the titles and abstracts of all references identified in the data searches to assess their relevance within the RAYYAN application, starting the inclusion or exclusion stage. In cases of disagreement, these were reconciled through a

discussion between them and a third reviewer. In the second stage, all potentially eligible studies were read in full independently (Supplementary Material 2–S2) and those that met the inclusion criteria were selected. Relevant data were extracted and the primary results of the included articles were presented graphically and descriptively throughout the “Results” section.

## Results

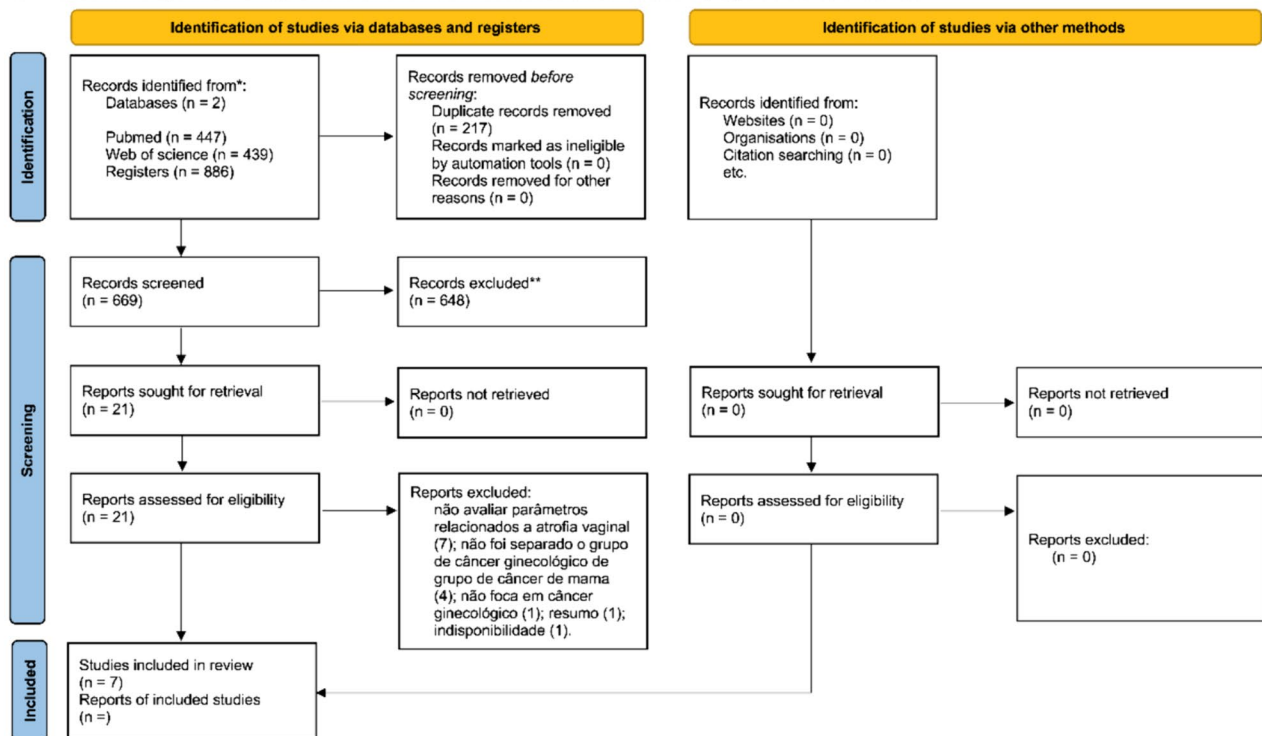
### Flowchart and general characteristics of included studies

The database search for studies addressing the use of treatments for vulvovaginal atrophy resulted in 886 articles. After excluding duplicated articles (217), a total of 669 works remained. Following the evaluation of the title and abstract of each study, 21 potential works were included and read in full. Of these 21, 14 were excluded for the following reasons: not assessing parameters related to vulvovaginal atrophy (7); not distinguishing the gynecological

cancer group from the breast cancer group (4); not focusing on gynecological cancer (1); abstract only (1); unavailability (1). Finally, 7 studies were included in the systematic review and underwent qualitative and descriptive evaluation (Fig. 1).

Regarding the general characteristics of the included studies, the analysis covered the publication year (Fig. 2a), the location where the study was conducted (Fig. 2b), and the study type (Fig. 2c). The first article on the topic was published in 2004 (1), with a 13-year gap to the next publication year, 2017, where two articles were published. Subsequently, publications in 2020 (2), 2021 (1), and 2023 (1) followed. Additionally, Italy had the highest number of publications (50%), followed by the United States (25%), San Marino, and France, each with the same number of studies (12.5%). Prospective studies represented the majority of published works, accounting for 28.6% of the total included studies. The remaining studies corresponded to the same percentage, with 14.28% for pilot investigation studies, case reports, retrospective studies, prospective phase I–II clinical studies, multicenter randomized pilot-controlled studies, and single-blind studies.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



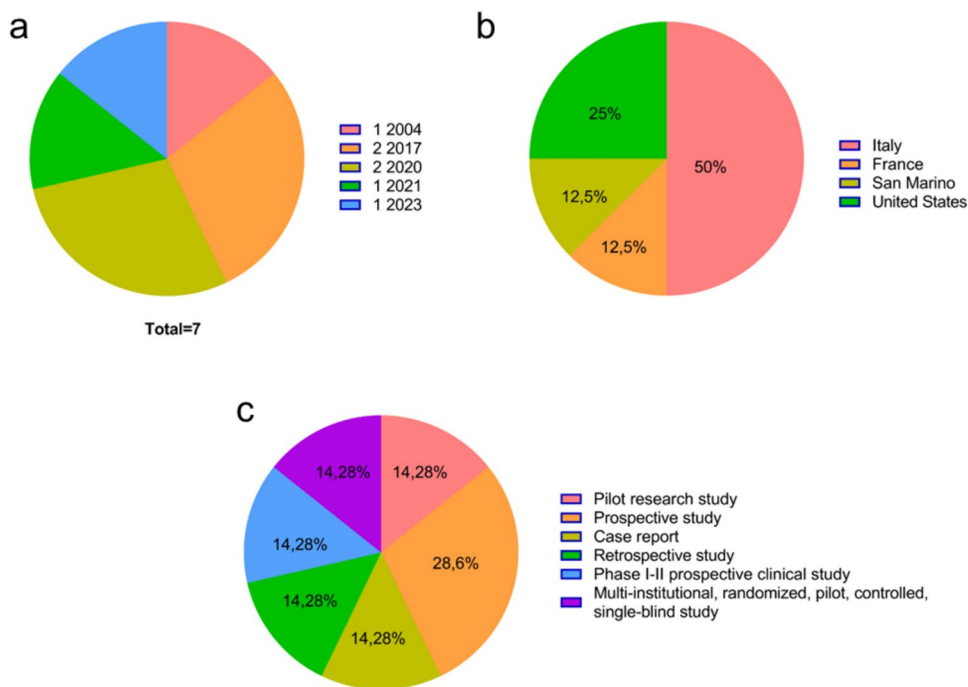
\*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

Fig. 1 Official PRISMA Flowchart. List of included and excluded articles

**Fig. 2** General characteristics of the included studies. **a** Number of articles published per year. **b** Location where the studies were conducted. **c** Type of study conducted (data extracted from the methodology of each included article)

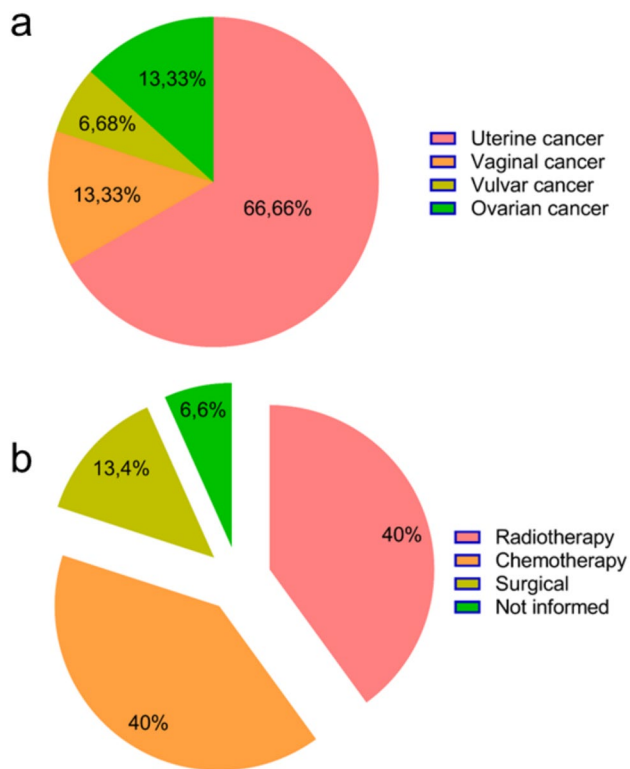


**Tumor types and included treatments**

Regarding the general characteristics of tumors and treatments in which vulvovaginal atrophy was evaluated, the focus was on the relationship between tumor type/location (Fig. 3a) and the chosen treatment type (Fig. 3b). Most studies focused on patients with uterine cancer (66.66%), followed by vaginal and ovarian cancer (13.33%), and vulvar cancer (6.68%). For treatments, radiotherapy and chemotherapy were the most reported in the included studies, accounting for 80%. Next, surgical procedures accounted for 13.4% of reports. Nevertheless, 6.6% did not report the types of treatments the patients underwent. The complete description of treatment types is presented in Table 1.

**Interventions for vaginal atrophy and evaluated outcomes**

Regarding interventions used to reduce vulvovaginal atrophy (Fig. 4a), CO2 laser was the most frequent, accounting for 42.88% of reports. Subsequently, all other treatments represented the same frequency in the included studies, with 14.28% for the use of vaginal suppository, oral medication, surgical procedure, and the use of vaginal dilator. For the evaluated outcomes, i.e., assessing the impact of treatments on parameters that may be altered in cases of atrophy, various phenomena were analyzed (Fig. 4b). To check if the interventions induced positive impacts, the parameter hydration and the presence of vaginal fluids were the most frequent, at 18.42%. Following this, dyspareunia and burning

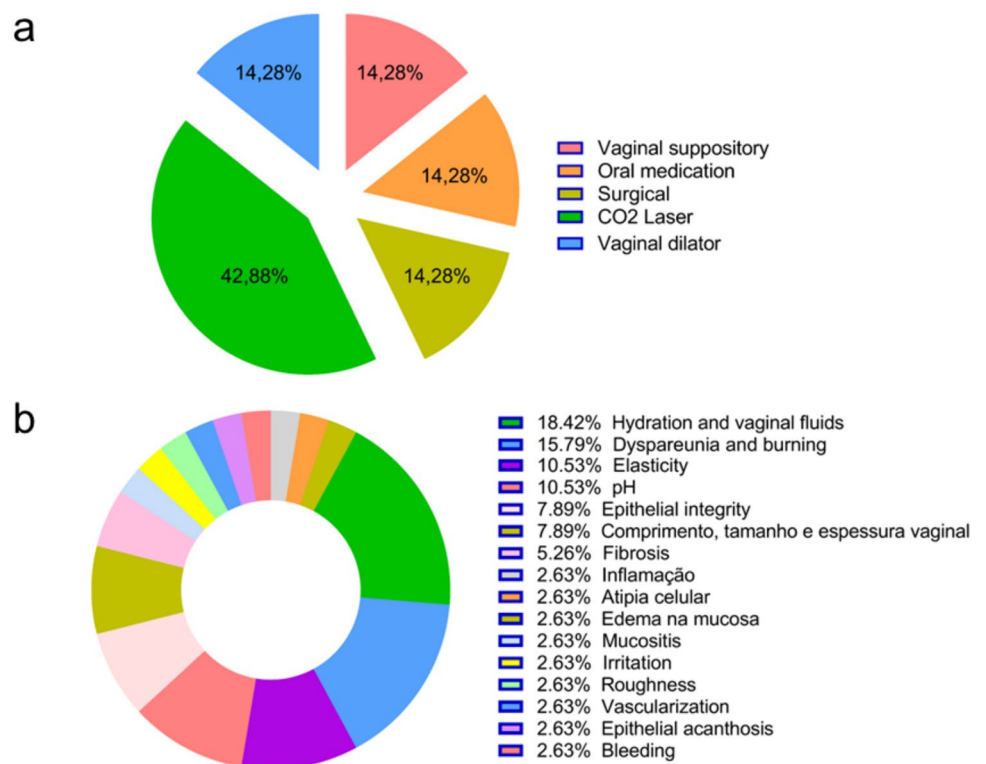


**Fig. 3** General characteristics related to **a** tumor type and **b** the treatment of choice highlighted by the included articles

**Table 1** Specific characteristics regarding cancer treatment and the study-focused groups

References	Cancer treatment
[21]	Not specified
[33]	External beam radiotherapy + Cisplatin + 5-fluorouracil
[22]	External beam radiotherapy + Brachytherapy + Chemotherapy External beam radiotherapy + Brachytherapy + Chemotherapy + Surgery External beam radiotherapy + Brachytherapy + Surgery External beam radiotherapy + Chemotherapy + Surgery External beam radiotherapy + Chemotherapy External beam radiotherapy + Surgery Brachytherapy + Surgery
[23]	Radiotherapy Chemotherapy Surgery
[16]	Radical hysterectomy + Bilateral salpingo-oophorectomy + Pelvic lymph node dissection Radical hysterectomy + Bilateral salpingo-oophorectomy + Pelvic lymph node dissection + Aortic lymph node sampling
[44]	Brachytherapy Chemotherapy
[46]	External beam radiotherapy Brachytherapy Surgery

**Fig. 4** General characteristics related to **a** the type of treatment chosen for vaginal atrophy by the included articles and **b** outcomes



were also evaluated, representing 15.79%. Subsequently, elasticity (10.53%), pH (10.53%), epithelial integrity (7.89%), and parameters related to vaginal size (7.89%) also showed higher frequencies in the included studies. Finally, the remaining parameters were analyzed less frequently in the works (fibrosis, inflammation, cellular atypia, mucosal

edema, mucositis, irritation, roughness, vascularization, epithelial acanthosis, and bleeding). The complete description of the type of treatment and the methodologies for evaluating outcomes is presented in Table 2.

Concerning the outcomes assessed regarding the overall (Fig. 5a) and sexual (Fig. 5b) quality of life of oncological

**Table 2** Specific characteristics regarding the treatment for vaginal atrophy and the methodologies used for the evaluation of vaginal parameters, overall quality of life, sexual, emotional, and adverse effects

References	Vaginal atrophy treatment	Vaginal parameter assessment methodology	Overall, sexual, emotional quality of life assessment methodology	Adverse effects assessment methodology
[21]	Fractionated CO2 Laser	Gynecological examination + VAS	Not evaluated	Not evaluated
[33]	LMW-HA + Vitamin E + Vitamin A	Biopsy + VAS	Not evaluated	Not evaluated
[22]	Non-ablative CO2 Laser	Gynecological examination + VHI	FSFI	Patient reports
[23]	Microfractionated CO2 Laser	Gynecological examination + VAS + VuAS	FSFI	Adverse events v4.0 (CTCAE)
[16]	Ospemifene	Gynecological examination + VHI	EORTC Quality of Life Questionnaire (EORTC QLQ-CX24)	Patient reports
[44]	Modified Laparoscopic Davydov Colpoplasty	Gynecological examination	Not evaluated	Not evaluated
[46]	Vaginal Dilator	Vaginal probe (FSFI)	(FSFI)	Not evaluated

VAS Vaginal Assessment Scale, VHI Vaginal Health Index, VuAS Vulvar Assessment Scale, FSFI Female Sexual Function Index, EORTC European Organisation for Research and Treatment of Cancer

patients with vulvovaginal atrophy undergoing treatments, various parameters were analyzed. Among the included studies, 15% did not assess any outcome related to overall quality of life, representing the majority of the works. Consequently, and subsequently, overall health status was the first and most frequently evaluated parameter, at 10% frequency in the included studies. In addition to these parameters, 5% of the studies analyzed other points related to overall health status, such as physical, emotional, cognitive, and social functioning (Fig. 5a). Regarding sexual parameters (Fig. 5b), sexual pain was the most frequently evaluated parameter (15.38%).

### Parameters with improvement after treatment completion and side effects

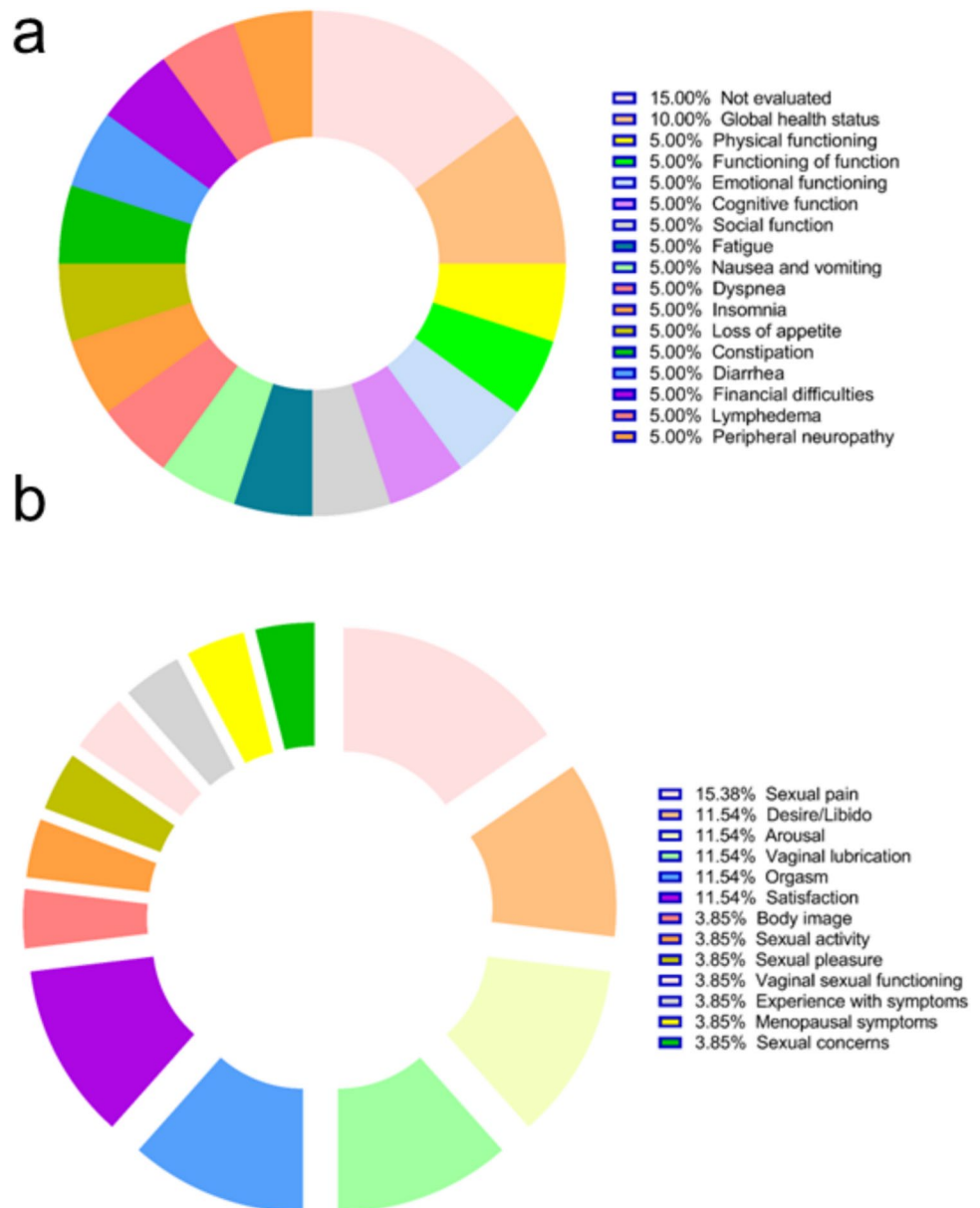
Regarding the impact of treatments on vulvovaginal atrophy in patients with gynecological cancer, the outcomes varied depending on the type of treatment and the parameters analyzed in the studies (Table 3). In general, all treatments resulted in improvement in at least one parameter, whether in the analysis of vaginal changes or in parameters related to overall, sexual, or emotional quality of life, as outlined in Table 3. Concerning side effects, only one study reported adverse effects after CO2 laser treatment, while in other works, either this parameter was not assessed, or patients did not report any side effects.

## Discussion

The present study summarizes and systematically characterizes the state of the art of therapeutic possibilities tested for vaginal atrophy in survivors of gynecological cancer. In general, the literature reveals five types of interventions: CO2 laser, hyaluronic acid, colpoplasty by modified Davydov laparoscopic procedure, ospemifene, and vaginal dilator. Regardless of the therapeutic approach used, all demonstrated potential application and safety for survivors of different types of gynecological cancers. Above all, due to their use, they showed improvement in parameters related to vaginal health and the patient herself, leading to an overall improvement in general, emotional, and sexual quality of life.

The use of CO2 laser, the most frequently mentioned treatment in the included studies (42.88%), is an alternative non-hormonal approach with potential for the treatment of vulvovaginal atrophy in oncology patients, both for breast and gynecological cancers. This study demonstrated that the three included studies using this approach reported improvement in the vaginal health index (in symptoms such as dryness, dyspareunia, burning, introitus pain, pH, vaginal length, etc.). However, they did not show any significant improvement in the sexual health of

**Fig. 5** Outcomes assessed regarding overall **a** and sexual **b** quality of life



the patients after the end of the analyzed period in each study [21–23].

Currently, treatments such as creams, gels, moisturizers with or without hormones, and vaginal dilators are available to combat vaginal atrophy [24, 25]. However, these interventions may have some disadvantages compared to the use of CO2 laser. Topical treatments are reported to be uncomfortable and difficult to adhere to due to the method of application, and may develop side effects such as vaginal discharge, requiring continuous use for long periods to prevent symptom recurrence [26]. In another scenario, estrogen-based treatments may not be very responsive for patients who have undergone radiation therapy, as this procedure reduces receptors for this hormone [22, 25].

No articles were found comparing CO2 laser and other treatments in patients with gynecological cancer and vulvovaginal atrophy. In this regard, in postmenopausal women with GSM (genitourinary syndrome of menopause), topical estrogen therapy or CO2 laser treatment were considered equivalent in improving GSM symptoms [27]. In another study, still in postmenopausal patients, it was demonstrated that CO2 laser therapy associated with topical estriol resulted in improvement in vaginal dryness and dyspareunia, while estriol monotherapy resulted in worse outcomes [28]. Additionally, the use of CO2 laser was shown to be more effective than some topical treatments such as promestriene cream or lubricants in postmenopausal women [29, 30].

**Table 3** General characteristics regarding the effects of different treatments for vaginal atrophy in patients with gynecological cancer

References	Intervention	Parameters with improvement	Reported adverse effects
[33]	LMW-HA + Vitamin E + Vitamin A	Treatment reduced inflammation, cellular atypia, fibrosis, bleeding, pain, and mucositis	Not reported
[16]	Ospemifene	Treatment increased elasticity, fluid volume, epithelial integrity, moisture, and vaginal pH; Improvement in overall health, emotional and social functioning, body image, and sexual pleasure; Reduction in scores of sexual symptom experience and concern	No side effects reported
[44]	Modified laparoscopic Davydov colpoplasty	Clinical examination after four months of surgery demonstrates gratifying size and elasticity of the new vaginal cavity	No side effects reported
[21]	Fractionated CO2 laser	Treatment improved dryness, dyspareunia, burning, introitus pain, and pH	No side effects reported
[22]	Non-ablative CO2 laser	Treatment induced improvement in vaginal length, vaginal health index, and female sexual function index	Cystitis (1 patient) and spots (1 patient)
[23]	Fractionated CO2 laser	Although some patients showed improvement in some vaginal parameters, no improvement was considered statistically significant; Treatment induced improvement; Improvement in female sexual function index (orgasm and desire);	No side effects reported
[46]	Vaginal dilator	Increase in vaginal length;	Vaginal discharge; Vaginal dryness; Vaginal pain; Vaginal inflammation

In fact, the use of CO2 laser induces the restoration of the vaginal epithelium, with ultrastructural changes such as thickening of the stratified squamous epithelium, increased collagen and mucopolysaccharides support, increased glyco-gen supply in epithelial cells, increased fibroblasts, increased local vascularization, and the presence of subepithelial papillae [31, 32]. Moreover, no treatment induced serious adverse effects for the patients, suggesting a safe therapeutic scheme and impact. However, further studies focused on morphological and molecular aspects are needed for a better understanding of the biological mechanisms.

Another form of non-hormonal intervention is based on the vaginal administration of hyaluronic acid and vitamins A and E. An included article focused on the use of this type of treatment for patients with cervical cancer. In this study, the treatment was able to reduce inflammation, cellular atypia, fibrosis, bleeding, pain, and mucositis, demonstrating that this type of intervention can be used in the context of vaginal atrophy in patients with cervical cancer [33].

Clinical studies demonstrate that formulations of hyalu-ronic acid such as liquids, gels, or suppositories can be used to reduce vaginal pain, dyspareunia, vaginal pH, vaginal dry-ness, vaginal itching, and burning sensation, consequently improving the vaginal health index and reducing vaginal atrophy [34, 35]. Gold et al. (2013) demonstrated that this intervention had an impact similar to CO2 laser treatment

in the same group [36]. Another example reported in the literature (postmenopausal breast cancer survivors) is the combination of hyaluronic acid with platelet concentrate for intramucosal administration (vaginal or vulvar). In this case, the treatment improved vaginal dryness, dyspareunia, and enhanced hydration and integrity of the vaginal epithe- lium, consequently improving the vaginal health index [37]. Hyaluronic acid is a glycosaminoglycan present and essen- tial in the extracellular matrix, with a crucial lubricating and hydrating function. Widely known for its water-binding capacity, which is associated with its hydrating ability in the body [38]. By associating with water in the tissue, this phenomenon can improve vaginal dryness in oncological patients.

Ospemifene was also used with the aim of improving vaginal atrophy. Unlike the treatments mentioned earlier, ospemifene is an agonist/antagonist of the estrogen recep- tor, also known as a selective estrogen receptor modulator (SERM) [16]. It is indicated for the treatment of moderate to severe vaginal atrophy in postmenopausal women, especially for those who have contraindications or are not candidates for local estrogen therapy [39]. The included study demon- strated that this intervention, increased elasticity, fluid vol- ume, epithelial integrity, moisture, and vaginal pH. Moreo- ver, it was also able to improve overall health, emotional and social functioning, body image, and sexual pleasure [16].



Indeed, ospemifene promotes improvement in vaginal pH, vaginal dryness, petechiae, paleness, friability, and redness of the vaginal mucosa are also parameters for which the treatment has been reported to be effective [14, 40]. Additionally, this intervention is capable of inducing collagen production (preferably type 1) in both the vaginal mucosa and vestibule, which has been associated with increased resistance and strength of the vaginal tissue [41]. Ospemifene treatment reduce pain during sexual intercourse and increasing desire and arousal [42, 43]. Therefore, ospemifene can be considered as a treatment for survivors of gynecological cancers with vulvovaginal atrophy.

Only one surgical procedure was used in the studies included in this work: modified laparoscopic Davydov colpoplasty. In this case report, a 36-year-old survivor of vaginal cancer, who underwent chemotherapy and radiotherapy, reported significant vaginal atrophy with vaginal shortening [44]. The Davydov procedure involves creating a neovagina using a part of the pelvic peritoneum [45], followed by bilateral nymphoplasty of the small lips to create the lower cutaneous part of the neovagina. In this study, sexual function was not assessed because the patient had not resumed sexual activity at the first post-procedure consultation (4 months) [44].

Therapy based on vaginal dilators has also been used in patients with endometrial cancer during the process of radiotherapy or surgery. The study included in this work demonstrated that the use of vaginal dilators induces the maintenance of vaginal length and an increase in sexual satisfaction, both in women who underwent surgery alone and in women who received adjuvant radiotherapy [46]. However, there is still much discussion about how this type of intervention should be used. Miles and Johnson (2014) concluded that there is data suggesting that dilation may be harmful, with a rare possibility of vaginal rupture [25]. Conversely, other studies show that the use of dilators, even minimally, reduces vaginal stenosis after radiotherapy [47–49] and improves sexual quality of life [46].

Although the articles represent potential treatments for GSM, they have limitations: (1) a small number of included patients, (2) analysis of long-term side effects, (3) short intervention time, (4) lack of emotional, sexual, and social analysis, (5) methodologies consisting only of a clinical perspective and a lack of histological and molecular analyses, and (6) analysis of short-term outcomes. In addition, the extraction and interpretation of the evaluated outcomes are complex due to the lack of standardization of terms found in the included studies.

## Conclusion

All the treatments mentioned here (CO<sub>2</sub> laser, hyaluronic acid, modified laparoscopic Davydov colpoplasty, ospemifene, and vaginal dilator) hold potential in the

context of the study, whether by improving parameters of vaginal health or sexual and emotional well-being. However, further studies are needed for the development of treatments for vaginal atrophy in gynecologic oncology patients.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00404-024-07552-9>.

**Author's contribution** AG Medeiros: Search of databases, Titles and abstracts analysis, Data collection, Inclusion/exclusion criteria, Project development, Data analysis, Manuscript writing/editing. MMM Cintra: Data collection, Project development, Data analysis, Manuscript writing/editing. MA Reis: Data analysis, Project development, Manuscript writing/editing. LP Rocha: Data analysis, Project development, Manuscript writing/editing. JR Carmo Neto: Search of databases, Titles and abstracts analysis, Data collection, Definition of inclusion/exclusion criteria, Project development, Data analysis, Manuscript writing/editing. JR Machado: Definition of the research question, Protocol definition, Inclusion/exclusion criteria, Data analysis, Manuscript writing/editing.

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**Data availability** The authors confirm that the data supporting the findings of this study are available within the article.

## Declarations

**Conflict of interest** The authors have no relevant financial or non-financial interests to disclose.

**Ethical approval** Ethics committee approval is not required to carry out systematic review research.

**Consent to participate** Not applicable for systematic review manuscripts.

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