Gynecologic Oncology 170 (2023) 123–132

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Vaginal changes, sexual functioning and distress of women with locally advanced cervical cancer treated in the EMBRACE vaginal morbidity substudy

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HIGHLIGHTS

- Physician-assessed vaginal changes and patient-reported functioning problems were assessed in cervical cancer survivors.
- Physician-assessed vaginal changes were mostly mild, such as grade 1 mucositis (13%) and stenosis (37%) at 24 months.
- Almost half of sexually active women reported vaginal functioning problems over 2-years.
- Rates of substantial sexual problems (20%) and sexual distress (8%) were relatively low in sexually active women.
- No or only small associations between vaginal changes and functioning problems and sexual distress were found.

ARTICLE INFO

Article history:
Received 19 October 2022
Received in revised form 5 January 2023
Accepted 5 January 2023
Available online 20 January 2023

Keywords:
Cervical cancer
Brachytherapy
Adaptive radiotherapy
Vaginal changes
Sexual functioning
Sexual distress

ABSTRACT

Objective. The EMBRACE-vaginal morbidity substudy prospectively evaluated physician-assessed vaginal changes and patient-reported-outcomes (PRO) on vaginal and sexual functioning problems and distress in the first 2-years after image-guided radio(chemo)therapy and brachytherapy for locally advanced cervical cancer.

Methods. Eligible patients had stage IB1-IIIB cervical cancer with ≤5 mm vaginal involvement. Assessment of vaginal changes was graded using CTCAE. PRO were assessed using validated Quality-of-Life and sexual questionnaires. Statistical analysis included Generalized-Linear-Mixed-Models and Spearman's rho-correlation coefficients.

Results. 113 eligible patients were included. Mostly mild (grade 1) vaginal changes were reported over time in about 20% (range 11–37%). At 2-years, 47% was not sexually active. Approximately 50% of the sexually active women reported any vaginal and sexual functioning problems and distress over time; more substantial vaginal and sexual problems and distress were reported by up to 14%, 20% and 8%, respectively. Physician-assessed vaginal changes and PRO sexual satisfaction differed significantly ($p \leq .05$) between baseline and first follow-up, without further significant changes over time. No or only small associations between physician-assessed vaginal changes and PRO vaginal functioning problems and sexual distress were found.

Conclusions. Mild vaginal changes were reported after image-guided radio(chemo)therapy and brachytherapy, potentially due to the combination of tumors with limited vaginal involvement, EMBRACE-specific treatment optimization and rehabilitation recommendations. Although vaginal and sexual functioning problems and sexual distress were frequently reported, the rate of substantial problems and distress was low. The lack of association between vaginal changes, vaginal functioning problems and sexual distress shows that sexual functioning is more complex than vaginal morbidity alone.

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https://doi.org/10.1016/j.ygyno.2023.01.005

1. Introduction

The combination of modern image-guided external beam radiotherapy with concurrent cisplatin-based chemotherapy and image-guided adaptive brachytherapy (EBRT+IGABT), as developed and implemented by the international collaborative EMBRACE-group (international studies on MRI-guided brachytherapy in locally advanced cervical cancer [1]), has substantially improved local disease control and survival in cervical cancer patients, and led to reduced toxicity compared to older treatment techniques [2–4]. A growing number of cervical cancer survivors, mostly young or middle-aged, may still experience long-term bowel and bladder symptoms, fatigue and sexual problems that may compromise their health-related quality of life (QoL) [5–9]. Sexual problems experienced by survivors include decreased sexual desire, arousal, enjoyment, satisfaction and vaginal functioning problems during intercourse or other sexual activity, such as pain, reduced lubrication, tightening and shortening of the vagina, and blood loss at sexual activities [7,8,10,11]. These adverse effects of radiotherapy (RT) may be caused by treatment-induced morphological vaginal mucosal changes, known as vaginal morbidity (VM) [12].

Common vaginal changes after EBRT+IGABT include mucositis, changes to the microvasculature leading to atrophy, telangiectasia, reduced lubrication, adhesions, and fibrosis in the upper vagina which may lead to vaginal stenosis and shortening. Only in very rare cases ulceration, necrosis and fistulae are seen [13,14]. Vaginal changes are mostly rated by physicians as low-grade adverse events according to Common Terminology Criteria for Adverse Events (CTCAE), and their direct impact on sexual QoL remains unclear [7,15,16]. As vaginal functioning problems are experienced by patients during sexual activity, and vaginal mucosal changes are observed by the physician during vaginal examination, the consequences of these vaginal mucosal changes for vaginal and sexual functioning vary between individuals. Some women do not report vaginal functioning problems even when significant mucosal changes are observed, while others experience persisting sexual problems with clinically minor mucosal changes [17]. It has been shown that vaginal functioning problems are associated with sexual distress, defined as distress regarding sexual activity or worries about painful intercourse [18]. However, sexual functioning problems in terms of sexual health (desire, arousal, orgasm, sexual satisfaction, and sexual enjoyment) may not be related only to vaginal functioning problems. As sexual functioning problems are a complex interplay between physiological, psychological and relationship factors, there remains a lack of knowledge to which extent these factors are relevant for overall sexual functioning of cervical cancer survivors. Improved understanding of vaginal mucosal changes and the relation to vaginal functioning problems as experienced by survivors will provide rationale and focus for strategies to improve their sexual health. The VM substudy was initiated to evaluate physician-assessed vaginal changes and patient-reported outcomes (PRO) on vaginal functioning problems, sexual functioning problems and sexual distress in the first 2-years after treatment; and the association between physician-assessed vaginal changes and PRO.

2. Method and materials

The VM study was a prospective longitudinal study designed as a substudy of the EMBRACE-I study and continued during initial years of the EMBRACE-II study [1]. The background, rationale, design, and results of the EMBRACE-studies have been published previously [2,3]. Recruitment and data collection for the VM substudy were conducted in 6 of 24 gynecologic radiation oncology centers participating in the EMBRACE-I study. The VM substudy was approved in all participating centers by their Ethics Committees.

Women who participated in the EMBRACE-studies were eligible for the VM substudy when diagnosed with cancer of the uterine cervix, Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) 2009 stage IB1-IIIB, with biopsy-proven squamous-cell carcinoma, adenocarcinoma, or adeno-squamous cell carcinoma, with no or only limited (≤5 mm) vaginal involvement. Exclusion criteria were pre-existent major vaginal morbidities, or severe medical or psychological conditions. All participating women provided written informed consent.

2.1. Treatment

Women were treated in accordance with the EMBRACE-I or II protocols [1–3,6]. In summary, pelvic EBRT was given either by three-dimensional (3D) conformal or intensity-modulated radiation therapy (IMRT) to a total dose of 45–50 Gy in 1.8–2 Gy daily fractions, with concomitant weekly cisplatin chemotherapy (≥5 cycles of cisplatin 40 mg/m^2), and IGABT to a total dose of 30–50 Gy EQD2 specified to the high-risk clinical target volume (HR-CTV). Target volume doses and constraints for organs at risk (OAR) were according to the EMBRACE protocols. In the VM substudy, all women received counseling on sexual rehabilitation after treatment and a set of four different dilators was made available to them (free of cost). Women were recommended to start dilation 4–6 weeks after treatment (after resolving of acute VM), for at least 3 times per week at least during the first 2-years after treatment.

2.2. Assessments

In addition to the EMBRACE assessments on disease, morbidity and QoL, the VM substudy included a detailed extra VM assessment by vaginal and pelvic examination and additional questionnaires on vaginal and sexual functioning problems and sexual distress. Timepoints of clinical assessments were baseline, 4–6 weeks after completion of treatment, and at 3, 6, 12 and 24 months follow-up. PRO questionnaires were completed at the same timepoints, except for 4–6 weeks.

2.2.1. Vaginal morbidity assessed by the physician

Vaginal morbidity was assessed by the treating radiation oncologists and/or gynecologic oncologists. The Common Terminology Criteria for Adverse Events (AE) version 3 (CTCAE v3.0) and a detailed and comprehensive assessment protocol were used to grade vaginal changes, including dryness, stenosis, mucositis, and bleeding (for CTCAE definitions see supplementary table S1). Vaginal length and width were measured with standardized cylinders. Vaginal adhesions, fibrosis, telangiectasia, mucosal color, fragility/bleeding, and ulceration were scored on four or five-point scales. The scoring was based on a comprehensive photographic atlas with detailed description of morphological vaginal changes as assessed with vaginoscopies (for details see Kirchheiner, 2012 [12]).

2.3. Patient-reported outcomes (PRO)

The PRO measurements consisted of a combination of internationally established and validated questionnaires. *Vaginal functioning problems and sexual distress* were assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynecological Cancer Module (EORTC QLQ-CX24, completed in

conjunction with the EORTC QLQ-C30 core questionnaire [19,20] and the Sexual Activity Questionnaire (SAQ [21]). *Sexual functioning problems* were assessed with the EORTC QLQ-CX24 [20] and the gynecologic Leiden Questionnaire (LQ [22]).

The SAQ also includes a section regarding reasons for sexual inactivity [21]. Women who were not sexually active were asked to indicate the reasons and if they would like to become sexually active again. Finally, all women were asked how important sexuality in general was for them.

2.4. Statistical methods

While the overall study design was explorative without restriction of exact case number calculation, a total number of at least 100 women was intended for prospective evaluation of vaginal changes and patient-reported outcomes, and approximately 40 of these 100 women were expected to be sexually active, based on the proportion of sexually active women in the EMBRACE-I study. Data were reported with mean (*M*) and standard deviation (*SD*) or median (*Md*) and interquartile range (IQR). Proportions were given as number of women with and without the characteristic and as a percentage (mean and range). Statistical significance was considered for $p \leq .05$. Analyses were conducted with the Statistical Package for Social Scientists (SPSS, version 25) and the Generalized-Linear-Mixed-Models (GLMM)-adaptive package in R.

To evaluate differences between physician-assessed vaginal changes and patient-reported sexual functioning problems and sexual distress at baseline (pre-treatment) and the follow-up moments, a GLMM analysis based on the continuation ratio model for ordinal data was conducted [23]. The GLMM models handle missing values as 'missing at random'. The scores on vaginal changes, patient-reported sexual functioning problems and sexual distress were entered as dependent variables, with 'patient' as random effect and 'follow-up moments (time)' as fixed factors. When ≤5 women scored in one category (e.g. CTCAE grade 3), this category was merged with one category below (e.g. grade 2). The same method was used to evaluate potential differences between vaginal changes, and patient-reported sexual functioning problems and sexual distress immediately after treatment and subsequent follow-up moments, using Wald tests based on appropriately defined contrasts. Due to the limited number of sexually active women, we refrained from analysis of changes over time for these PRO results because of lack of power. Spearman's rho correlation coefficients (*r*) were conducted to examine the associations between the physician assessments and patient-reported vaginal and sexual functioning problems. Observations were pooled over all timepoints of follow-up. We report associations with an effect size of medium and above ($r \geq 0.3$) [24].

3. Results

3.1. Participants

Between June 2012 and November 2018, a total of 118 women were included in the VM substudy; 5 women were excluded because vaginal involvement at diagnosis exceeded 5 mm, leaving 113 women in the analysis. Data of 36 women (32%) were not available at different timepoints during the 24 month-follow-up period (for an overview, see Fig. 1): 22 women (20%) died because of the disease, and for 13 women (12%) data were largely incomplete due to non-compliance with assessments or follow-up.

Patient, disease and treatment characteristics are summarized in Table 1. The characteristics of the VM study cohort differed from the overall EMBRACE cohorts regarding FIGO stage and vaginal tumor extension. These differences were reflected in several treatment parameters (key characteristics are depicted in supplementary table S2). Results of QoL functioning and symptom subscales over time are provided in supplementary tables S3. and S4. In line with findings of previous EMBRACE reports, fatigue and insomnia were present at baseline and slightly increased after treatment, after which they remained at similar rates over the follow-up period (supplementary table S3) [9,15].

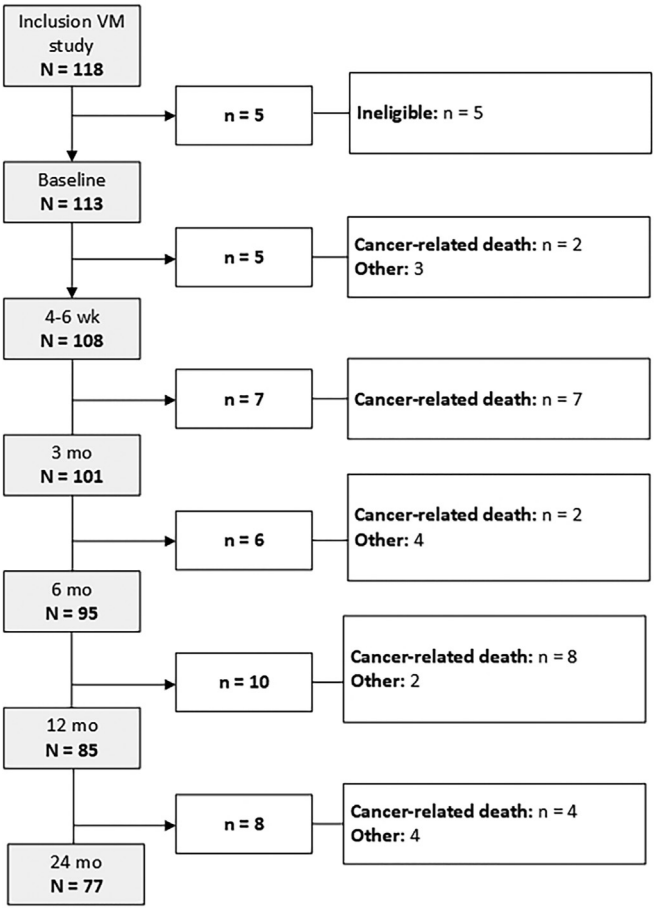

Fig. 1. Inclusion overview and reasons of data unavailable per timepoint.
mo = months; N = total sample; n = subsample; Other = non-compliance with assessments or follow-up; VM = vaginal morbidity; wk. = weeks.

3.2. Vaginal changes assessed by the physician

Significant differences between baseline and follow-up were found for all physician-assessed vaginal changes (See Figs. 2A and 2B-II-VIII). However, for most vaginal changes, there was no further change between the first and later follow-up timepoints. The prevalence rates of physician-reported vaginal mucositis, width, fibrosis, and adhesions significantly differed between 4–6 weeks and later follow-up timepoints. In more detail, the prevalence rates for grade 1 vaginal dryness increased from 17% at 4–6 weeks to 23% at 6 months and slightly decreased again to 18% at 24 months. Grade 1 stenosis gradually increased from 11% at 4–6 weeks to 37% at 24 months. The prevalence rates for grade 1 vaginal mucositis decreased over time from 29% at 4–6 weeks to 13% at 24 months. Grade 1 vaginal bleeding, at baseline caused by the tumor, decreased from 44% to 15% at 4–6 weeks post-treatment, with no further changes over time. During follow-up, vaginal morbidity prevalence of moderate (up to 2% grade 2 on average) and especially severe (<1% grade 3 on average) -related adverse events of dryness, stenosis, mucositis and bleeding were rare. The median vaginal length assessed by physicians varied over time between 9 and 10 cm. For vaginal width, 3 cm and 3.5 cm were most often reported, at all timepoints. Regarding the degree of fibrosis, in most women (79%, range: 72–89%) the vaginal tissue was reported to be soft and mobile

Table 1
Patient, disease and treatment characteristics in 113 EMBRACE VM study patients.

Patient and disease characteristics (at time of diagnosis) of $N = 113$ patients analyzed		
Age	Median in years (IQR)	48 (40.5–59.0)
BMI	Normal (18.8–24.9)	58 (51.3%)
	Underweight (<18.5)	5 (4.4%)
	Overweight (25–19.9)	31 (27.4%)
	Obese (>30)	19 (16.8%)
Partner	Yes	79 (69.9%)
	No	34 (30.1%)
Vaginal delivery*	Yes	53 (46.9%)
	No	15 (13.3%)
	Missing N (%)	45 (39.8%)
Menopausal status	Premenopausal	59 (52.2%)
	Postmenopausal	51 (45.1%)
	Missing N (%)	3 (2.7%)
WHO performance score	WHO PS0	85 (75.2%)
	WHO PS1	25 (22.1%)
	WHO PS2	3 (2.7%)
	WHO PS3	0
FIGO 2009 stage	1B	28 (24.8%)
	2A	5 (4.4%)
	2B	62 (54.9%)
	3A	0
	3B	16 (14.2%)
	4A	2 (1.8%)
Tumor extension in the vagina (clinical)	Not involved	91 (80.5%)
	Upper third	22 (19.5%)
	Middle third	0
Treatment characteristics (at time of diagnosis) of N = 113 patients analyzed		
EBRT PTV-E total dose	Median dose (Gy) (IQR)	45 (45–45)
	Missing N (%)	0
EBRT technique	3D conformal	20 (17.7%)
	IMRT/VMAT	93 (82.3%)
EBRT PTV-N Nodal boost	Yes	43 (38.1%)
	No	70 (61.9%)
Concomitant chemotherapy given	Yes	111 (98.2%)
	No	0
	Missing N (%)	2 (1.8%)
EBRT+BT HR-CTV D90 in EQD2	Median dose (Gy) (IQR)	91.1 (89.4–93.6)
	Missing N (%)	2 (1.8%)
Total ICRU Rectum in EQD2	Median dose (Gy) (IQR)	62.2 (57.8–65.3)
	Missing N (%)	5 (4.4%)

* Only EMBRACE-I VM study patients, not assessed in EMBRACE-II VM study patients.
Note 3D = three-dimensional; BMI = Body Mass Index; BT = brachytherapy; EBRT = external beam radiotherapy; EBRT PTV-E = external beam radiotherapy total dose prescribed to the elective planning target volume; EBRT PTV-N = external beam radiotherapy total dose prescribed to the lymph nodes planning target volume; EBRT +BT HR-CTV D90 = external beam radiotherapy + brachytherapy dose received by 90% of the high-risk clinical target volume; EMBRACE = image guided intensity modulated External beam radiochemotherapy and MRI based adaptive BRAchytherapy in locally advanced Cervical cancer; EQD2 = equivalent dose in 2-Gy fractions; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; Gy = gray; IMRT = intensity modulated radiotherapy; IQR = interquartile range; *N* = total sample; VM = vaginal morbidity; VMAT = volumetric modulated arc radiotherapy; WHO PS = World Health Organization performance status.

during the follow-up period. Adhesions in the proximal vagina were reported shortly after treatment in 20% of the women and these proportions remained comparable during follow-up. Adhesions in the middle third of the vagina were reported in 7% at 24 months. Erythema and/or moderate surface fragility with minimal bleeding at examination were reported in 14% (range: 11–17%) of the women. Telangiectasia up to 4 cm^2 had developed after treatment in 27% of the women at 4–6 weeks, increasing over time to 79% at 24 months. The mucosal color changed over time from uniform pink at baseline (95%) to mildly mottle pale (79%) at 24 months. Some superficial ulceration was reported in 6% of the women shortly after treatment, which healed over time, with none reported at 24 months.

3.3. Patient-reported sexual activity

Up to 29% of the women reported that sexuality in general was 'not at all' important in their life (see Table 2). Many women reported not to be sexually active at baseline (79%), most often because of disease related problems (54%), followed by 'loss of interest in sex' (40%). From 3 to 24 months post-treatment the proportion not being sexually active decreased to 47% at 24 months, with the most frequently reported reason being 'loss of interest in sex' (69%), followed by 'not having a partner' (47%). At three months after treatment, about 25% of the non-sexually active women stated that they would 'very much like to become sexually active again', which decreased to 6% at 24 months.

3.4. Patient-reported vaginal functioning

The time pattern of prevalence rates of vaginal functioning problems of sexually active women is shown in Fig. 3. Any vaginal tightness, shortness, dryness, and pain (response categories 'a little', `quite a bit` and 'very much') showed an immediate increase from the proportions at baseline (5%, 5%, 10%, and 20% for feelings of tightness, shortness, dryness and pain, respectively) to 3 months after treatment (51%, 47%, 46%, and 43%, respectively), when they reached a plateau. Any vaginal bleeding during intercourse or other sexual activity was most often reported at baseline (68%), being a symptom of the disease, and decreased to 39% (range: 34–43%) of the sexually active women in follow-up, being a symptom of fragility of vaginal mucosa after treatment. During follow-up, more substantial feelings of tightness, shortness, dryness, pain and bleeding during intercourse or other sexual activity ('quite a bit' and 'very much') was reported by 8%, 8%, 14%, 7% and 7% on average of the sexually active women, respectively.

3.5. Patient-reported sexual distress and sexual functioning problems

Sexual dissatisfaction decreased significantly between baseline and follow-up, with no further change between the earliest and later follow-up timepoints (see Fig. 4-II). No significant differences were found between sexual desire and worries about painful intercourse over time (see Fig. 4-I and III). In more detail, 31% of all women were 'dissatisfied' or 'very dissatisfied' with their present sexual life at baseline, which decreased to 15% at 24 months, while 24% reported being 'quite a bit' or 'very much' worried that sex would be painful at baseline, which decreased to 13% at 24 months. During the study period, up to 46% of all women reported that they 'seldom' or 'never' felt sexual desire.

Among the sexually active women, 4% reported that they 'seldom' or 'never' felt sufficient lubrication during sexual arousal at baseline, which increased to 20% at 24 months after treatment. At baseline, about 22% reported that they 'seldom' or 'never' experienced an orgasm during intercourse, which remained comparable over time (30% on average, range: 38–23%). In addition, 6% reported to 'seldom' or 'never' reached an orgasm during masturbation at baseline, which decreased to 0% at 24 months. Over all timepoints, around 20% (range: 16–25%) of the sexually active women reported that sexual activity had been 'a little' or 'not at all' enjoyable, and around 8% (range: 5–11%) reported that they were 'quite a bit' or 'very much' distressed about sexual activity.

3.6. Associations between physician-assessed vaginal changes and patient-reported vaginal functioning problems and sexual distress

There was only a significant negative association ($r = -0.34$) with a medium effect size found between patient-reported dryness and physician-assessed vaginal width, suggesting a trend for women who reported a dryer vagina to have a narrower vagina (as measured in cm) (see supplementary table S5).

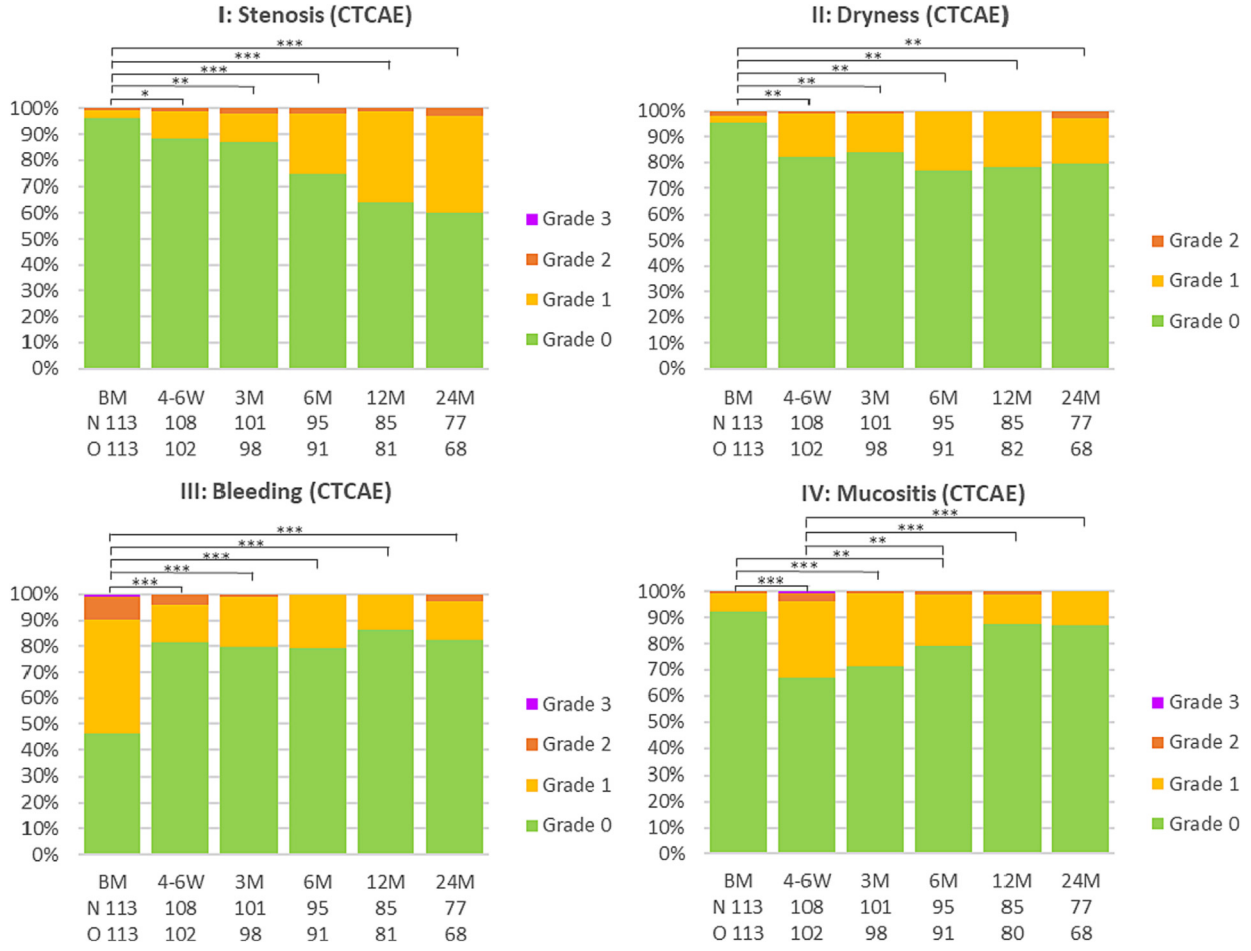

Fig. 2A. Vaginal morbidity clinical measurements over time.
The proportion of women is shown in percentages. BM = baseline measurement; CTCAE = Common Terminology Criteria for Adverse Events; M = months; N = number of women at risk at the specific timepoint, O = observed number of women at the specific timepoint.
$^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

4. Discussion

The EMBRACE-vaginal morbidity substudy prospectively evaluated physician-assessed vaginal changes and patient-reported outcomes (PRO) on vaginal and sexual functioning problems, and sexual distress in the first 2-years after radio(chemo)therapy with image-guided adaptive brachytherapy for locally advanced cervical cancer, and to explore the association between these. Mostly mild physician-assessed vaginal changes were reported, such as grade 1 (not interfering with sexual functioning) mucositis (13%) and stenosis (37%) at 24 months after treatment, without clear changes during the 2-year follow-up. Higher grades were reported in <3% of the women. Almost half of the women in the total cohort reported not being sexually active at 24 months, mostly because of losing interest in sex or lacking a partner. Any vaginal and sexual functioning problems and distress were reported by almost half of the sexually active women over 2-years after treatment. More substantial problems and distress were reported by a up to 14%, 20% and 8% of the sexually active women, respectively. Most vaginal changes and sexual satisfaction differed significantly between baseline and follow-up, without further significant change between the earliest and later follow-up moments. Vaginal functioning problems and sexual distress, as reported in the PRO outcomes, were not or only weakly associated with the physician-assessed vaginal changes.

No or only mild physician-assessed vaginal changes were reported over time for most women, and moderate and severe vaginal changes were very rare. Although mild vaginal stenosis increased after treatment, in the large majority a 'normal' range for average vaginal length [25] and width [26] were reported. An explanation for our relatively favorable results as compared to earlier literature data could be that women who were eligible for the VM substudy had no or very minimal vaginal involvement at baseline. A previous EMBRACE-I analysis showed that the risk of developing mild or moderate stenosis by 2-years after treatment was 15% for women with cancers without vaginal involvement, compared to 28% for those with vaginal involvement [27]. Martins et al. [13] found that a more advanced tumor stage (IIIA or IIIB) resulted in more frequent and severe reductions in vaginal diameter and length. With more advanced tumors with more extensive vaginal involvement a higher vaginal volume and longer segment of the vagina will receive the full target dose, resulting in more subsequent vaginal changes, especially vaginal stenosis [27,28]. As the VM study cohort consisted of women with none to limited vaginal involvement, the vaginal length receiving the full EBRT dose and a significant dose contribution from brachytherapy will have been relatively limited [28]. In addition, these women were treated according to EMBRACE protocol. It has already been shown that the EMBRACE-related dose optimization decreases vaginal VM substantially [29]. Besides, the 6 centers that participated in the VM substudy were relatively large and experienced gynecological radiation oncology centers participating in EMBRACE from early on. These centers had already introduced standard approaches for patient information and awareness on sexual issues and vaginal dilation as standard of care before the VM substudy [17,30–33]. Women

Fig. 2B. Vaginal morbidity clinical measurements over time.
The proportion of women is shown in percentages, except for vaginal length, which is shown in median length in centimeter. BM = baseline measurement; Dm = diameter; cm = centimeter; M = months; Med = Median; N = number of women at risk at the specific timepoint, O = observed number of women at the specific timepoint, W = weeks.
*p < .05, **p < .01, ***p < .001.

Table 2
Sexual activity (SAQ).

	Baseline ($N = 113$)	3 months ($N = 101$)	6 months ($N = 95$)	12 months ($N = 85$)	24 months ($N = 77$)
Importance of sexuality in general life					
Not at all	29 (25.7%)	24 (23.8%)	26 (27.4%)	25 (29.4%)	20 (26.0%)
A little	17 (15.0%)	22 (21.8%)	11 (11.6%)	17 (20.0%)	14 (18.2%)
Quite a bit	27 (23.9%)	23 (22.8%)	32 (33.7%)	18 (21.2%)	18 (23.4%)
Very much	31 (27.4%)	19 (18.8%)	17 (17.9%)	18 (21.2%)	12 (15.6%)
Missing	9 (8.0%)	13 (12.9%)	9 (9.5%)	7 (8.2%)	13 (16.9%)
Subgroup of non-sexually active women* (N)	89 (78.8%)	57 (56.4%)	41 (43.2%)	39 (45.9%)	36 (46.7%)
Reasons, because (more answers are possible)					
I do not have a partner (yes)	24 (27.0%)	19 (33.3%)	21 (51.2%)	22 (56.4%)	17 (47.2%)
I have lost interest in sex (yes)	36 (40.4%)	34 (59.6%)	23 (56.1%)	26 (66.7%)	25 (69.4%)
My partner has a problem (yes)	4 (4.5%)	5 (8.8%)	2 (4.9%)	1 (2.6%)	2 (5.6%)
Because of disease/treatment related problems (yes)	48 (53.9%)	16 (28.1%)	3 (7.3%)	3 (7.7%)	5 (13.9%)
Would you like to become sexually active again					
Not at all	25 (28.1%)	16 (28.1%)	20 (48.8%)	20 (51.3%)	20 (55.6%)
A little	7 (7.9%)	20 (35.1%)	12 (29.3%)	11 (28.2%)	7 (19.4%)
Quite a bit	18 (20.2%)	4 (7.1%)	2 (4.9%)	2 (5.1%)	2 (5.6%)
Very much	36 (40.4%)	14 (24.6%)	4 (9.8%)	4 (10.3%)	2 (5.6%)
Missing	3 (3.4%)	3 (5.3%)	3 (7.3%)	2 (5.1%)	5 (13.9%)

Note $N = 113$ at baseline, $N = 101$ at 3 months, $N = 95$ at 6 months, $N = 85$ at 12 months, $N = 77$ at 24 months. N = total sample. SAQ = Sexual Activity Questionnaire.
* Non-sexually active in the past four months (according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynecological Cancer Module (EORTC QLQ-CX24) question regarding sexual activity).

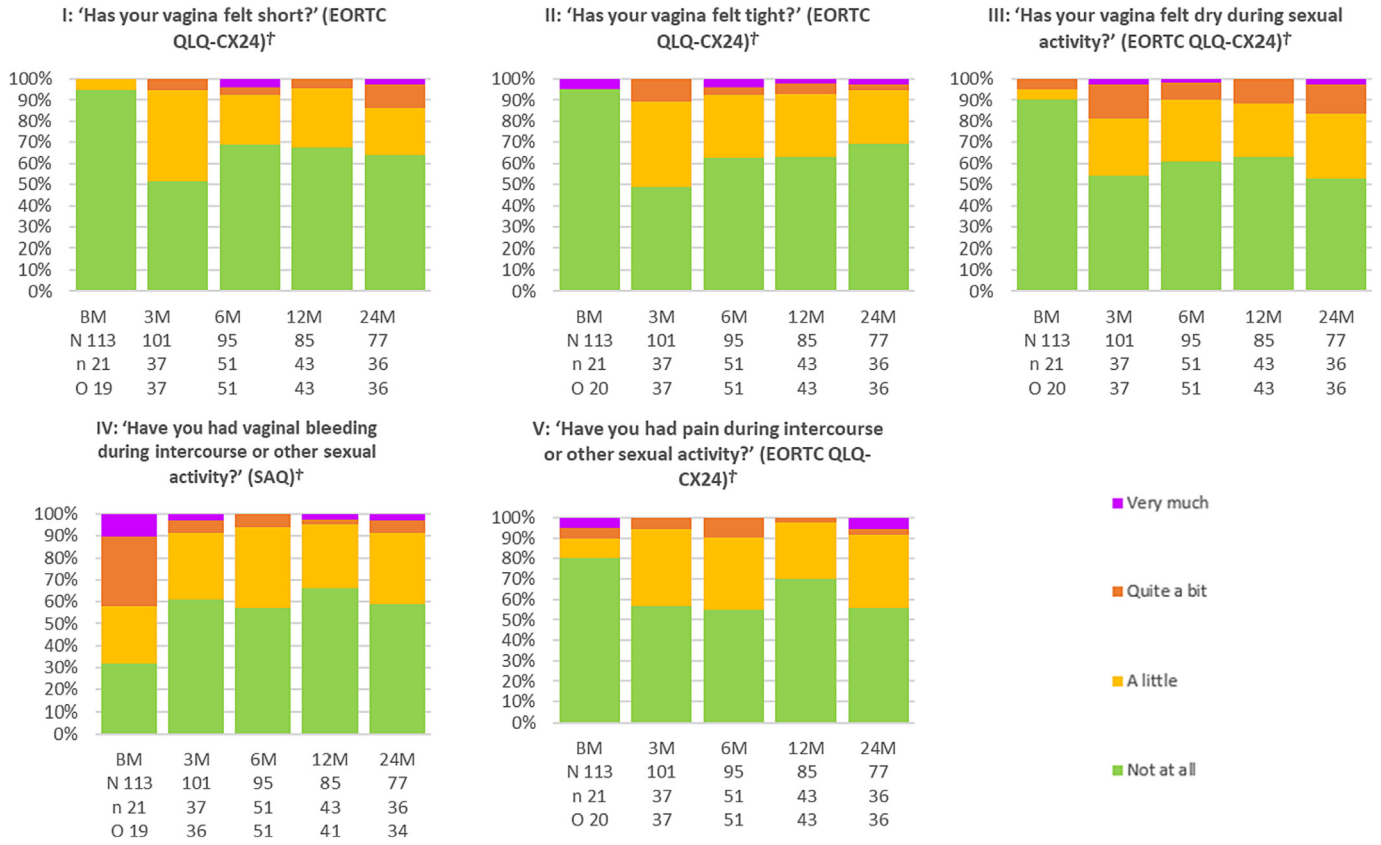

Fig. 3. Patient-reported vaginal functioning problems of sexually active women in the past four weeks on single item level over time.
The proportion of women is shown in percentages with the answer categories "not at all", "a little", "quite a bit" and "very much". BM = baseline measurement; EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynecological Cancer Module; M = months; N = number of women at risk at the specific timepoint, n = number of sexually active women at risk at the specific timepoint, O = observed number of women at the specific timepoint, SAQ = Sexual Activity Questionnaire.
†GLMM-analysis were only conducted with PRO including the total population, so not with PRO including the sexually active subgroup only.

who chose to participate in the VM study were also likely to be motivated to comply to vaginal dilation and resume sexual activities (now or when no partner present, with future partners), as they were also regularly reminded by receiving the follow-up measurements and questionnaires regarding these topics. Martins et al. [33] showed that daily vaginal dilator use positively influence the maintenance of sexual activity with less discomfort, preventing the progression from grade 1 to grade 2 stenosis. Women in the VM study who were under 50 years of age at diagnosis were recommended to receive hormonal replacement therapy until age of about 50.

The VM results show that only about one out of four women were sexually active before treatment, most likely due to symptoms of their cervical cancer, and that sexual activity increased to only about half of the women at 24 months. Even in this motivated cohort of women participating in the VM study, the proportion resuming sexual activity remained relatively low. Previous studies reported similar prevalence rates of sexual activity varying between 40 and 60% after treatment for cervical cancer survivors with primary chemoradiation and brachytherapy [7,10,34,35]. Importantly, these rates are like those reported after radical surgery alone, and after surgery with postoperative EBRT, thus suggesting that the diagnosis and treatment of cervical cancer as such has a profound impact on subsequent sexual functioning, activity and distress [10,34].

Compared to the analysis of the EMBRACE-I cohort [7], sexually active women in the VM substudy reported less often substantial vaginal functioning problems such as vaginal dryness, shortness, tightness, or pain during sexual activity. The reported prevalence rates of substantial vaginal functioning problems, sexual functioning problems and sexual distress in an older, non-EMBRACE study cohort [35] were even higher, with 40% reporting vaginal dryness, 29% vaginal shortening and tightening, 17% vaginal pain during intercourse, and 35% persistent lubrication problems, compared to 12% dryness, 5% shortening and 7% tightening, 2% pain and 4% lubrication problems in our study at 12 months after treatment. In addition to the more favorable selection of motivated patients in the VM substudy, excluding tumors with more than minimal vaginal involvement, the EMBRACE-treatment standards may have added to reduction of severe changes. While vaginal bleeding during intercourse was a symptom of the disease before treatment, about a third of the women reported minor bleeding during sexual activity or examination at 24 months, in line with previous data [35,36].

Even though most of the women in the VM study had no or only mild physician-reported vaginal changes over time, any vaginal functioning problems (mild to substantial) were reported by half of the sexually active women. These findings highlight the complexity of interpreting sexual outcomes. In the current study, even after pooling observations over all timepoints of follow-up, we found that the subjective perception of vaginal changes and sexual distress as experienced by the women during sexual activity were not or only weakly associated with the objective assessments of the physicians. Previous studies that compared physician-assessed vaginal CTCAE items and patient-reported symptoms also showed that there is a high level of discrepancy between objective and subjective symptoms [37,38]. This underlines the necessity of reporting both physician-assessed and patient-reported vaginal functioning problems for a complete evaluation of changes after cervical cancer treatment, as done in the VM study. In addition, as vaginal functioning problems such as pain, and feeling of a tight, short and/or dry vagina are subjective symptoms, they can be influenced by additional biopsychosocial factors, such as pelvic floor

Fig. 4. Patient-reported sexual functioning problems and sexual distress on single item level over time.
The proportion of women is shown in percentages. BM = baseline measurement; EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Gynecological Cancer Module; LQ = gynecologic Leiden Questionnaire; M = months; N = number of women at risk at the specific timepoint, n = number of sexually active women at risk at the specific timepoint, O = observed number of women at the specific timepoint, SAQ = Sexual Activity Questionnaire.
Panel II: *p < .05, **p < .01, ***p < .001. Panel I and III: # No significant differences were found. †‡ GLMM-analysis were only conducted with PRO including the total population, so not with PRO including the sexually active subgroup only.

functioning, menopause and infertility as result of treatment, fatigue, and relationship and work-related problems. Interpretation of vaginal functioning problems in relation to these factors might be helpful.

Substantial sexual functioning problems, such as 'seldom' or 'never' reaching an orgasm during masturbation, 'seldom' or 'never' lubricated during sexual arousal and 'a little' or 'not at all' enjoyable sex, were reported by up to 20% of the sexually active women. For 'seldom' or 'never' reaching an orgasm during sexual intercourse, this percentage was higher (30%), however, from previous research we know that for many women sexual intercourse alone is not the best stimulus to climax [39]. Therefore, we did not define this as a substantial sexual problem. For sexual distress, approximately 30% of all women reported being 'a little', 'quite a bit' or 'very much' worried that sex would be painful at 24 months. This result is comparable with findings of a previous study, where 29% of all women were worried about painful intercourse after treatment for cervical cancer, even when in their cohort the minority (29%) received EBRT and brachytherapy [18]. Bakker [18] also showed that higher levels of vaginal functioning problems were associated with higher levels of sexual distress. In a subsequent study a nurse-led intervention for sexual rehabilitation after cervical cancer treatment with EBRT and brachytherapy was developed and pilot tested, aiming to reduce such distress and improve sexual outcomes by coaching women to use vaginal dilation and resume sexual activities [40]. The effects of frequency of dilator use and early resuming and frequency of sexual activity in the VM study on vaginal and sexual functioning problems and distress will be further evaluated and be topic of a subsequent analysis.

This non-randomized study has obvious limitations. Although the CTCAE is the most comprehensive grading system, the reporting of vaginal changes relies on the thoroughness and interpretation of vaginal and pelvic examination, which can be cumbersome for the patient both before and after treatment. However, both physicians and patients were strongly motivated by the rational and the standardized structure of the VM-study protocol. Another limitation is that the time frame of the questions of the EORTC QLQ-CX24 [20] is set with 'in the past 4 weeks'. Women who were sexually active before, but not during the past 4 weeks might be inaccurately categorized as inactive. The proportion of vaginal functioning problems for such women could therefore have been underestimated, as these might have contributed to very infrequent sexual activity. In addition, although the questions of the EORTC QLQ-CX24 are vaginal penetration oriented, 'sexual activity' is not well operationalized, leading to a lack of knowledge regarding the meaning in terms of vaginal intercourse or any other sexual activity,

both in the EORTC QLQ-CX24 and SAQ [21]. Although standard approaches for patient information and coaching on sexual issues and recommendations for vaginal dilation were included in the VM study, there was no information on compliance of centers with such rehabilitation measures.

In conclusion, in the EMBRACE VM substudy, most of the women treated with primary radio(chemo)therapy and image-guided brachytherapy for locally advanced cervical cancer had no or only mild vaginal changes over time. The results are favorable compared to previous data, potentially due to the combination of no or only limited vaginal involvement and EMBRACE-related dose optimization and rehabilitation recommendations. About half of the women were sexually active at 24 months after treatment, and although any vaginal and sexual functioning problems and distress were frequently reported, the rate of more substantial vaginal and sexual functioning problems was relatively low. The lack of association between vaginal changes, vaginal problems and sexual distress shows that sexual functioning is much more complex than vaginal morbidity alone.

Author contributions

Study conception and design: Kirchheiner, Nout, Sturdza, Van Limbergen, Lindegaard, Jürgenliemk-Schulz, Chargari, Tanderup, Pötter.

Analysis and interpretation of data: Suvaal, Putter, ter Kuile, Kirchheiner, Nout, Creutzberg.

Drafting of manuscript: Suvaal, ter Kuile, Kirchheiner, Nout, Creutzberg.

Critical revision: all authors.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Acknowledgements

The EMBRACE-vaginal morbidity substudy was supported by Elekta AB and Varian Medical Systems through unrestricted research grants and study sponsoring through the Medical University of Vienna. We acknowledge the principal investigators at the participating centers (Aarhus University Hospital, Institute Gustave-Roussy, Leiden University Medical Center, Medical University of Vienna, University Hospitals Leuven, University Medical Center Utrecht) for all their work and involvement in the EMBRACE-vaginal morbidity substudy. We are greatly indebted to the women who participate in the substudy and complete the questionnaires over the years.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.01.005.

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