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Title Page

Title

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Running title

Vaginitis, a neglected side effect of radiotherapy

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Vaginal mucositis in patients with gynaecological cancer undergoing (chemo-)radiotherapy: A retrospective analysis

Abstract

Purpose

The objective of this retrospective analysis was to determine the incidence and extent of vaginal mucositis (VM) in women with gynaecological cancer undergoing external (chemo)radiation therapy (CRT).

Methods

A retrospective analysis was set up to collect data on the incidence and severity of VM in women treated with external pelvic RT for gynaecological cancer at the Jessa Hospital, Hasselt and ZOL, Genk, BE between January 2017 and June 2018. At the start and end of their external (C)RT, they rated the frequency and intensity of five common symptoms of VM.

Results

33 patients treated with RT for gynaecological cancer met the inclusion criteria. A non-negligible proportion of patients already experienced at least one VM symptom to any degree before the start of RT, a proportion that further increased toward the end of the RT (73%). At the end of RT, on average, about 25% of these patients reported moderate-to-severe symptoms (against about 7% before the (C)RT).

Conclusion

These results suggest that VM is a rather frequent side effect in gynaecological cancer patients that aggravates during treatment up to a moderate severity level. Although the small sample size, these data highlight the need for attention to VM.

Summary statement

What is already known about this topic?

Radiotherapy plays an important role in the treatment of gynaecological malignancies. A debilitating complication in patients undergoing pelvic radiotherapy is vaginal mucositis, an inflammation of the vaginal mucosal lining. To date, the incidence of vaginal mucositis is still not well documented.

What this paper adds?

A non-negligible proportion of patients already experienced at least one symptom related to vaginal mucositis before the start of radiotherapy. Most patients presented mild to moderate vaginal mucositis symptoms at the end of external pelvic radiotherapy. Burning sensation, pruritus, and pain were the most frequently documented radiotherapy-induced complications.

The implications of this paper:

Vaginal mucositis is an underrated side effect of pelvic radiotherapy that needs to be tackled multidisciplinary by a team of nurses, radiotherapists, oncologists, and gynaecologists. The team should tackle the complication from the start of radiotherapy by using the most appropriate measures. Due to a possible link between acute vaginal mucositis and late vaginal toxicity, the team needs to follow-up patient's post-radiotherapy to support patients in late complications and advise/encourage patients in performing vaginal dilatation to prevent vaginal stenosis.

Keywords

Gynaecology; Gynaecologic cancer; Oncology; Radiotherapy; Vaginal mucositis; Vaginitis

Main Text

Introduction

In 2018, worldwide 1 013 751 women were diagnosed with a gynaecological malignancy and this number is expected to increase with up to 500 000 new cases in 2040 (Ferlay *et al.*, 2019). Gynaecological malignancies are heterogeneous diseases with varying risk factors and treatment protocols. Radiation therapy (RT) plays an important role in the management of gynaecological cancers and consists of external beam therapy and/or brachytherapy. It can be applied as a primary treatment or following surgery (i.e., adjuvant RT). In some cases, RT is administered with concurrent chemotherapy (chemoradiotherapy, CRT). RT is indicated in up to 60 percent of cervical cancer patients and 45 percent of endometrial cancer patients (Delaney *et al.*, 2004b, Delaney *et al.*, 2004a).

RT can lead to side effects due to damage to both cancer and healthy surrounding cells. The incidence and severity of RT-related complications depend on both treatment- and patient-related factors (e.g., treatment site, treated volume, treatment schedule, RT technique, concomitant therapies, comorbidities, age, smoking status, BMI,). RT-related toxicity can be subdivided into three categories: acute, subacute and late toxicity. Acute toxicity occurs during RT or shortly after termination of RT. Subacute toxicity generally manifests four to twelve weeks after RT has been completed. Subacute side effects generally represent prolonged recovery from significant acute toxicity. Late toxicities occur after three months and are usually irreversible (Kirchheiner *et al.*, 2014, Kirchheiner *et al.*, 2016a, Kirchheiner *et al.*, 2016b).

A frequent complication in patients undergoing RT is vaginal toxicity, which is related to sexual dysfunction and can significantly reduce the patients' quality of life (QoL). Women can experience vaginal mucositis (VM), also known as vaginitis, during or following pelvic RT (Kirchheiner *et al.*, 2014, Zolciak-Siwinska *et al.*, 2015). The pathogenesis of VM is similar to RT-induced changes observed at other mucosal surfaces (e.g., oral mucositis). VM ranges from erythema to superficial ulceration, possibly with exudative changes, serous discharge and a predisposition to infection. The National Cancer Institute uses the CTCAE v3.0 morbidity score to distinguish between the several degrees in VM (Table 1)**.** Low-grade VM is generally well-tolerated, but higher-grade toxicity such as ulcerations, vaginal necrosis, and rectovaginal fistulas can significantly impact the patients' daily life (National Cancer Institute, 2006).

The current treatment of VM is based on a multidisciplinary approach consisting of vulvar cleansing with mild soap or Sitz baths to remove topical irritants (e.g. urine). Furthermore, vaginal washes with diluted hydrogen peroxide and water or the local anaesthetic and anti-inflammatory agent, benzydamine, can improve symptoms (Denton and Maher, 2003).

To date, the incidence of VM is still not well documented. However, a few retrospective and prospective studies are conforming CTCAE grade 1-3 VM in a significant number of patients (Bergmark *et al.*, 1999, Solhjem *et al.*, 2005, Bahng *et al.*, 2012, Zolciak-Siwinska *et al.*, 2015, Kirchheiner *et al.*, 2016a). The objective of this study is to determine the incidence and extent of VM in women with gynaecological cancer receiving external (C)RT and the standard institutional care for VM.

Materials and Methods

Study design and setting

This retrospective analysis was performed at the Limburg Oncology Centre (LOC, Jessa Hospital, Hasselt and ZOL, Genk, Belgium) based on data collected between January 2017 and June 2018. The study received positive advice of the ethics committees of the Jessa Hospital and ZOL and was conducted according to the Declaration of Helsinki (registration number: 19.12/onco19.04).

Study population

Candidates were retrospectively screened from the patient database of the LOC between January 2017 and June 2018 by using electronic medical records to identify eligible patients. Patients were included if they underwent RT for gynaecological cancer with or without surgery, brachytherapy, and/or chemotherapy. All patients must have received a prescribed dose of 45–50 Gy (1.8-2 Gy/fraction, 5 fractions/week) to the planned target volume (PTV) with whole-pelvis Volumetric Modulated Arc Therapy (VMAT) or Intensity Modulated Radiotherapy (IMRT) in 25 fractions using a 6, 10 or 15 MV photon beam produced by a linear accelerator (Clinac® DHX, Varian Medical Systems, Palo Alto, CA). All included patients were placed in a supine position with their feet and legs fixated by a combifix. Patients were excluded if they did not complete external RT and could not perform the vaginal washes during RT.

Intervention

Standard institutional vaginal care during pelvic RT

Each patient received the standard institutional supportive care for pelvic RT. As such, patients were advised to wash the irradiated region with water and mild soap and to wear no tight, cotton clothes. Further, patients were prohibited to sunbathe, swim, use a sauna, and have sexual intercourse during RT and up to 4-6 weeks post-RT. To reduce discomfort, patients were instructed to apply twice a day a topical, hydroactive colloid gel (Flamigel®, Flen Pharma, Kontich, Belgium) on the irradiated zone (groins and gluteal cleft). Further, patients performed once a day in the morning vaginal washes with a povidone-iodine solution (Iso-betadine® Gynaecological solution, Meda Pharma, Brussels, Belgium) using a vaginal irrigator. Between weeks four and six of post-RT patients started using a vaginal dilator three times a week (10-15 minutes) to prevent vaginal stenosis.

Outcome measures

Patient data

Clinical information regarding the patient's personal and disease- and treatment-related characteristics was collected via patient's medical charts.

Severity of VM

Data on the frequency and intensity of five common symptoms of VM: discharge, pruritus, pain, burning sensation, and dryness was collected from the patient files. The scoring was performed on an 11-point Numerical Rating Scale (NRS, 0 = no symptom, 10 = worse symptom) at the start and the end of external (C)RT (before boost) by the patient.

Statistical analysis

The NRS scores evaluating the severity of VM of the patients at the start and the end of RT were analysed by a paired t-test. The frequency and distribution of VM symptoms was analysed using two-sample proportion tests. The level of statistical significance for all analyses was set assuming a significance level of 5% ($p < 0.05$, two-tailed). SPSS 24.0 (IBM, Chicago, IL) was used for all analyses.

Results

Patient characteristics

33 patients with a gynaecological malignancy matched the inclusion criteria for the retrospective analysis (around 40% of the screened patient population). The majority of the patients had undergone primary surgery (70%) and almost half of them underwent CRT (49%). About 33% of the patients underwent neo-adjuvant CT. The mean age of the patients was 61. Up to 60% of patients were post-menopausal before diagnosis. Up to 80% of the patients did not smoke or were a former smoker and 70% of the patients did not consume alcohol or only 1 unit/week. All the patients' characteristics are presented in Table 2-3.

The frequency of VM symptoms

The frequency of VM symptoms in patients before and after their pelvic external (C)RT (before boost) is presented in Figure 1A. About 61 % of the patients already presented at least one symptom before the start of (C)RT, which remained stable towards the end of (C)RT ($p>0.05$). The VM symptoms that significantly more frequently appeared in patients were

pruritus (i.e., itchiness), a burning sensation, and pain (Ps<0.05). The appearance of vaginal discharge and dryness remained stable.

The intensity of VM symptoms

Figure 1B presents the severity of the VM symptoms rated by the patient before and after their external pelvic (C)RT (before boost). The NRS scores for the symptoms, pruritus, burning sensation, and pain significantly increased towards the end of external (C)RT (Ps<0.05). The NRS scores for discharge and dryness did not significantly change towards the end of external (C)RT. In overall, the mean NRS scores for all the VM symptoms are rather low at the end of external pelvic (C)RT (mean range 1.5-2.5).

Distribution of scores of VM symptoms

In Figure 2 the distribution of the NRS scores per VM symptom before and after pelvic (C)RT (before boost) is shown. The NRS scores were split up into four categories (0, 1-3, 4-6, and > 6). At the end of (C)RT (before boost), the highest proportion of patients is present in the category 0-3 for all the symptoms (73%). For each VM symptom, the proportion of patients in category ≥ 4 was compared before and after (C)RT. In overall, the proportion of patients in the category ≥ 4 increased significantly from 7% towards 27% at the end of RT (p= 0.031). This increase was mainly contributed by three VM symptoms: pruritus, burning sensation, and pain, which increased with 21%, 30%, and 24% patients in category ≥ 4, respectively (Ps<0.05). The proportion of patients in category ≥ 4 for vaginal discharge and dryness remained stable (Ps >0.05).

Discussion

Main findings

In this retrospective analysis we observed that overall, a high proportion of the patients with a gynaecological malignancy already presented a VM symptom before the start of their external pelvic (C)RT. The most frequent symptoms that were documented after external (C)RT were pruritus, a burning sensation, and pain. RT and the standard institutional care did not significantly influence vaginal discharge and dryness. The patient NRS scores for all the symptoms were rather low, as about 73% of the patients gave a score between 0-3, with a mean score of 1.9. The symptoms that aggravated the most towards the end of external (C)RT were pruritus, a burning sensation, and pain.

One concern based on our results is that still 27% of patients rate one or more VM symptoms with a score of 4 or higher at the end of external (C)RT. This implies that this group of patients needs more supportive care measures consisting of the use of analgesics and a stricter follow-up by the RT team. One of the frequently described VM symptoms is pruritus, as confirmed in other trials (Kirchheiner *et al.*, 2014, Zolciak-Siwinska *et al.*, 2015). This symptom could be aggravated since pelvic RT makes the patients more vulnerable to yeast infections due to damage to the vaginal mucosa. Vaginal yeast infections are characterized by itchiness, a burning sensation, irritation, odour, and vaginal discharge. In case of yeast infections special measures have to be taken into account such as antifungal creams, ointments or suppositories with miconazole or clotrimazole (Hainer and Gibson, 2011). Pain and a burning sensation are two symptoms, which are hard to differentiate. A burning sensation during urination could also be caused by cystitis, which is a common complication of patients undergoing pelvic RT (Hainer and Gibson, 2011). Moreover, the pain score could have been influenced by the general

pain felt by the patient due to dermatological, gastrointestinal, skeletal, or genitourinary toxicity (Viswanathan *et al.*, 2014).

There is little to no data on the incidence and severity of acute VM after external pelvic (C)RT without brachytherapy. The EMBRACE trial, a large, prospective, observational study with 588 patients who underwent (C)RT in combination with image-guided adaptive brachytherapy demonstrated that VM played a minor role before treatment (CTCAE grade 0 incidence >90%). The crude incidence of VM over a median follow-up time of 15 months was 29% for CTCAE grade ≥1, 4% for grade ≥2, and <1% for grade ≥ 3. Most patients presented minimal to mild VM symptoms, which seemed to decrease slightly over time (Kirchheiner *et al.*, 2014). A retrospective study by Bahng et al. evaluated the severity of VM in 100 patients who underwent total hysterectomy and bilateral salpingo-oophorectomy with or without lymph node dissection and adjuvant intravaginal brachytherapy. Their results showed that 33% of the patients experienced CTCAE Grade 1 VM, 11% experienced grade 2, and 3% experienced grade 3 (Bahng *et al.*, 2012). A prospective, observational study with 100 patients with endometrial cancer who were treated with surgery and postoperative vaginal high-dose-rate brachytherapy demonstrated a VM incidence of 17% (grade 1-2) (Solhjem *et al.*, 2005).

It is difficult to compare our results with previous studies, because they investigated VM in patients undergoing brachytherapy alone or in combination with external pelvic (C)RT, while our trial only evaluated patients who underwent external pelvic (C)RT before boost. Moreover, in our trial, we went more into detail by using a specific scoring system for each VM symptom, while other trials used the CTCAE grading system. Still, our results are in line with previously described trials, as most of the patients presented mild VM symptoms at the end of external pelvic (C)RT.

Limitations

Our study is not without limitations. First, for this retrospective study, the only available data were subjective ratings of VM symptoms by the patient. These subjective symptoms are important as they reflect the impact of treatment on the patient and they put the patient experience in the centre of attention. Therefore, they should be taken into consideration. There are objective scoring systems available, such as CTCAE v3 (National Cancer Institute, 2006) or the Vaginal Health Index (Bachmann, 1995). Despite the retrospective nature of this study, neither these objective measures nor QoL questionnaires were taken into account. However, the introduction of these measures would certainly contribute to a future study.

Secondly, in the current study, the patients performed vaginal washes with a povidone-iodine solution once a day during RT, which is included in our institutional standard of care for patients who undergo (C)RT for gynaecological cancers. This measure was introduced based on two main principles. First, it has been proven that iodine solutions are effective in managing vaginitis caused by yeast infections (Ratzan, 1969, Yu and Tak-Yin, 1993). Second, during vaginal washes, patients are dilating their vagina with a vaginal irrigator, which will reduce vaginal adhesion. Vaginal dilatation is a proven measure to prevent vaginal stenosis (Bahng *et al.*, 2012, Kirchheiner *et al.*, 2016a, Akbaba *et al.*, 2019). Yet, there is no data about the efficacy of vaginal washes during pelvic RT included in the clinical guidelines published by Denton et al (Denton and Maher, 2003). Therefore, it is hard to compare the results of our trial with other clinical trials, as our supportive care approach could have led to the weakening of the VM symptoms. Likewise, our institute does not have a reference value before the introduction of the vaginal washes.

Third, the small sample size makes it difficult to conclude. However, it is not easy to collect data from a large group of patients, since the number of patients that are irradiated for gynaecological tumours within one year is limited, even in large radiation centres. Yearly around 90 patients are treated for cancer of the cervix or endometrium at our RT centre. Half of them undergo external RT in combination with brachytherapy as a boost and the other half undergoes only brachytherapy.

Finally, although VM can worsen until a few weeks after the end of RT, we decided not to include data after the last day of the external RT. The main reason for this was that standardization could no longer take place after the end of the external RT, as the different therapies varied considerably from that point (internal or external boost, the moment of performing brachytherapy, etc.).

Future implications

Cancer-therapy related VM represents both acute and subacute toxicity. However, there is growing evidence for a link between acute vaginal toxicity and late damage such as vaginal and vulvar atrophy and stenosis (Bergmark *et al.*, 1999, Cerentini *et al.*, 2019). Late vaginal damage not only has a significant impact on the patient's QoL; it also makes vaginal examination during the patient's cancer follow-up difficult to impossible. The assumed link between acute reactions and consequential late damage underlines the importance of preventive measures and the treatment of these acute reactions (Kirchheiner *et al.*, 2014). Therefore, both physician and nurse should be alert for signs of VM during (C)RT. There is a strong need for further research to give patients the correct treatment for cancer-therapy induced VM (Denton and Maher, 2003). At our RT department, a current study is investigating whether the use of a hormone-free, gel-based moisturizing cream can reduce VM complaints following radio- and/or CT for gynaecological cancer. Moreover, informing the patient about the possible side effects of the

RT treatment and asking them to score their complaints leads to more openness and awareness about the topic. This makes the patient more prepared for the potential late side effects and therefore makes it easier for them to take preventive measures, such as vaginal dilatation. The limited number of patients that are irradiated for gynaecological tumours within one year makes it more difficult to conduct large studies on this patient population, which contributes to the lack of knowledge about VM. With this study, we hope to raise awareness about VM during cancer therapy not only to reduce vaginal complaints of the patients during their therapy, but also to be able to reduce late side effects. More research is necessary, especially to confirm the described link between acute vaginal toxicity and late vaginal damage.

Conclusion

Knowledge about VM is still limited due to the lack of large prospective, observational trials and therefore the attention to VM, both in research and in clinical practice, is still rather poor. This is related to the relatively low number of patients with gynaecological cancer treated at the RT department, which implies that a prospective trial will take a long time. Our retrospective data indicate that VM is a rather frequent side effect in gynaecological cancer patients that aggravates during treatment up to a moderate severity level and might, therefore, affect the patient's QoL. Despite the small sample, these data highlight the need for attention to VM, both in research and in clinical practice.

VM is an underrated side effect of cancer therapy that needs to be tackled multidisciplinary, and therefore the whole treatment team should be alert for signs of VM during (C)RT. Currently, at our RT department, we take more actions in the field of supportive care of patients with gynaecological malignancies. The RT nurses pay more attention to patients with gynaecological cancers by informing patients on guidelines on how to manage the side effects.

Moreover, the institutional supportive care guidelines for pelvic RT were improved. Now, each patient is advised to apply twice a day a topical, hydroactive colloid gel (Flamigel®, Flen Pharma, Kontich, Belgium) on the irradiated zone (groins and gluteal cleft). In case of irritation, the patients can use wipes (Cavilon Continence Care Wipes, 3M Health Care, Minnesota, USA) to clean, moisturize and protect the skin after each toilet visit. Patients perform vaginal washes with a povidone-iodine solution (Iso-betadine® Gynaecological solution, Meda Pharma, Brussels, Belgium) once a day in the morning to prevent yeast infections. In case of vaginal irritation, a Kamillosan sitz bath (>1x/day) is recommended. A foam, absorbent, self-adhesive silicone dressing (Mepilex, Mölnlycke Health Care, Gothenburg, Sweden) is used in the case of painful skin reactions and to prevent friction from the patient's underwear. To prevent late vaginal toxicity (e.g., vaginal stenosis) patients use a vaginal dilator from week 4 - 6 post-RT, three times a week (10-15 min.). In the case of a pain score ≥ 4 patients receive analgesics. Further, patients get advice concerning the prevention of cystitis and rectitis. Further, we are performing more research to improve our protocol. Via these measures, our department tries to prevent and manage VM and limit complications during and after (C)RT to improve the patients' QoL. Finally, gynaecologists also play an important role in the follow-up of patients with a gynaecological malignancy after (C)RT. They are needed to support patients in late complications and advise/encourage patients in performing vaginal dilatation. As such a multidisciplinary approach in the follow-up of patients with a gynaecological malignancy is strongly recommended.

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Disclosure of interest

The authors report no conflict of interest.

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Tables

Table 1: Vaginal Mucositis - CTCAE V3 criteria (National Cancer Institute, 2006)

Grade				
0	1	2	3	4
No change over baseline	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences

Table 2: Baseline disease- and treatment-related characteristics of patients (N = 33)

Characteristic	*n*	%
Disease-related		
Tumour Location		
Cervix	15	45.5
Endometrium	16	48.5
Endocervical	1	3
Uterus	1	3
Tumour type		
Squamous cell carcinoma	15	45.5
Adenocarcinoma	8	24.2
Carcinosarcoma	4	12.1
Serous carcinoma	2	6.1
Endometrioïd	1	3
Leiomyosarcoma	1	3
Mixed serous and clear cell	1	3
Missing	1	3
Tumour Grade		
1	3	9.1
2	13	39.4
3	9	27.3
Missing	8	24.2

Table 2: continued

FIGO stage *		
IA	2	6.1
IB	8	24.2
IIB	11	33.3
IIIA	1	3
IIIC	7	21.2
IV	1	3
Missing	3	9.1
Other cancer therapy		
Surgery	23	69.7
Concurrent Chemotherapy	16	48.5
Chemotherapy prior to radiotherapy	11	33.3
Radiotherapy-related		
Fractionation Regimen		
25 x 2 Gy	7	21.2
25 x 1.8 Gy	26	78.8
Technique		
VMAT	32	97
IMRT	1	3
Energy level		
6 MV	3	9.1
10 MV	2	6.1
15 MV	28	84.8

Table 2: continued

Brachytherapy boost		
None	3	9.1
Intra-uterine	9	27.3
Ovoid	10	30.3
Intra-vaginal	11	33.3
External RT boost	7	21.2

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics; IMRT, Intensity Modulated Radiotherapy; RT, radiotherapy; VMAT, Volumetric Modulated Arc Therapy;

* FIGO staging of gynaecologic malignancies (Bhatla and Denny, 2018)

Table 3: Baseline patient-related characteristics (N=33)

Characteristic	Mean ± SD	
Age (years)	61.1 ± 11.8	
Body Mass Index (BMI)	28.9 ± 7	
	n	%
WHO weight classification*		
Underweight (BMI < 18.50)	1	3
Normal (BMI 18.50-24.99)	9	27.3
Overweight (BMI 25-29.99)	9	27.3
Obese (BMI ≥ 30)	13	39.4
Missing	1	3
Smoking habits		
Never smoked	17	51.5
Former smoker	10	30.3
Smoker	5	15.2
Missing	1	3
Menopausal status (before diagnose)		
Pre-Menopausal	9	27.3
Post-menopausal	20	60.6
Missing	4	12.1

Table 3: Continued

Alcohol consumption (drink/ week)		
0 - 1	24	72.7
1-3	3	9.1
3-10	4	12.1
10-20	1	3
Missing	1	3
Comorbid diseases [a]		
None	15	45.5
Circulatory System Diseases [b]	9	27.3
Hypercholesterolemia	5	15.2
Thyroid disorder	5	15.2
Diabetes mellitus	4	12.1
Rheumatoid arthritis	4	12.1
Other [c]	11	33.3

Abbreviations: SD, standard deviation; WHO, World Health Organization.

[*] World Health Organization (2000) Obesity: preventing and managing the global epidemic (Akram et al., 2000).

[a] Some patients may present multiple comorbidities, as such percentages are not adding up.

[b] Circulatory System Diseases included hypertension, heart failure, varicose veins, and vasculitis.

[c] Other comorbidities included fibromyalgia, lung diseases (e.g., tuberculosis), kidney stone disease, and skin diseases (e.g., eczema

Figure captions

Figure 1. Frequency and severity of VM before the start and at the end of external (C)RT

A) Percentage of patients reporting any degree of VM symptom. Significant difference within the group before the start and at the end of external RT (*P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001; two-sample proportion test, two-tailed).

B) Mean NRS score per symptom before the start and after external (C)RT (0-10 NRS, Score > 0). Significant difference within the group before the start and the end of external RT (*P ≤ 0.05; ***P ≤ 0.001; paired t-test, two-tailed).

CRT, chemoradiotherapy; NRS, Numerical Rating Scale; RT, radiotherapy; VM, vaginal mucositis.

Figure 2. Distribution of numerical rating scale scores for each VM symptom before the start and at the end of external (C)RT.

*Significant difference within the group before the start and at the end of external (C)RT (P < 0.05; two-sample proportion test, two-tailed.)

CRT, chemoradiotherapy; NRS, Numerical Rating Scale; RT, radiotherapy; VM, vaginal mucositis.