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(chemo-)radiotherapy: a retrospective analysis

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Title Page

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Title

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

Running title

Vaginitis, a neglected side effect of radiotherapy

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

35

36 **Abstract**

37

38 **Purpose**

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

42 **Methods**

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

47 **Results**

48 33 patients treated with RT for gynaecological cancer met the inclusion criteria. A non-
49 negligible proportion of patients already experienced at least one VM symptom to any degree
50 before the start of RT, a proportion that further increased toward the end of the RT (73%). At
51 the end of RT, on average, about 25% of these patients reported moderate-to-severe symptoms
52 (against about 7% before the (C)RT).

53 **Conclusion**

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

57

58

59 **Summary statement**

60 What is already known about this topic?

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

65 What this paper adds?

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

70 The implications of this paper:

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

77

78 **Keywords**

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

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Main Text

85 Introduction

86 In 2018, worldwide 1 013 751 women were diagnosed with a gynaecological malignancy
87 and this number is expected to increase with up to 500 000 new cases in 2040 (Ferlay *et al.*,
88 2019). Gynaecological malignancies are heterogeneous diseases with varying risk factors and
89 treatment protocols. Radiation therapy (RT) plays an important role in the management of
90 gynaecological cancers and consists of external beam therapy and/or brachytherapy. It can be
91 applied as a primary treatment or following surgery (i.e., adjuvant RT). In some cases, RT is
92 administered with concurrent chemotherapy (chemoradiotherapy, CRT). RT is indicated in up
93 to 60 percent of cervical cancer patients and 45 percent of endometrial cancer patients (Delaney
94 *et al.*, 2004b, Delaney *et al.*, 2004a).

95

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

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

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

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

129

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131

132 **Materials and Methods**

133 *Study design and setting*

134 This retrospective analysis was performed at the Limburg Oncology Centre (LOC, Jessa
135 Hospital, Hasselt and ZOL, Genk, Belgium) based on data collected between January 2017 and
136 June 2018. The study received positive advice of the ethics committees of the Jessa Hospital
137 and ZOL and was conducted according to the Declaration of Helsinki (registration number:
138 19.12/onco19.04).

139 *Study population*

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

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155 ***Intervention***

156 *Standard institutional vaginal care during pelvic RT*

157 Each patient received the standard institutional supportive care for pelvic RT. As such,
158 patients were advised to wash the irradiated region with water and mild soap and to wear no
159 tight, cotton clothes. Further, patients were prohibited to sunbathe, swim, use a sauna, and have
160 sexual intercourse during RT and up to 4-6 weeks post-RT. To reduce discomfort, patients were
161 instructed to apply twice a day a topical, hydroactive colloid gel (Flamigel[®], Flen Pharma,
162 Kontich, Belgium) on the irradiated zone (groins and gluteal cleft). Further, patients performed
163 once a day in the morning vaginal washes with a povidone-iodine solution (Iso-betadine[®]
164 Gynaecological solution, Meda Pharma, Brussels, Belgium) using a vaginal irrigator. Between
165 weeks four and six of post-RT patients started using a vaginal dilator three times a week (10-
166 15 minutes) to prevent vaginal stenosis.

167 ***Outcome measures***

168 *Patient data*

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

171 *Severity of VM*

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

176

177

178 ***Statistical analysis***

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

184

185 **Results**

186 ***Patient characteristics***

187 33 patients with a gynaecological malignancy matched the inclusion criteria for the
188 retrospective analysis (around 40% of the screened patient population). The majority of the
189 patients had undergone primary surgery (70%) and almost half of them underwent CRT (49%).
190 About 33% of the patients underwent neo-adjuvant CT. The mean age of the patients was 61.
191 Up to 60% of patients were post-menopausal before diagnosis. Up to 80% of the patients did
192 not smoke or were a former smoker and 70% of the patients did not consume alcohol or only 1
193 unit/week. All the patients' characteristics are presented in Table 2-3.

194 ***The frequency of VM symptoms***

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

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

201

202 *The intensity of VM symptoms*

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

209 *Distribution of scores of VM symptoms*

210 In Figure 2 the distribution of the NRS scores per VM symptom before and after pelvic
211 (C)RT (before boost) is shown. The NRS scores were split up into four categories (0, 1-3, 4-6,
212 and > 6). At the end of (C)RT (before boost), the highest proportion of patients is present in the
213 category 0-3 for all the symptoms (73%). For each VM symptom, the proportion of patients in
214 category ≥ 4 was compared before and after (C)RT. In overall, the proportion of patients in the
215 category ≥ 4 increased significantly from 7% towards 27% at the end of RT ($p = 0.031$). This
216 increase was mainly contributed by three VM symptoms: pruritus, burning sensation, and pain,
217 which increased with 21%, 30%, and 24% patients in category ≥ 4 , respectively ($P_s < 0.05$). The
218 proportion of patients in category ≥ 4 for vaginal discharge and dryness remained stable (P_s
219 > 0.05).

220

221

222 **Discussion**

223 *Main findings*

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

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

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

247 There is little to no data on the incidence and severity of acute VM after external pelvic
248 (C)RT without brachytherapy. The EMBRACE trial, a large, prospective, observational study
249 with 588 patients who underwent (C)RT in combination with image-guided adaptive
250 brachytherapy demonstrated that VM played a minor role before treatment (CTCAE grade 0
251 incidence >90%). The crude incidence of VM over a median follow-up time of 15 months was
252 29% for CTCAE grade ≥ 1 , 4% for grade ≥ 2 , and <1% for grade ≥ 3 . Most patients presented
253 minimal to mild VM symptoms, which seemed to decrease slightly over time (Kirchheiner *et*
254 *al.*, 2014). A retrospective study by Bahng *et al.* evaluated the severity of VM in 100 patients
255 who underwent total hysterectomy and bilateral salpingo-oophorectomy with or without lymph
256 node dissection and adjuvant intravaginal brachytherapy. Their results showed that 33% of the
257 patients experienced CTCAE Grade 1 VM, 11% experienced grade 2, and 3% experienced
258 grade 3 (Bahng *et al.*, 2012). A prospective, observational study with 100 patients with
259 endometrial cancer who were treated with surgery and postoperative vaginal high-dose-rate
260 brachytherapy demonstrated a VM incidence of 17% (grade 1-2) (Solhjem *et al.*, 2005).

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

268

269

270 ***Limitations***

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

279

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

293

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

300

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

306 ***Future implications***

307 Cancer-therapy related VM represents both acute and subacute toxicity. However, there is
308 growing evidence for a link between acute vaginal toxicity and late damage such as vaginal and
309 vulvar atrophy and stenosis (Bergmark *et al.*, 1999, Cerentini *et al.*, 2019). Late vaginal damage
310 not only has a significant impact on the patient's QoL; it also makes vaginal examination during
311 the patient's cancer follow-up difficult to impossible. The assumed link between acute reactions
312 and consequential late damage underlines the importance of preventive measures and the
313 treatment of these acute reactions (Kirchheiner *et al.*, 2014). Therefore, both physician and
314 nurse should be alert for signs of VM during (C)RT. There is a strong need for further research
315 to give patients the correct treatment for cancer-therapy induced VM (Denton and Maher,
316 2003). At our RT department, a current study is investigating whether the use of a hormone-
317 free, gel-based moisturizing cream can reduce VM complaints following radio- and/or CT for
318 gynaecological cancer. Moreover, informing the patient about the possible side effects of the

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

328 **Conclusion**

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

337

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

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

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368 **Acknowledgements**

369 All authors contributed to equally to the manuscript. All authors read and approved the final
370 manuscript.

371 **Disclosure of interest**

372 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	<i>n</i>	%
<i>Disease-related</i>		
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
Endometrioid	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
<i>Other cancer therapy</i>		
Surgery	23	69.7
Concurrent Chemotherapy	16	48.5
Chemotherapy prior to radiotherapy	11	33.3
<i>Radiotherapy-related</i>		
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 \pm SD	
Age (years)	61.1 \pm 11.8	
Body Mass Index (BMI)	28.9 \pm 7	
	<i>n</i>	%
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 \geq 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 (* $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$; 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 (* $P \leq 0.05$; *** $P \leq 0.001$; 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.

