Late G2 vagina toxicity in post-operative endometrial carcinoma is associated with a 68 Gy dose equivalent to 2 Gy per fraction$_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of vagina

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Abstract

Purpose: To evaluate if the dose equivalent to 2 Gy per fraction (EQD2)$_{(\alpha/\beta=3Gy)}$ at 0.1 cm^3, 1 cm^3, and 2 cm^3 of vagina in vaginal-cuff-brachytherapy (VBT) (high-dose-rate [HDR] ^{192}Ir-source) ± external-beam-irradiation (EBRT) is associated with toxicity in post-operative endometrial carcinoma (P-EC).

Material and methods: From June 2014 till November 2015, 67 consecutive P-EC patients underwent VBT ± EBRT; 44 patients received EBRT (median, 45 Gy; range, 44-50.4) + VBT (7 Gy), and 23 exclusive-VBT (6 Gy x 3 fractions). The upper 2.5 cm of vagina was delineated on computed tomography (CT). The active-length source was 2.5 cm, and the brachytherapy dose was prescribed at 5 mm from the applicator. D$_{90}$, V$_{100}$, and EQD2$_{(\alpha/\beta=3Gy)}$ at 0.1 cm^3, 1 cm^3, and 2 cm^3 of the most exposed part of the vagina were calculated. Vaginal toxicity assessment was completed with a LENT-SOMA-objective-criteria. Statistics were done with the use of χ^2 and Student's-t test.

Results: The mean follow-up was 23.2 months (7.6-46.8). Median D90 was 7.8 Gy$_{(\alpha/\beta=3Gy)}$. Late toxicity: 8 G1 and 9 G2. Median EQD2$_{(\alpha/\beta=3Gy)}$ in vagina was 88.6 Gy (62.8-177.6) for 0.1 cm^3, 72.4 Gy (57.1-130.4) for 1 cm^3, and 69 Gy (53-113.4) for 2 cm^3. Exclusive VBT vs. EBRT+VBT showed no differences in vaginal toxicity. There was no relationship between EQD2$_{(\alpha/\beta=3Gy)}$ at 0.1 cm^3 and 1 cm^3 of vagina with G1-G2 toxicity ($p = 0.62$ and $p = 0.58$, respectively). G2 toxicity was related to EQD2$_{(\alpha/\beta=3Gy)}$ at 2 cm^3 ($p = 0.03$). EQD2$_{(\alpha/\beta=3Gy)}$ > 68 Gy caused G2 late toxicity in 20.5% patients. All patients presenting G2 toxicity received > 68 Gy EQD2$_{(\alpha/\beta=3Gy)}$.

Conclusions: More than 68 Gy EQD2$_{(\alpha/\beta=3Gy)}$ at 2 cm^3 was related to G2 toxicity in P-EC-VBT. Further studies including larger number of patients are needed to confirm these results. Patients receiving these doses should be informed of the risk of toxicity, with individualized treatment planning and follow-up to reduce G2 toxicity.

Purpose

Few studies in the literature have adequately analyzed vaginal toxicity after irradiation. Along the years, vaginal toxicity has frequently been under-reported and has only recently been more accurately analyzed. In post-operative endometrial brachytherapy, the range of toxicity after irradiation, when described, has historically been wide. In external beam radiotherapy (EBRT), toxicity is associated with vaginal dose and irradiated vaginal volume. With regard to vaginal-cuff brachytherapy (VBT), vaginal surface dose, cylinder diameter, fractionation, and the length of the active source are the main factors associated with the presence of late complications. On the other hand,

a lower number of vaginal stenoses has been described in patients using vaginal dilators after treatment [1,2,3,4,5]. Nevertheless, the difficulties in analyzing toxicity seem to be the same for radical or curative and post-operative treatments.

With the aim of reducing vaginal toxicity after brachytherapy in patients with cervical cancer undergoing image-guided adaptive brachytherapy (IGABT), the GEC-ESTRO Group performed a dose equivalent to 2 Gy per fraction (EQD2) vaginal dose analysis. The EMBRACE study did not find any relationship between vaginal toxicity and EQD2 dose at 2 cm^3 of vagina. Other studies by this group and others are currently ongoing to analyze and reduce vaginal toxicity in patients with cervical cancer [4,6,7,8].

Considering that vaginal dose in IGABT for cervical cancer is a completely different scenario to that of post-operative radiotherapy in endometrial cancer, our purpose was to analyze the EQD2$_{(\alpha/\beta=3Gy)}$ at 0.1 cm^3, 1 cm^3, and 2 cm^3 of the most exposed region of the vagina in 67 patients, to determine a possible relationship with late toxicity. To our knowledge, this is the first time that this analysis has been carried out in post-operative endometrial cancer.

Material and methods

From June 2014 to November 2015, 67 patients were treated with post-operative brachytherapy for endometrial carcinoma at our Radiation Oncology Department. After the diagnosis of endometrial carcinoma and image study by magnetic resonance imaging (MRI) and/or positron emission tomography (PET), and/or computed tomography (CT) and/or ultrasonography, 31 patients underwent surgery: vaginal hysterectomy plus laparoscopy-assisted bilateral oophorectomy (VHLABO), and laparoscopic lymphadenectomy. Also, para-aortic lymphadenectomy was carried out in 23 of these patients. Exclusive VHLABO was performed in 12 patients. In 11 patients, a surgery consisted of abdominal hysterectomy plus bilateral oophorectomy, and pelvic and para-aortic lymphadenectomy, with the addition of omentectomy in 4 other patients. The remaining 9 patients underwent other surgical procedures. Surgical approaches varied according to differences in age and morbidities of these patients. After pathologic analysis, 23 patients were classified as the intermediate-risk group, without poor prognostic factors received exclusive VBT, and the remaining patients underwent associated EBRT. Table 1 shows the mean follow-up after surgery and the patient characteristics. Prior to radiotherapy, 19 patients received chemotherapy with 4 to 6 cycles of carboplatin plus placlitaxel.

Forty-four patients received EBRT with 18 MV beam photons after 3D planning, using the RTOG recommendations for tumor volume definition [9]. The median dose was 45 Gy (range, 44 Gy to 50.4 Gy), and the dose per fractionation was 1.8-2 Gy/day, 5 fractions/week.

All the patients received high-dose-rate (HDR)-VBT with the following schedule: 1 fraction of 7 Gy after EBRT and 3 daily fractions of 6 Gy in exclusive VBT (2 of the latter received 5.5 Gy per fraction). VBT was administered

after CT-based 3D planning. In all patients, the vagina was delineated on CT every 1 mm along the first cylinder. The treatment planning system employed was the Oncentra Brachy planning system (v. 4.1) (Elekta®, Nucletron BV, Veenendaal, The Netherlands). The vaginal cylinder was not included in the vagina delineation. In order to avoid problems with surface cylinder contouring uncertainties of the vaginal volume, we created the cylinder contour by automatic "Hounsfield units (HU) threshold" contouring and the external (solid) vaginal volume manually. Finally, using boolean subtraction, we eliminated the cylinder volume from the external vagina contour to obtain the (hollow) vagina volume. The CT and

Table 1. Characteristics of the 67 patients studied

Mean age (years)	65.51 (range, 47-90)
2009 Figo stage	
IA	20 (29.8%)
IB	22 (32.8%)
II	7 (10.4%)
IIIA	3 (4.4%)
IIIB	1 (1.4%)
IIIC1	5 (7.4%)
IIIC2	4 (5.9%)
IVA	1 (1.4%)
IVB	4 (5.9%)
Pathological types	
Endometrioid	56 (83.5%)
Serous	6 (8.9 %)
Clear cells	3 (4.4 %)
Adenosquamous	2 (2.9 %)
Grade	
1	10 (14.9 %)
2	30 (44.7%)
3	27 (40.2%)
Myometrial invasion	
No	0 (0%)
≤ 50%	25 (37.3%)
> 50%	42 (62.7%)
VLSI	
No	47 (67.1%)
Yes	19 (27.1%)
NA	1 (1.4%)

VLSI – vascular lymphatic space invasion, NA – not available
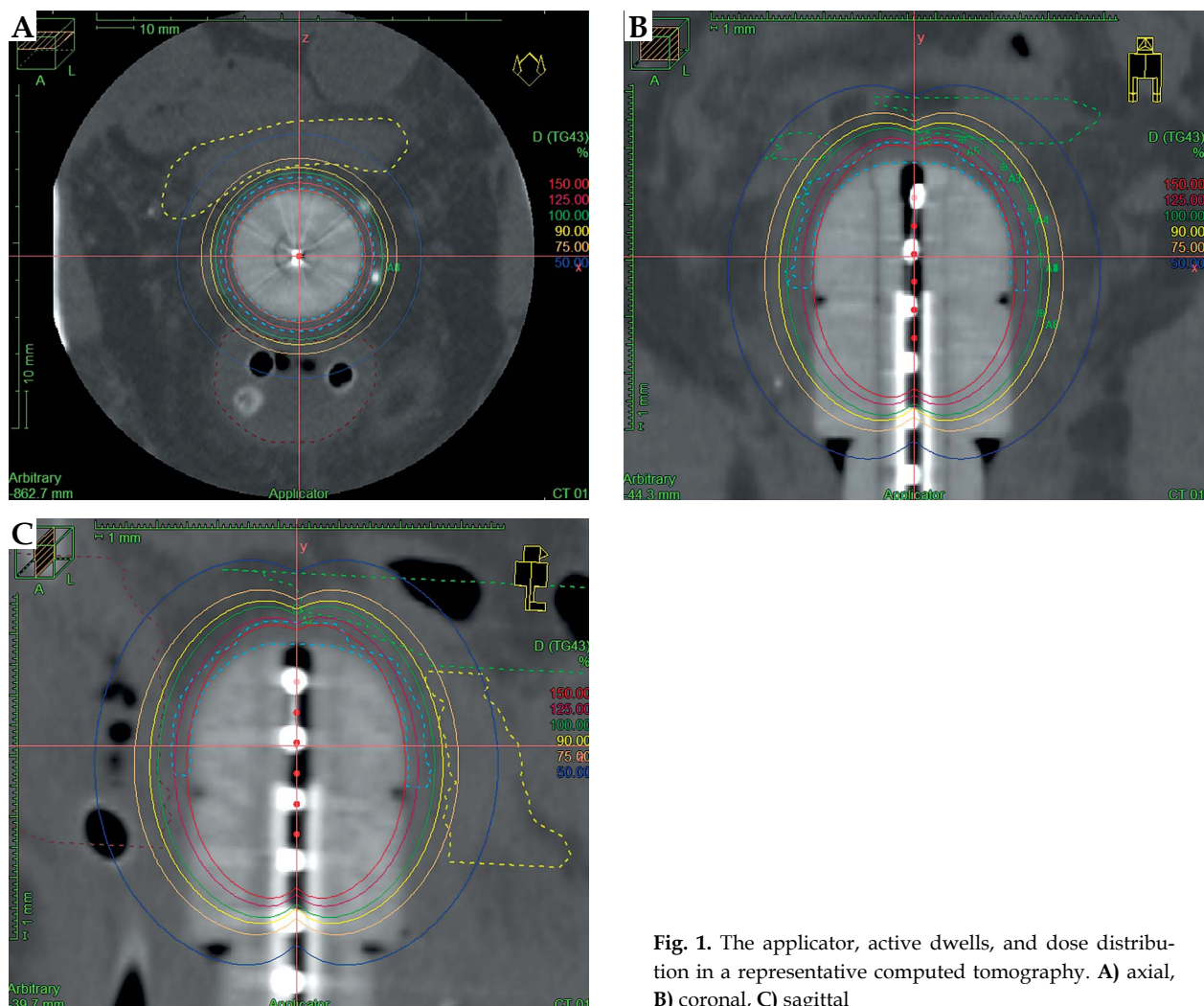
Fig. 1. The applicator, active dwells, and dose distribution in a representative computed tomography. **A)** axial, **B)** coronal, **C)** sagittal

MR compatible vaginal CT/MR applicator set from Nucletron BV, Veenendaal (The Netherlands) was designed and used for treatment of the vaginal cuff. This applicator is available in different cylinder diameters to reduce the surface dose (2 cm, 2.5 cm, 3 cm, and 3.5 cm). The cylinder can be adapted to patient's anatomy by varying the number of segments and length.

The organs at risk (rectum, bladder, and small bowel) were also contoured on CT in. All, but one patient, were treated using the vaginal cylinder technique (diameter of

Table 2. Late toxicity by the objective late effects of normal tissues – subjective, objective, management, analytic (LENT-SOMA) criteria for the vagina

G1	Atrophy, telangiectasias adherences, < 1/3 shortened vaginal length
G2	Bleeding telangiectasias, symptomatic dryness, 1/3 and 2/3 shortened vaginal length, partial synechiae
G3	Vaginal length < 1/3, deep ulceration, complete synechiae
G4	Obliteration, fistula, persistent bleeding

3.5 cm in 52 patients, 3 cm in 10 patients, 2.5 cm. in 4 patients), with the remaining patient being treated with the colpostat technique. The VBT dose was prescribed at 0.5 cm from the applicator surface (in the plane of the base of the hemisphere of the first vaginal cylinder segment and perpendicular to the catheter), with an active source length of 2.5 cm. Optimization was based on applicator points located at 0.5 cm from the cylinder cuff. The VBT procedure has been described elsewhere [10]. Figure 1 shows the applicator, active dwells, and dose distribution in a representative CT.

After the treatment, the patients underwent follow-up every 3-4 months with clinical and imaging studies; all gynecological examinations were performed by the same physician. Daily use of vaginal dilators was strongly recommended. Late toxicity was prospectively assessed using RTOG scores for the bladder and rectum, and the objective late effects of normal tissues; subjective, objective, management, analytic (LENT-SOMA) criteria were used for the vagina (Table 2) [11,12]. Sexual function was not assessed.

$EQD2_{(\alpha/\beta=3Gy)}$ at the vaginal surface was calculated using a point located at the applicator surface in the same direction as the prescription point, being the sum

of the VBT ± EBRT dose. EQD2$_{(\alpha/\beta=3Gy)}$ was calculated at 0.1 cm^3, 1 cm^3, and 2 cm^3 of the most exposed part of vagina, in the most cranial part of the applicator (the isodose representing D 0.1 cm^3 was always inside the applicator, except for the cranial part). VBT ± EBRT were calculated in order to determine a possible correlation with late vaginal toxicity. Statistical analysis was performed using the χ^2 and Student's t test, with an alpha error of 0.05 [13,14].

Results

With a mean follow-up of 23.2 months (range, 7.6-46.8), one patient staged as IIIC1 developed vaginal-cuff relapse (VCR) at 11 months after brachytherapy. Vaginal relapse was treated with pelvic exenteration (the patient died 4 months later due to complications associated with the surgical procedure).

Late toxicity

Regarding rectal toxicity, two patients developed late rectal G1 and G2 complications. Bladder toxicity appeared in one patient (1 G1). Rectal and bladder toxicity appeared only in patients receiving EBRT. Vaginal toxicity developed in 17 patients (8 G1 and 9 G2) (25.4%), similarly to what was found in previous fractionation schedules in our center during the same follow-up period [15,16,17]. Twelve of the 17 patients with vaginal toxicity had received EBRT, in comparison with 5 with exclusive brachytherapy. EQD2$_{(\alpha/\beta=3Gy)}$ EBRT in patients with G2 toxicity ranged between 43.2 Gy and 46 Gy, and was 2.5 cm in 2 patients, 3 cm in 1 patient, and 3.5 cm in the rest. The EQD2$_{(\alpha/\beta=3Gy)}$ dose in EBRT + VCB patients ranged between 68.42 Gy and 77.04 Gy. In the exclusive brachytherapy group with G2 vaginal toxicity, one patient had been treated with cylinder diameter of 2.5 cm and the remaining patients with 3.5 cm. EQD2$_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of vagina ranged from 99.12 Gy to 113.41 Gy. Table 3 shows the D$_{90}$ and V$_{100}$ of the vaginal wall presented as a dose per pulse and EQD2$_{(\alpha/\beta=3Gy)}$ at 0.1 cm^3, 1 cm^3, and 2 cm^3. Differences were found in the mean EQD2$_{(\alpha/\beta=3Gy)}$ at the vaginal mucosa between EBRT + VBT patients and exclusive VBT patients (74.05, SD 4.31 and 68.70, SD 4.24, p = 0.001). Nevertheless, there were no differences in vaginal toxicity considering EBRT treatment (p = 0.83) and therefore, all the EQD2$_{(\alpha/\beta=3Gy)}$ values were analyzed as the same population study (data not shown).

There were no differences between G0, G1, G2 late toxicity and EQD2$_{(\alpha/\beta=3Gy)}$ values for 0.1 cm^3, 1 cm^3, 2 cm^3 (Table 3). Nevertheless, when patients with G0 and G1 were analyzed and compared with the EQD2$_{(\alpha/\beta=3Gy)}$ values of G2 patients, a dose relationship was found for G2 complications at 2 cm^3 (mean 73.09, SD 10.81 for G2

Table 3. D$_{90}$, V$_{100}$ values and EQD2$_{(\alpha/\beta=3Gy)}$ at 0.1 cm^3, 1 cm^3, and 2 cm^3 of high-dose area in vaginal wall

	V$_{100}$ (cm³) per fraction	D$_{90}$ (Gy) per fraction	EQD2$_{(\alpha/\beta=3Gy)}$ (Gy) (VBT ± EBI)		
			0.1 cm³	1 cm³	2 cm³
Mean	7.78	7.53	94.38	73.74	68.75
Median	7.86	7.76	88.59	72.37	68.97
Minimum	5.4	5.62	62.79	57.12	52.91
Maximum	10.79	8.92	177.60	130.43	113.41
SD	1.43	0.84	22.04	10.62	9.01

EQD2 – dose equivalent to 2 Gy per fraction, VBT – vaginal-cuff-brachytherapy, 0.1 cm³, 1 cm³, and 2 cm³ – dose in the most exposed part of the vagina, D$_{90}$ – the minimum dose received by 90% of the vagina volume, V$_{100}$ – the percentage of the vagina volume receiving 100% of the prescribed dose or more

Table 4. EQD2$_{(\alpha/\beta=3Gy)}$ and vaginal toxicity at 0.1 cm^3, 1 cm^3, and 2 cm^3 considering G0-G1 vs. G2 toxicity

EQD2$_{(\alpha/\beta=3Gy)}$/G0-G1 vs. G2	Number	Mean	Standard deviation	Student's t, p value
0.1 cm³				
G0-G1	57	92.78	17.72	0.62
G2	10	96.29	31.64	
1 cm³				
G0-G1	57	72.27	5.97	0.58
G2	10	73.51	5.27	
2 cm³				
G0-G1	57	67.57	6.20	0.03
G2	10	73.09	10.81	

Dose equivalent to 2 Gy per fraction (EQD2)
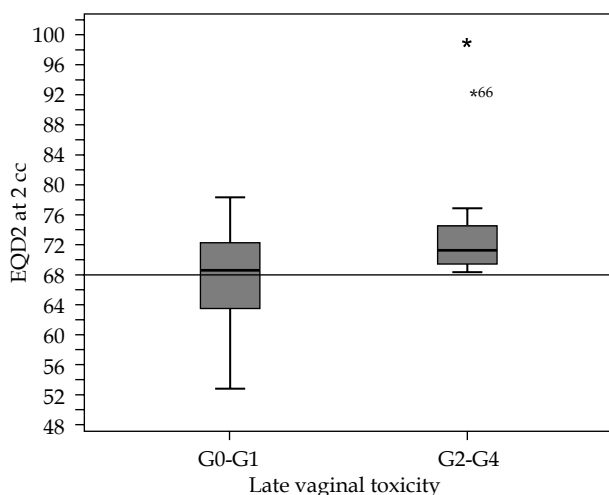
Fig. 2. $EQD2_{(\alpha/\beta=3Gy)}$ values at 2 cc of the most irradiated part of vagina and G0-G1 vs. G2 vaginal late toxicity: 100% of patients with G2 toxicity received over 68 $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3

toxicity patients vs. mean 67.57, SD 6.20 for G0-G1 patients, $p = 0.03$) but not at 0.1 and 1 cm^3 vagina ($p = 0.62$ and $p = 0.58$, respectively) (Table 4). Doses over 68 Gy $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of vagina were associated with G2 toxicity in 20.5% of the patients. All the patients with G2 toxicity had received doses over 68 Gy $EQD2_{(\alpha/\beta=3Gy)}$ (Figure 2). EBRT + BT vs. BT was analyzed. G2 vaginal complications appeared in 11.5% of patients with exclusive brachytherapy, and in 16.7% of the patients receiving EBRT + BT. According to the Fisher exact test, the p value was 0.73, and therefore no differences were found in toxicities between these two groups.

Discussion

Vaginal-cuff brachytherapy is an excellent treatment for vaginal control in EC. Although EC is the most frequent gynecological tumor, analysis of vaginal toxicity has been sparse topic in the literature. It has been recommended not to increase 80-85 Gy EQD2 on vagina surface, but few studies support these data [7,17]. Late toxicity in the literature ranges between 10% for G1-2 RTOG scores to 14% for complete vaginal stenosis, and this may vary according to the grading scoring system used [16,18,19]. In 320 patients with EC treated in our department from 2003 to 2011, late vaginal toxicity appeared in 24% using the objective criteria of LENT SOMA. All, but 2 patients with complete vaginal stenosis, who had received EBRT developed only G1-G2 problems. The active source length used for our treatments was 2.5 cm, which allowed good coverage of the vagina as shown in Table 2 [20]. In the present series, the volume of treated vagina led to fewer complications than with more extensive length sources (mean V_{100}, 7.78 cm^3; median V_{100}, 7.86 cm^3, range, 5.4-10.8 cm^3).

Late toxicity in post-operative VBT has been associated with the length of the vagina treated, fractionation schedule, overall brachytherapy treatment time interval, cylinder diameter, overall dose, and dose per fraction. In previous studies, we did not observe any influence

of the overall BT treatment time on late complications, and consequently BT was administered daily in our patients [18,20,21,22]. Our fractionation schedule and dose per fraction did not show an increase of late toxicity in comparison to other schedules, and the cylinder diameter was 3.5 cm in most of the patients. In order to know the relationship of the vaginal surface dose and toxicity considering cylinder diameter, the $EQD2_{(\alpha/\beta=3Gy)}$ was calculated in previous studies and in the present study, with no relationship with late toxicity being found [22].

Taking into consideration the type of fractionation and overall dose, in 2000, Sorbe et al. compared 4 fractionation techniques treating 2/3 of vagina, and reported 31% of vaginal shortening with the lowest dose per fraction schedule of 4.5 Gy x 6 fractions [23]. These results are poorer than our previous series with similar fractionation [20]. In another study performed in 2005, Sorbe et al. compared 2.5 Gy x 6 fractions vs. 5 Gy x 6 fractions, and the results in vaginal shortening were better with the second schedule. Interestingly, the remaining vaginal complications were similar between these two studies [24]. In our study and others from our group, patients had a lower incidence of late bladder rectal complications using 6 Gy x 3 fractions in exclusive treatment [16].

Considering the current lack of information, our objective was to analyze if there was a relationship with the dose received at 0.1 cm^3, 1 cm^3, and 2 cm^3 of vagina and late toxicity. $EQD2_{(\alpha/\beta=3Gy)}$ was calculated at these volumes. However, we failed to find any relationship between the doses received at 0.1 cm^3, and 1 cm^3. Nevertheless, a relationship was found between the $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 and G2 late toxicity. With a mean follow-up of 2 years, 20.4% of all the patients receiving $EQD2_{(\alpha/\beta=3Gy)}$ greater than 68 Gy at 2 cm^3 developed late G2 vagina toxicity, while 100% of the patients with G2 toxicity received over 68 $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3. We accepted 68 Gy as a safe cut-off for the hypothesis. Moreover, 68 Gy is the median value obtained for the patients without G2 toxicity.

In a single communication in the ASTRO 2016 meeting, Susko et al. [25] reported a rate of G1+ vaginal toxicity greater than 63.1% (95% CI 47.8-78.4) in 53 patients using CTCAE v. 4.0 scores [25]. Late G2+ toxicity (stenosis involving half of the vagina) was 21% at 2 years. They also reported a cut-off of 130 Gy $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 for G2+ vaginal toxicity (16.1% below 130 Gy and 75.0% above, $p = 0.003$). In the present series, late G2 toxicity included bleeding telangiectasias, adherences or partial or complete stenosis of one third of the vagina. The differences between the present series and that by Susko et al. are probably related to the VBT dose used, the length of the treated vagina, prescription of the dose, and the use of a different scoring system for reporting toxicity. The objective LENT SOMA score is more sensitive than CTCAE v. 4.0, and provides a higher incidence of G1-G2 vagina toxicity [26]. The vaginal toxicity rate in the present study was less than that of Susko et al. and similar to that of previous series by our group with different schedules [10,15,16,18,20,22]. In any case, it could be assumed that > 68 $EQD2_{(\alpha/\beta=3Gy)}$ in 2 cm^3 is related to stenosis problems in one third of the vagina, while > 130 $EQD2_{(\alpha/\beta=3Gy)}$ is re-

lated to stenosis involving half of the vagina or more. The results of the present study may help to select patients at risk of G2 complications. At present, in selected patients with EQD2 doses over 68 Gy, we reduce brachytherapy dose in order to eliminate G2 toxicity. Nonetheless, this should be confirmed in other studies.

In the present series, patients were encouraged to use the dilators daily. A Cochrane Database of Systematic Review by Miles and Johnson in 2014 [27] concluded that frequent dilation practice is associated with lower rates of stenosis. The authors considered that dilation is effective, and that women with a healthy vagina are more likely to comply with dilation therapy instructions compared to women with strictures. A recent study in 33 patients reported benefits in vaginal toxicity using hyaluronic acid topically in the vagina, but this should be further evaluated in a larger number of patients [28].

One limitation of this study is that the dose volume relationship found could be related to the effect of EBI, but in the present series, there was no relationship between vaginal toxicity and the EBRT administration. Other factors that have never been considered in analyzing vaginal toxicity are age, the extent of surgery, or additional chemotherapy. The present study is the first to describe a dose relationship with vagina toxicity, showing similar results compared to our previous series. The differences found by Susko *et al.* need to be validated by further studies using similar treatments and scoring systems to analyze this topic. A limitation of the present study is the low number of cases with G2 toxicity that can generate instability of estimations in the sample. Therefore, the present results should be confirmed in a study including a larger number of patients. The prevention of the vaginal stenosis is a rational concern for patients wanting to lead a healthy sexual life, and usually occurs among younger patients. In older patients, it is also important because vaginal stenosis does not allow correct vaginal examination to detect vaginal relapses. In view of the present results, patients receiving EQD2$_{(\alpha/\beta=3Gy)}$ doses should be informed of the risk involved, and patient characteristics should be considered individually for treatment planning and during the follow-up to reduce G2 toxicity. The importance of using vaginal dilators in young patients that are at risk of G2 complications should be stressed, and these patients should be more strictly followed in comparison to older patients, who do not want to use vaginal dilators. Moreover, prospective studies are needed in order to determine whether geometric optimization benefits these patients that are at risk of G2 toxicity.

Conclusions

In the present study, 68 Gy EQD2$_{(\alpha/\beta=3Gy)}$ at 2 cm^3 was related to G2 toxicity in post-operative endometrial cancer VBT. The limitations of present analysis are related to relatively small sample size, short follow-up, and the low number of events; therefore, the present data need to be confirmed in a larger number of patients and follow-up. Indeed, prospective studies aiming to reduce the dose to 2 cm^3 vagina under 68 Gy EQD2$_{(\alpha/\beta=3Gy)}$ are necessary and are currently ongoing in our center.

Disclosure

Authors report no conflict of interest.

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