Reports of Practical Oncology and Radiotherapy 25 (2020) 227–232

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Postoperative endometrial carcinoma treated with external beam irradiation plus vaginal-cuff brachytherapy. Is there a dose relationship with G2 vaginal complications?*sstarf*;

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ARTICLE INFO

Article history:
Received 31 October 2019
Accepted 10 January 2020
Available online 14 January 2020

Keywords:
Postoperative endometrial cancer
Brachytherapy
Late vaginal toxicity

ABSTRACT

Aim: To analyse the possible relationship between the $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of the vagina and late toxicity in vaginal-cuff-brachytherapy (VBT) after external-beam-irradiation (EBRT) for postoperative endometrial carcinoma (EC).

Materials and methods: From 2014 to 2016, 62 postoperative EC patients were treated with EBRT + VBT. The median EBRT dose was 45 Gy (44 Gy–50.4 Gy). VBT involved a single 7 Gy dose. Toxicity was prospectively evaluated using the RTOG score for the rectum and bladder and the objective LENT-SOMA criteria for the vagina. $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of the most exposed part of the vagina was calculated by the sum of the EBRT + VBT dose. Statistics: Boxplot, Student's t and Chi-square tests and ROC curves.

Results: Mean follow-up: 39.2 months (15–68). Late toxicity: bladder:0 patient; rectum:2 patients-G1; Vagina: 26 patients-17G1, 9G2; median $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 in G0-G1 patients was 70.4 Gy(SD2.36), being 72.5 Gy(SD2.94) for G2p. The boxplot suggested a cut-point identifying the absence of G2: 100 % of G2p received >68 Gy, ROC curves showed an area under the curve of 0.72 (sensitivity of 1 and specificity of 0.15).

Conclusions: Doses >68 Gy $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 to the most exposed area of the vagina were associated with late G2 vaginal toxicity in postoperative EC patients treated with EBRT + VBT suggesting a very good dose limit to eliminate the risk of G2 late toxicity. The specificity obtained indicates the need for prospective analyses.

1. Introduction

Several studies have demonstrated the effectiveness of vaginal-cuff brachytherapy (VBT) in postoperative endometrial carcinoma (EC), and it has a low profile of late toxicity.[1–3] In 95 % of the patients with PEC the lymphatic vessels located in the first 3 mm of vagina are responsible for vaginal-cuff relapses (VCR) and VBT prevents relapse in this area.[4] According to current guidelines VBT is widely used to reduce VCR from 15 % to 2 % or less.[5,6] Nonetheless, several questions remain to be answered regarding the best VBT fractionation schedule or the extent of vaginal volume to be treated. In addition, vaginal toxicity has been poorly analysed in the literature with the incidence in different series ranging between 8.8 % and 27.7 %. Although severe G3–4 complications are usually rare (0%–3.6%), they cannot be ignored because of the possible impact on the patient's sexual function, and most of the series report the presence of G1-G2 problems (4.9 %–25.5 %).[3,7–12]

The common late gynecologic side effects of radiotherapy include vaginal narrowing or shortening and some degree of steno-

sstarf; The present work has been presented in part as oral poster at 2019 ASTRO Annual Meeting at Chicago.

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https://doi.org/10.1016/j.rpor.2020.01.002
1507-1367/

sis or cleysis may appear. The latter makes it impossible to perform gynecologic examination and vaginal cytology and can also cause psychological problems in severe cases. A study by Agnes Y. et al. demonstrated that the use of a vaginal dilator at least two or three times a week was significantly associated with a decreased risk of vaginal stenosis, and different reports recommend their use.[13–15] Therefore, the use of a vaginal dilator is often suggested for the prevention of vaginal stenosis by radiation oncologists. Other late complications such as atrophy, telangiectasias, vaginal bleeding, adherences and symptomatic dryness can appear.

In VBT the principal factors considered to be related to the appearance of late vaginal toxicity are the vaginal surface dose administered, the fractionation schedule, cylinder diameter and the length of the vagina treated. Few studies have evaluated these prognostic factors of late vaginal toxicity.[13,16] One preliminary study by our centre including patients treated with exclusive VBT and external beam irradiation (EBRT) + VBT showed that a 68 Gy dose equivalent to 2 Gy per fraction $(EQD2)_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of vagina was associated with late G2 vaginal toxicity.[17] Considering the heterogeneity in treatments of the previous report, the aim of the present study was to analyse the relationship between the $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of the most exposed region of the vagina and late vaginal toxicity in a larger number of patients treated with vaginal brachytherapy after EBRT for postoperative EC.

2. Material and methods

Compliance with ethical standards: All subjects provided informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Clinical Research Ethics Committee of our centre (IRB: No.HCB/2014/0575).

From July 2014 to December 2016, 62 consecutive patients with postoperative EC were treated with high-dose-rate (HDR) VBT after EBRT in our department.

Before surgery computed tomography (CT) and/or magnetic resonance imaging and/or vaginal ultrasonography and/or positron emission tomography was performed. According to age and comorbidities, they all underwent surgery: 20 (32.3 %) vaginal hysterectomy plus bilateral salpingo-oophorectomy (HBO) and pelvic with or without paraaortic lymphadenectomy by laparoscopy, 8 (12.9 %) abdominal hysterectomy plus bilateral salpingo-oophorectomy and pelvic lymphadenectomy and 5 (8.1 %) with the addition of paraaortic lymphadenectomy and ommentectomy, 16 (25.8 %) exclusive HBO, 3 (4.8 %) simple hysterectomy and 10 (16.1 %) other surgical procedures. According to the pathological analysis, these patients were classified using the International Federation of Gynecology and Obstetrics (FIGO) 2009 classification. In accordance with the protocol of our hospital, patients were treated with EBRT + VCB when considered intermediate-risk with: vascular and lymphatic space invasion, type 2 PEC, and age, and tumour size > 2 cm could also be considered. Patients with high risk and stages II-IV also received EBRT + VCB. Patients with stage FIGO IA G1–2 received irradiation mainly in the case of the presence of extensive vascular and lymphatic space invasion and type 2 pathological types. Node involvement was absent in 47 patients and positive nodes were found in patients having the following stages: 7 IIIC1, 6 IIIC2, 1 IVA, and 1 IVB.

Twenty-four patients underwent chemotherapy with 3–6 cycles of carboplatin plus placlitaxel prior to radiotherapy. Twenty-four patients received chemotherapy based on carboplatine + taxol (3 patients received 3 cycles; 10 patients, 4 cycles; and 11 patients, 6 cycles) and in the remaining 38 patients, chemotherapy was not administered. Table 1 shows the patient characteristics.

Table 1
Characteristics of the 62 patients studied.

Mean age (years)	64.7 (40–83)
FIGO 2009 stage	
IA	14 (22.6 %)
IB	18 (29 %)
II	7 (11.3 %)
IIIA	3 (4.8 %)
IIIB	2 (3.2 %)
IIIC1	7 (11.3 %)
IIIC2	6 (9.7 %)
IVA	3 (4.8 %)
IVB	2 (3.2 %)
Pathological type	
Endometrioid	52 (83.9 %)
Serous	7 (11.3 %)
Clear cell	2 (3.2 %)
Mixed	1 (1.6 %)
Grade	
1	7 (11.3 %)
2	35 (56.5 %)
3	20 (32.3 %)
Myometrial invasion	(58.1 %)
≤ 50 %	26 (41.9 %)
> 50 %	36 (58.1 %)
VLSI	
No	38 (61.3 %)
Yes	20 (32.3 %)
NA	4 (6.5 %)
Mean tumour size (cm)	3.6 (1–10) NA-13
Chemotherapy	
Carboplatin-paclitaxel 3 cycles	3(4.8 %)
4 cycles	11(17.7 %)
6 cycles	10(16.1 %)
No	38(61.3 %)
Lymph nodes involved	
Negative	47(75.8 %)
Positive	15(24.2 %)
Type of surgery	
Vaginal HBO + Pelvic ± PAo L	20(32.3 %)
Abdominal HBO + Pelvic L	8(12.9 %)
Abdominal HBO + Pelvic LAo	5(8.1 %)
L + Ommentectomy, Exclusive HBO	16(25.8 %)
Simple Hysterectomy	3(4.8 %)
Other procedures	10(16.1 %)

VLSI: vascular and lymphatic space invasion, NA: not available. HBO: hysterectomy plus bilateral salpingo-oophorectomy PAo: Para-aortic, L:lymphadenectomy.

EBRT was delivered with 6 or 18 MV photons after 3D treatment planning and delineation of clinical target volume (CTV) following RTOG rules.[18] The mean and median dose administered were 45.3 Gy and 45 Gy (range 44 Gy–50.4 Gy) with a dose per fraction of 1.8–2 Gy in 5 fractions per week. Paraaortic (PAo) irradiation was administered in patients in whom PAo lymph nodes were involved in the pathological study or according to the imaging studies.

After EBRT, all the patients received HDR VBT with a single dose of 7 Gy. The placement of applicators was carried out in the operating room, where the patients were examined to ensure the type, diameter and number of applicators. Sixty patients (96.8 %) were treated with the vaginal cylinder technique, and 2 patients (3.2 %) with the colpostat technique. The vaginal cylinder diameter was 3.5 cm in 50 patients (80.6 %), 3 cm in 7 patients (11.3 %) and 2.5 cm in 3 patients (4.8 %). The technique has been described elsewhere.[11] CT planning was then performed, and the CTV of the vagina was delineated every millimeter along the first cylinder with the automatic exclusion of the cylinder by the Oncentra Brachy planning system (v.4.1). Afterwards, the organs at risk contouring was performed followed by a dosimetric study using an active treatment length of 2.5 cm and 7 Gy were prescribed at 5 mm from the applicator surface with point optimization. V100 and D90 at 90 %, EQD2 $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of the vagina of the most exposed part of the vagina were recorded. Overall $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 was calcu-

Table 2
D90, V100 values and EQD2(α/β = 3 Gy) at 2 cm^3 of high-dose area in vaginal wall.

	V100 (cm^3)	D90 (Gy)	EQD2 (α/β = 3 Gy) at 2 cm^3
Mean	7.73	8.12	70.7
Median	7.82	8.12	70.2
Minimum	4.4	4.33	64.4
Maximum	11.32	9.57	77.0
Standard deviation	1.56	0.82	2.54

lated by the sum of the EBRT and VBT dose (Table 2). Patients were treated with a HDR 192-Iridium source using an afterloading system (Nucletron® microSelectron v3 digital HDR source afterloader (ELEKTA, Holland).

After the treatment, the patients were followed every 3–4 months during the first 2 years and then every 6 months up to 5 years. The patients were evaluated in terms of recurrence and side effects by clinical, gynecological examination and imaging studies. Late toxicity of the rectum and bladder was assessed using RTOG scores and late vaginal toxicity was evaluated with the objective criteria of LENT-SOMA (G1: Atrophy, telangiectasias, adherences, < 1/3 shortened vaginal length; G2: Bleeding telangiectasias, symptomatic dryness, 1/3 to 2/3 shortened vaginal length, partial synechiae; G3: Vaginal length < 1/3, deep ulceration, complete synechiae; G4: fistula, obliteration, persistent bleeding).[19,20]

2.1. Statistical analysis

Overall survival analysis was performed using the Kaplan and Meier Method. The possible association of G2 vaginal toxicity with type of applicator, the diameter of cylinders, the age, chemotherapy was analysed using t-student and Chi-square tests. D90, V100 and $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of the vagina were expressed as mean, median, minimum, maximum and standard deviation. Late toxicity was described by frequency tables. The relationship between $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of the vagina and late vaginal toxicity was analysed using the Student's t test, Chi-square test, boxplot and receiver operating characteristic (ROC) curves. Hypothesis contrasts were performed with an alfa error of 5 % and the estimates with a confidence interval of 95 %.[21,22] All the analyses were carried out using the statistical package SPSS v. 25.

3. Results

The mean follow-up was 39.2 months (range 15–68). One VCR was presented at 11 months after brachytherapy, representing 0.8 % of the entire series of 125 patients treated with this schedule. Considering relapses, the outcome of the patients was the following: One patient had an exclusive vaginal relapse, two patients had pelvic and distant metastases, one patient had exclusive pelvic relapse, three patients had exclusive distant metastasis, one patient relapsed as exclusive abdominal carcinomatosis and one patient developed node relapse in paraortic and supraclavicular areas. Fig. 1 shows the overall survival at 2 and 5 years of the entire series.

In the present series acute toxicity was presented as: rectal: G0 in 55patietns, (88.7 %), G1 in 6 patients (9.7 %) and as G2 in one patient (1.6 %); bladder toxicity was present in 11(17.7 %) patients having a G1 score and 51 patients did not develop acute toxicity(82.3 %); 50 patients (80.6 %) did not develop acute vaginal changes, 8 presented G1(12.9 %) problems and only 4 patients developed G2 changes (6.5 %). All the acute toxicity disappeared in the course of the first 3 months.

Two patients (3.2 %) developed late Grade 1 rectal toxicity manifested as mild diarrhoea and increased stool frequency. No patient presented late bladder toxicity. Twenty-six patients had late vaginal toxicity (17 G1 and 9 G2). The late G1 vaginal toxicities appeared as telangiectasias (14.5 %) and/or reducible adherences (12.9 %). Late G2 vaginal problems appeared in 14.5 % as low to moderate bleeding telangiectasias on vaginal examination in 3 patients (4.8 %) and/or 1/3 to 2/3 shortened vaginal length in 6 patients (9.7 %). No G3 and G4 vaginal toxicities were observed. Table 3 shows the late toxicity of the entire series.

Table 3
Late toxicity.

Late toxicity	
Rectum	G0: 60(96.8 %), G1:2(3.2 %), G2–4:0(0 %)
Bladder	G0:62(100 %), G1–4:0(0 %)
Vagina	G0:36(58.1 %), G1:17(27.4 %), G2: 9(14.5 %), G3–4:0(0%)

In the 9 patients with G2 vaginal toxicity, the diameter of the cylinders was 3.5 cm in 5 patients, 3 cm in one patient and 2.5 cm in 3 patients. No significant increase of G2 toxicity was found in those patients using colpostats in comparison to those treated with vaginal cylinders (p = 0.554). No patients receiving chemotherapy were found to have an increase in G2 toxicity as compared with those not receiving chemotherapy (p = 0.72). When the age was analyzed, no relation was found between G2 vaginal toxicity and age over 65 (p = 0.354).

The $EQD2_{(\alpha/\beta=3Gy)}$ for the EBRT received in patients that developed late G2 toxicity was 43.2 Gy in 5 patients, 44 Gy in 1 patient, 46 in 2 patients and 50 Gy in one patient. The mean dose to the vaginal surface was 74.1 Gy $EQD2_{(\alpha/\beta=3)}$ (range 58.1–79.7) and 63.6 Gy $EQD2_{(\alpha/\beta=10)}$ (range 56.7–68.9). The median $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of the vagina in patients presenting G2 late toxicity was 72.5 Gy (range 68.5 Gy–77 Gy, SD 2.94), and in patients having G0-G1 toxicity, the median value at 2 cm^3 of the vagina was 70.4 Gy (range 64.4 Gy–77.3 Gy, SD 2.36).

There was an association between G0-G1 toxicity and G2 toxicity on analysing $EQD2_{(\alpha/\beta=3Gy)}$(p = 0.018). The boxplot suggested a cut point to identify the absence of G2 toxicity: 100 % of G2 toxicity cases received doses greater than 68 Gy (Fig. 2). ROC curves showed an area under the curve of 0.72, and 68 Gy had a sensitivity of 1 and a specificity of 0.15 (Fig. 3).

4. Discussion

High-dose-rate VBT combined with EBRT is used in the treatment of patients with postoperative EC who have intermediate-risk with poor prognostic factors and in high-risk patients, as well as in patients with stage II and advanced stages of the disease. According to the different guidelines, the indications for treatment vary, with some not recommending VBT associated with EBRT. Nevertheless, the lack of randomized trials on treatment combinations and the low risk of G2-4 complications have led to this technique being accepted by other guidelines.[5,6,23–26] Another argument for not adding VBT is the presence of vaginal stenosis which has been reported in up to 13 % of patients.[27] Vaginal relapses in these patients range between 0 and 6% depending on the series with combined treatment. In our experience the VCR rate is 0.9 % with an exclusive fraction of 7 Gy. Despite excellent local control, some patients present side effects that can have a negative impact on the quality of life, such as the 14.5 % G2 problems in the present series but only 9.7 % of vaginal shortening of more than one third.

The isoeffective dose or EQD2 to 2 cm^3 of an organ using an alfa/beta of 3 is accepted to assess the dose in OAR for late effects. The literature provides recommended dose limits in the bladder, rectum and in sigma, but not for the vagina as an OAR for VBT.[5] Vaginal toxicity after radiotherapy has been discussed for years in patients with curative cervical cancer but not in postoperative treatments; however, the correlation of vaginal toxicity with the vaginal dose for patients with endometrial carcinoma is quite a

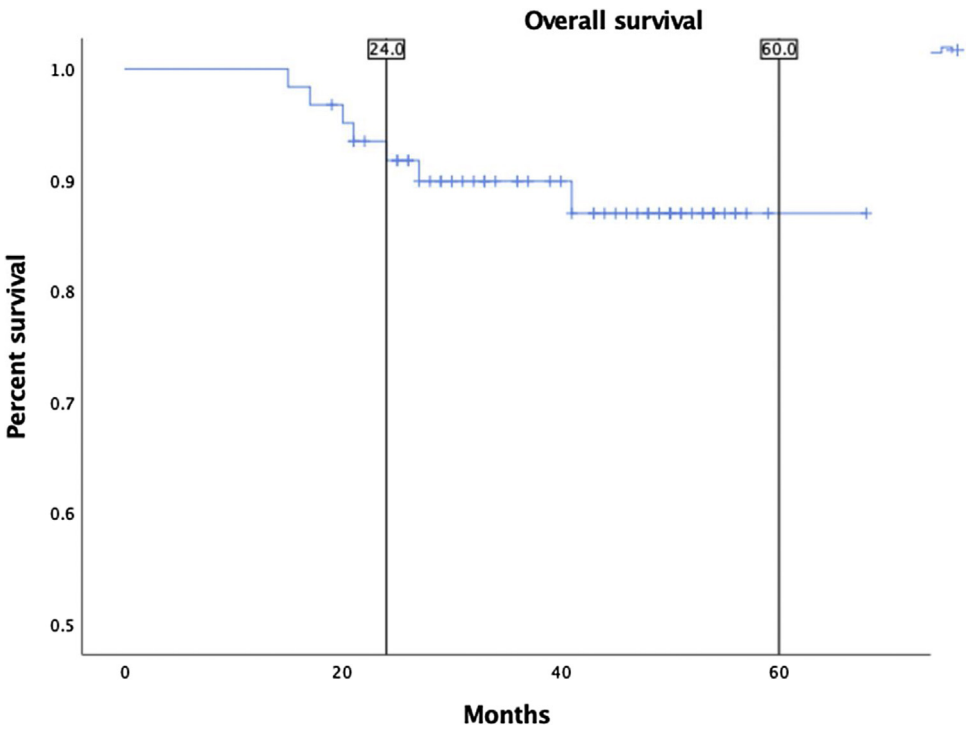

Fig. 1. Overall survival at 2 and 5 years.

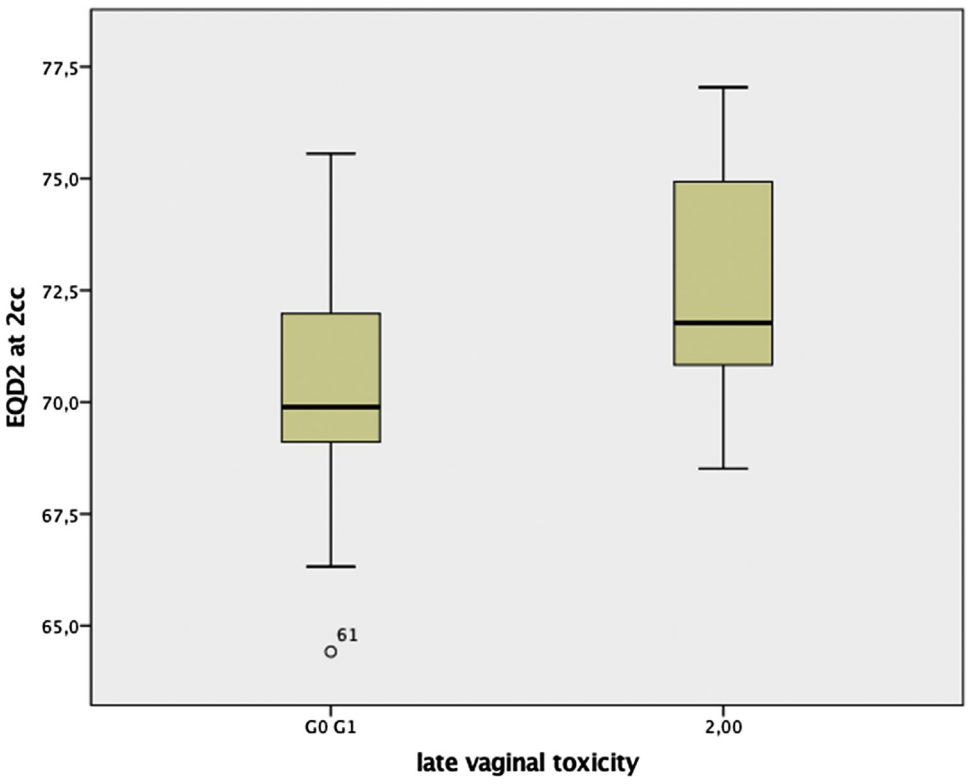

Fig. 2. $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of vagina and G0-G1 vs.G2 vaginal toxicity.

new topic in the literature. With the aim of analyzing the relationship between $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of the vagina and late vaginal toxicity in postoperative EC, we retrospectively evaluated 62 patients treated with EBRT + VBT and found that doses over 68 Gy $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of the most exposed area of the vagina were associated with late G2 vaginal toxicity. All of the patients who developed G2 toxicity received $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of the most exposed area of the vagina greater than 68 Gy. The ROC curves showed that 68 Gy had a sensitivity of 1 and a specificity of 0.15.

Multiple reported risk factors including fractionation schedule, age, chemotherapy cylinder diameter, overall vaginal surface dose and length of the vagina treated contribute to late vaginal toxicity.

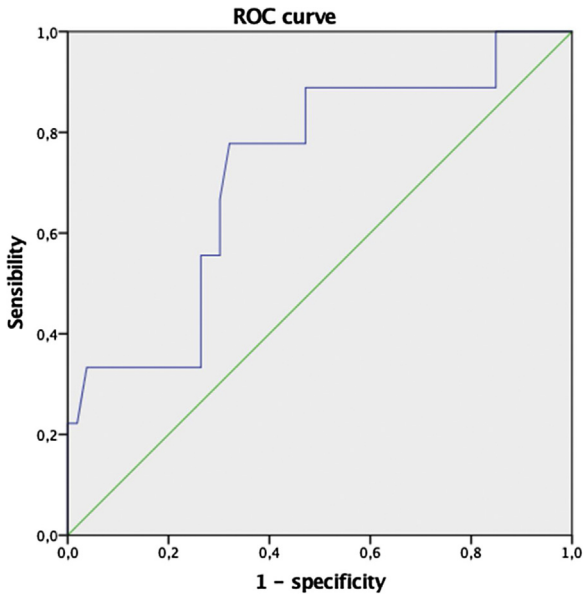

Fig. 3. ROC Curve 68 Gy had a sensitivity of 1 and a specificity of 0.15.

Agnes Y et al. retrospectively analyzed 100 patients with PEC who received exclusive VBT with the median follow-up of 24 months and found a correlation of the active length ≥ 5 cm with increased vaginal toxicity (p = 0.002).[13] In the present series, the active treatment length was 2.5 cm suggesting less shortening of the vagina, which was found to be > 1/3 in 9.7 % of the patients. Another study by Jack et al. recruited 304 patients treated with exclusive HDR brachytherapy after surgery for early stage endometrial carcinoma and demonstrated that small cylinders defined as a size of 2.3 cm or less were associated with higher risk of grade 1–2 vaginal stenosis (p = 0.007).[16] In the present series, the cylinder diameter was 3.5 cm in 80.6 % and 3 cm in 11.3 % and cylinders < 2.5 cm were not used, with a subsequent lower incidence of complications after EBRT. In the present series, age and chemotherapy were not associated with vaginal toxicity. In a previous report from our group, we did not find the incidence of vaginal toxicity to be associated with age (28). In the present series, the only 3 patients treated with 2.5 cm have developed G2 vaginal complications as reported in other studies. The smaller the cylinder diameter, the higher dose to the vaginal mucosa surface. In the present series, we found a cut off EQD2 of 68 Gy at 2 cm of the most exposed area of the vagina that allows to limit the vaginal G2 toxicity in the patients in need of ≤ 2.5 cm diameter of vaginal cylinders when associated with a pelvic radiotherapy dose superior to 45 Gy.

With regard to the fractionation schedule, Sorbe et al. performed a study comparing 2.5 Gy × 6 fractions vs. 5 Gy × 6 fractions and showed that vaginal shortening was significant in the 5 Gy group.[29] Moreover, in the Sorbe study there is no analysis of the cylinder diameter in the analyzed groups. Previous studies by our group have reported that a single dose of 7 Gy does not increase late vaginal toxicity in comparison with other schedules in the same institution. In addition, the incidence of late vaginal toxicity was within the lower range in the literature with an incidence of between 0 % and 17 %.[9,11,27]

A study including 53 women by Susko et al. reported the relationship between $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 of vagina and late vaginal toxicity assessed by CTCAE v.4.0 scores. EQD2 ($\alpha/\beta = 3$ Gy) at 2 cm^3 was found to be a significant predictor of G2+ vaginal toxicity with a rate of 21 % (95 %CI 8.4–33.5) at 2 years (p = 0.008). A cut off of 130 Gy EQD2($\alpha/\beta = 3$ Gy) at 2 cm^3 was significant for grade 2 or greater vaginal toxicity (p = 0.003).[30] Taking into account the differences in VBT dose, the active length and evaluation system for late toxicity in the study by Susko, we performed a study of 67 postoperative EC patients treated with VBT ± EBRT and found that late G2 toxicity was similarly associated with 68 Gy $EQD2_{(\alpha/\beta=3Gy)}$ at 2 cm^3 (p = 0.03) (17). Considering the lack of homogeneity in patient treatment, we carried out the present study to analyze this correlation in patients receiving only EBRT + VBT and a dose greater than 68 Gy was found to be related to late G2 vaginal toxicity.

According to the above results, G2 late vaginal toxicity would be minimized or eliminated by reducing the $EQD2_{(\alpha/\beta=3Gy)}$ dose to less than 68 Gy at 2 cm^3 of the vagina. In addition, guidelines and previous data recommend the use of dilators to prevent toxicity as well as the use of topical therapy with hyaluronic acid and estrogen creams for the vagina.[12–15]

In view of the limitation of the small number of patients included in the present study, further studies with a larger number of patients are needed to obviate bias. Moreover, there could be other factors that may affect vaginal toxicity, such as the type of surgery and age which have demonstrated a negative impact on vaginal status in a previous analysis.[28] Another limitation of the present study is the lack of information on vaginal relapses in patients receiving doses < 68 Gy $EQD2_{(\alpha/\beta=3Gy)}$. Nevertheless, there is currently a lack of consensus on adding VBT to EBRT, and patients treated only with EBRT always receive a dose in the vagina < 68 Gy $EQD2_{(\alpha/\beta=3Gy)}$. Considering the above, the constraint found in the present study, < 68 Gy $EQD2_{(\alpha/\beta=3Gy)}$ to 2 cm^3 of the most exposed area could be a sufficient dose to treat these patients to reduce G2 complications.[5,6,23–26] Nonetheless, further prospective studies are needed to establish the dose limit.

5. Conclusions

A dose greater than 68 Gy EQD2($\alpha/\beta = 3$ Gy) at 2 cm^3 of the most exposed area of the vagina was associated with late G2 vaginal toxicity in postoperative EC patients treated with EBRT + VBT. These results suggest that a dose < 68 Gy could be a very good dose limit to eliminate the risk of G2 late vagina toxicity, mainly vaginal shortening. The specificity of the present analysis generates the need for prospective analyses.

Financial disclosure

Grant Spanish Association Against Cancer Foundation (AECC) (PS141526ROVI).

Conflict of interest

None declared.

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