Radiotherapy and Oncology 189 (2023) 109909

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Are 7.5 Gy×2 fractions more efficient than 6 Gy×3 in exclusive postoperative endometrial cancer brachytherapy? A clinical and dosimetrical analysis

Faegheh Noorian [a,b], Rosa Abellana [b], Yaowen Zhang [c], Antonio Herreros [a,b], Clara Baltrons [a], Valentina Lancellotta [d], Luca Tagliaferri [d], Sebastia Sabater [f], Aureli Torne [e], Angeles Rovirosa [a,b,*]

[a] Radiation Oncology Dpt. Hospital Clínic Barcelona, C/ Villarroel, 170, 08036 Barcelona, Spain
[b] Fonaments Clínics Dpt. Faculty of Medicine, Universitat de Barcelona, C/ Casanovas 153, 08036 Barcelona, Spain
[c] Cancer Center, Henan Provincial People's Hospital, No.7 Weiwu Road, Zhengzhou 450003, China
[d] U.O.C. Radioterapia Oncologica, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome 00168, Italy
[e] Gynecological Cancer Unit, Hospital Clinic Barcelona, C/ Villarroel, 170, 08036 Barcelona, Spain
[f] Hospital General de Albacete, Albacete, Spain

ARTICLE INFO

Keywords:
Vaginal-cuff brachytherapy
Fractionation schedules
Endometrial cancer

ABSTRACT

Purpose: To compare two vaginal brachytherapy (VBT) schedules in postoperative endometrial carcinoma (PEC) patients considering vaginal-cuff relapses (VCR), late toxicities, dosimetry analysis and vaginal dilator use.
Material and methods: 110 PEC patients were treated with exclusive high-dose-rate VBT using two schedules. Group-1:44-patients received 6 Gy×3fractions (September-2011-April-2014); Group-2:66-patients were treated with 7.5 Gy×2fractions with a dose limit of equivalent total doses in 2-Gy fr ($EQD2_{(\alpha/\beta=3)}$) of 68 Gy in the most exposed 2 cm^3 of clinical target volume (CTV) (July-2015-November-2021). The dose was prescribed at 5 mm from the applicator surface. Were evaluated the overall radiation dose delivered to 90% of the CTV (D90), the CTV receiving 100% of the prescription dose (V100) and the $EQD2_{(\alpha/\beta=3)}$ received in the most exposed 2 cm^3 to dose in CTV. Late toxicity was prospectively assessed using RTOG scores for bladder and rectum and objective LENT-SOMA criteria for late vaginal toxicity (LVT). Statistics: Descriptive analysis, Chi-square, Student's t-tests and Kaplan and Meier method.
Results: The median follow-up was 60 months (15.9–60). There were no VCR or late toxicities in bladder or rectum. LVT ≥ G1 appeared in 26/44 (59.1%) in Group-1 and 25/66 (37.9%) in Group-2. The mean $EQD2_{(\alpha/\beta=3)}$ received by the most exposed 2 cm^3 of CTV was 63.7 Gy ± 10.0 in Group-1 and 60.5 Gy ± 3.8 in Group-2 ($p = 0.063$). There were no differences in adherence to vaginal dilator use ≥9 months, overall D90 and V100.
Conclusion: Considering the lack of vaginal relapses and similar LVT over time, 7.5 Gy×2fractions seem more efficient in terms of patient comfort, workload, and cost. This is the first study using dosimetry parameters to compare effectivity of schedules. Larger series are needed to confirm the present results.

Abbreviations: EC, Endometrial cancer; SD, standard deviation; CT, Computerized tomography; OAR, Organs at risk; 3D, Three dimensional; CI, Confidence interval; VBT, Vaginal brachytherapy; VLSI, Vascular and lymphatic space invasion; VCR, Vaginal-cuff recurrence; EBRT, External beam radiotherapy; HDR, High-dose-rate; LVT, Late vaginal toxicity; PEC, Postoperative endometrial cancer; CTV, Clinical target volume; D90, Overall radiation dose delivered to 90% of the CTV; V100, Volume of the CTV receiving 100% of the prescribed dose; EQD2, Equivalent total doses in 2-Gy fractions.

* Corresponding author at: Fonaments Clínics Dpt. Universitat de Barcelona, C/ Casanovas 153, 08036 Barcelona, Spain.
E-mail addresses: Fnoorian@clinic.cat (F. Noorian), rabellana@ub.edu (R. Abellana), 250522926@qq.com (Y. Zhang), HERREROS@clinic.cat (A. Herreros), baltrons@clinic.cat (C. Baltrons), valentina.lancellotta@policlinicogemelli.it (V. Lancellotta), luca.tagliaferri@policlinicogemelli.it (L. Tagliaferri), ssabatem@gmail.com (S. Sabater), ATORNE@clinic.cat (A. Torne), rovirosa@ub.edu (A. Rovirosa).

https://doi.org/10.1016/j.radonc.2023.109909
Received 20 May 2023; Received in revised form 4 September 2023; Accepted 5 September 2023
Available online 11 September 2023

Introduction

Endometrial cancer (EC) is the second most common gynecological malignancy worldwide and the first in developed countries, with a 5-year prevalence of 34.7%. In Spain, it is the third most common cancer in women following breast and colorectal cancer [1–4].

Vaginal brachytherapy (VBT) is often recommended and in patients treated with exclusive VBT, vaginal-cuff failure ranges from 0–3.1% and pelvic recurrences occur in 0–4.1% of patients depending on the series. Exclusive adjuvant VBT yields very low rates of vaginal-cuff recurrence (VCR) with minimal treatment toxicity compared to external beam radiotherapy (EBRT) [5–9].

Late vaginal toxicity (LVT) appears in up to 50% of cases depending on the series and the scoring system used, and can result in some cases of vaginal wall atrophy, bleeding, stenosis, and/or decreased vaginal length leading to sexual dysfunction and subsequent adverse impacts on patient quality of life. It is also important to maintain the vaginal canal open to facilitate pap-smear screening and gynecological examination to detect tumor recurrence. The total VBT dose, fractionation, length and depth of vagina treated all contribute to the risk of potential LVT. Interventions, such as the use of a vaginal dilator and resumption of sexual intercourse, is recommended to decrease the risk of LVT. In high-dose-rate (HDR) VBT there is no consensus regarding the optimal dose and fractionation schedule, vaginal treatment length, or depth of dose specification for VBT delivery. The dose is most prescribed to the proximal 5 mm or vaginal surface, and the treated length is the proximal 1/3–1/2 of the vagina, with no agreement among centers [9–14].

Our team has previously reported the results of comparing three different exclusive HDR brachytherapy schedules: 6 fractions (fr) of 4–6 Gy, 3-4fr per week, 4fr of 5–6 Gy administered daily and 6 Gy×3fr on 3 consecutive days (dose prescribed at 5 mm from the applicator surface). 6 Gy×3fr daily seemed to be safe and the optimal treatment of these 3 schedules. The results of previous retrospective studies showed the value of a dose limit for reducing G2 vaginal stenosis and the preliminary results of a prospective study establishing a 68 Gy-equivalent total doses in 2-Gy fr $(EQD2)_{(\alpha/\beta=3)}$ constraint in the most exposed 2 cm^3 of CTV in postoperative EC (PEC) VBT showed a reduction in complications without VCR [15,16]. The present study, compared the clinical outcomes of 7.5 Gy×2fr with a 68 Gy-$EQD2_{(\alpha/\beta=3)}$ constraint in the most exposed 2 cm^3 of CTV and 6 Gy×3fr in women with early-stage postoperative EC (PEC) undergoing exclusive VBT after surgery from 2011-2021. Age, late toxicities, vaginal dilator adherence $\geq$ 9 months and dosimetry parameters, such as clinical target volume (CTV), overall radiation dose delivered to 90% of the CTV (D90), and volume of the CTV receiving 100% (V100) were used for this comparison. For the first time, dosimetry parameters were used to compare schedules.

Material and methods

The present study was approved by the Institutional Ethical Review Board of our center (HCB 2022/0379) and patient consent for study participation was obtained. The patients analyzed were PEC patients treated with exclusive HDR VBT from 2011 to 2021 with at least 12 months of follow-up. One hundred ten patients fulfilled the inclusion criteria and were divided into two groups: Group-1: 44 patients treated with 6 Gy×3fr on three consecutive days from September 2011 to April 2014; Group-2: 66 patients treated with 7.5 Gy×2fr on two consecutive days from July 2015 to November 2021 in whom a limit of 68 Gy-EQD2 in the most exposed 2 cm^3 of CTV was established.

This was a retrospective review of prospectively collected patient data on toxicity and vaginal control. We analyzed these two fractionations in relation to VCR, late toxicities in vagina, rectum, and bladder, CTV, V100, $EQD2_{(\alpha/\beta=3)}$ in the most exposed 2 cm^3 of vagina, $EQD2_{(\alpha/\beta=3)}$ of overall D90 and use of dilators $\geq$ 9 months vs. no use or <9 months.

All the patients underwent surgery after the diagnosis of EC based on the clinical history, physical examination, pathological and imaging assessment including magnetic resonance, computerized tomography (CT) and/or ultrasonography and/or positron emission tomography. Staging was performed based on European Society for Gynecological Oncology-European Society for Treatment in Radiation Oncology-European Society of Pathology (ESGO-ESTRO-ESP9 guidelines and intermediate-risk patients underwent exclusive VBT after surgery [2].

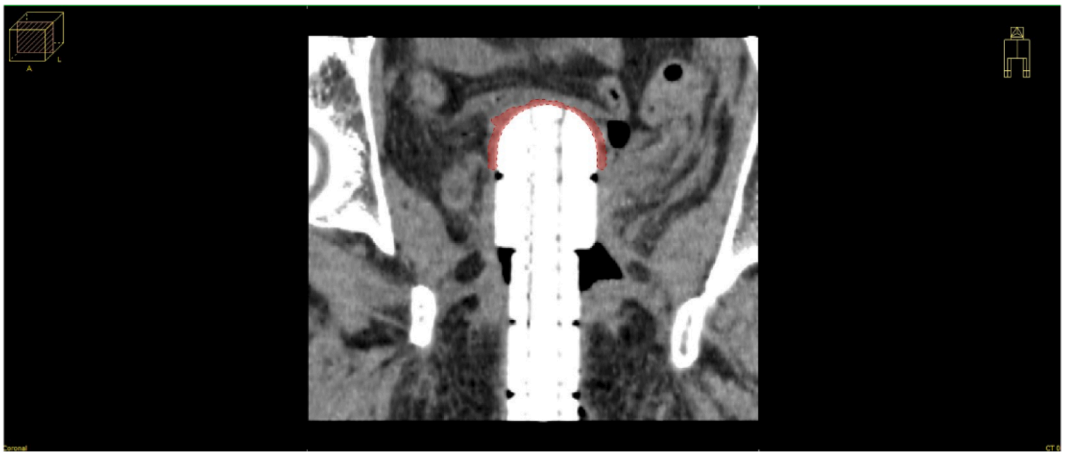
The first applicator placement was performed in the operating room, where patients were examined to confirm correct healing of the vaginal wound and determine the diameter of the applicator required. Then, CT images using 1 mm thick slices were obtained for 3-dimensional (3D) VBT-planning. After defining the treatment volume and organs at risk (OAR), treatment planning was performed in each patient. The vaginal CTV was delineated 2.5 cm along the first cylinder with automatic exclusion of the cylinder based on Hounsfield number discrimination. Thereafter, the CTV was manually corrected for excess or defect of inappropriate vaginal wall thickness (Fig. 1). OARs (bladder and rectum) were delineated outlining the outer contour. The CTV of the vagina was duplicated for also being considered as an OAR. The dose was prescribed at 5 mm from the applicator surface with point-based distance optimization of the dose distribution. The active source treatment length was 2.5 cm in the case of cylinders and colpostat's size was adapted to each patient.

The patients were followed at 15 days after treatment completion and then every 3 or 4 months in the first 2 years and every 6 months thereafter until 5 years. The presence of local, pelvic, or distant recurrence was assessed by clinical and radiological methods. Complications were determined by gynecological examination, clinical interview and, when necessary, radiological tests, among others. Rectal and bladder late toxicity were graded using RTOG criteria. The objective LENT-SOMA criteria are used for LVT: Late vaginal stenosis/shortening grade-1 is defined as shortening of vaginal length < 1/3 of the primary vaginal lengt; telangiectasias and adherences were also considered as grade-1. Grade-2 was considered as 1/3 to 2/3 of the primary vaginal length (vaginal bleeding is also included in grade-2), and grade-3 as vaginal length < 2/3 of the primary vaginal length. Evaluation of vagina shortening was first clinical (none or some visual images of shortening), then by manual exam (trying to open the vagina in all the cases and mainly when shortening is suspected). The next procedure is performed in the coronal CT topogram of the first application: measure of the distance from the top of applicator to the upper part of the pubic symphysis for comparison with the clinical exam. Vaginal cylinders are then used to confirm the previous aspects in doubtful cases. To analyze LVT, the $EQD2_{(\alpha/\beta=3)}$ was calculated for each patient at 2 cm^3 of the most exposed part to the dose in the CTV [17,18]. The overall D90 $EQD2_{(\alpha/\beta=3)}$ and V100 were also registered in each patient.

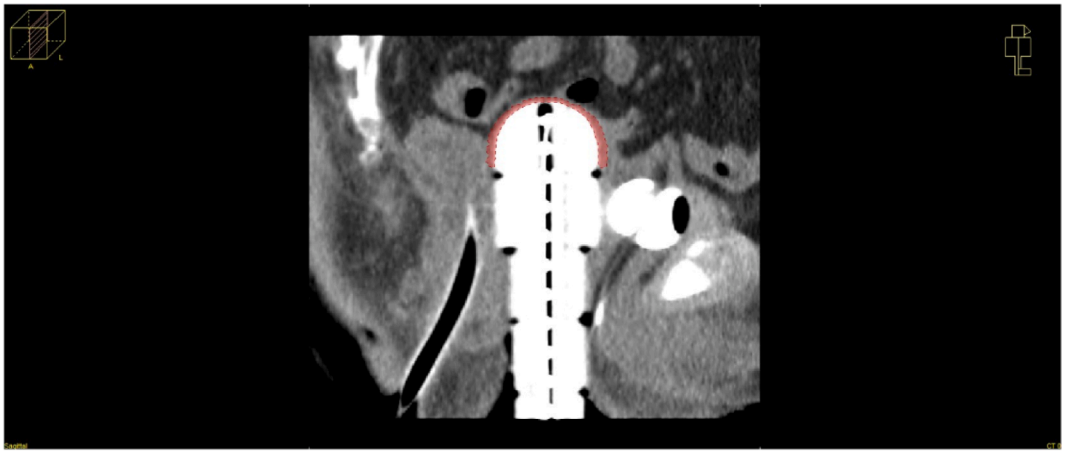
After treatment, patients were advised to use vaginal dilators, adapted to vaginal size, prophylactically every day until the last follow-up at five years.

Statistical analysis: Categorical variables were expressed using frequencies and percentages, while continuous data were described using mean and standard deviation (SD) or median and interquartile range. The homogeneity study between dose regimens groups was performed using the chi-square test for the categorical variables or a Student's t-test in the case of continuous variables. The mean, median or proportions differences between dose regimens groups were estimated with a 95% confidence interval (CI). The effect of dose regimen and other prognostic factors on time to LVT appearance was investigated using the Cox proportional hazards model. The Kaplan-Meier estimator was used to estimate the survival function (or probability that LVT will not appear during each month). The analyses were performed using R software version 4.2.2 package (R project for statistical computing; Vienna, Austria).

a) Coronal view



b) Sagittal view.



c : Axial view.

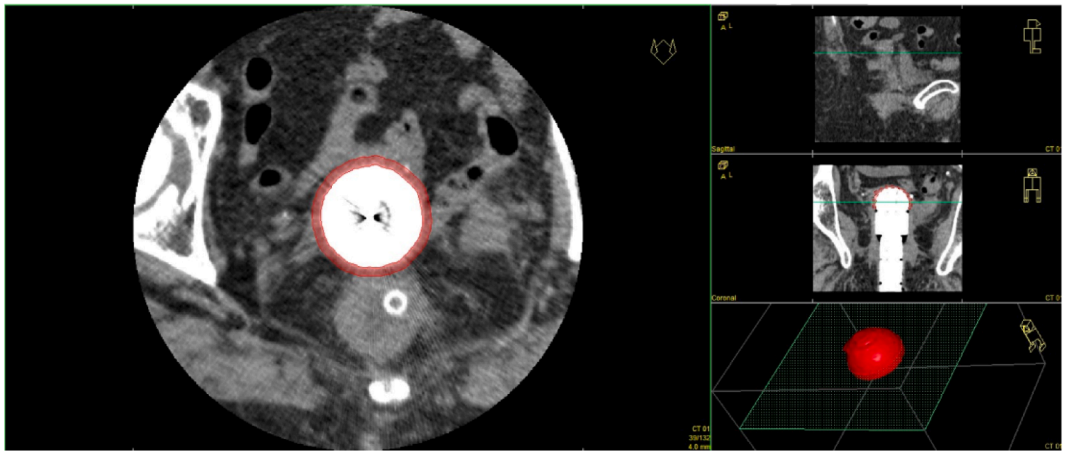


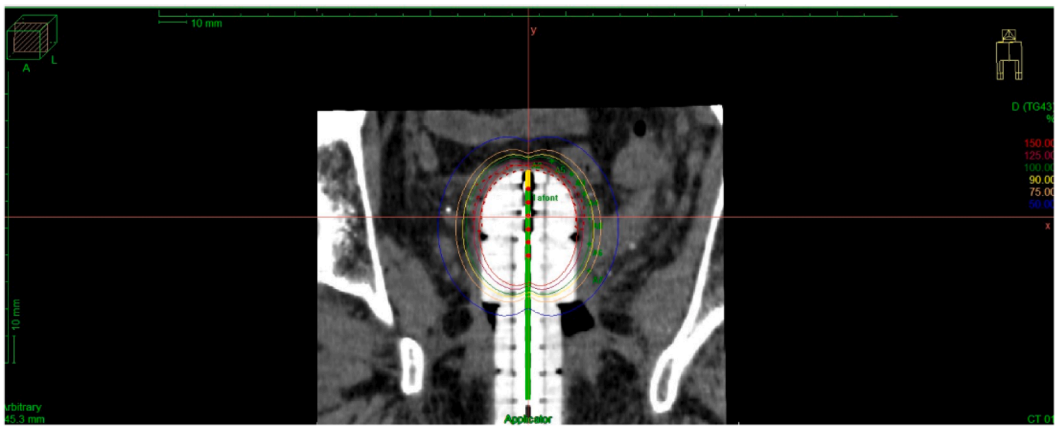
Fig. 1. 1.1: CTV is contoured adding 3 mm to the first cylinder with posterior automatic exclusion of the cylinder. Then, CTV is modified manually for excess or defect of vaginal wall. The color red shows the CTV. a) coronal view; b) sagittal view; c) axial view. 1.2 Dosimetry study. Dose prescription at 5 mm from the applicator surface with point-based distance optimization of the dose distribution. a) Coronal view. 1.2 Dosimetry study. b) Sagittal view. 1.2 Dosimetry study. c) Axial view.

Results

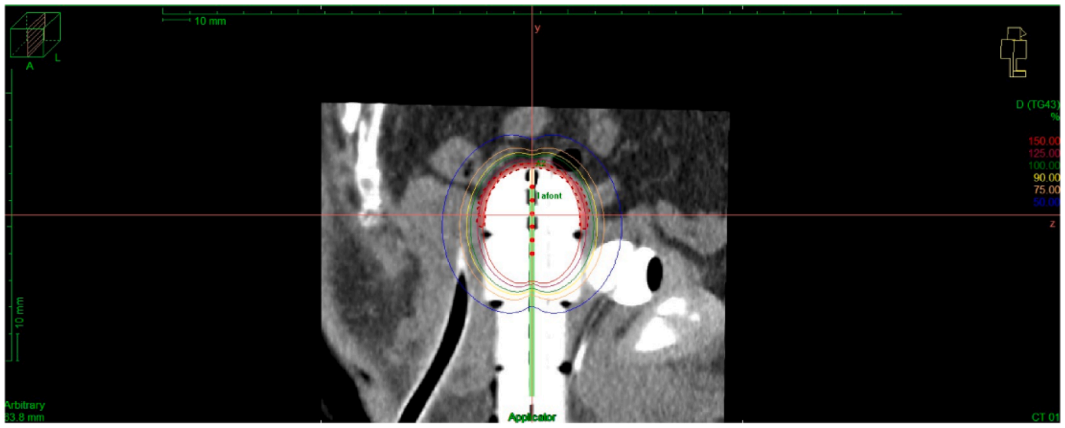
We followed 110 eligible patients for a median of 60 months (55.2–60.0) in Group-1 and 51.3 months (15.9–60.0) in Group-2.

Table 1 shows the comparison of prognostic factors of local recurrence between the two study groups. These values were homogeneous except for vascular and lymphatic space invasion (VLSI), which was focal in all the patients in whom it was found. The intention to treat was

a) Coronal view



b) Sagittal view.



c) Axial view.

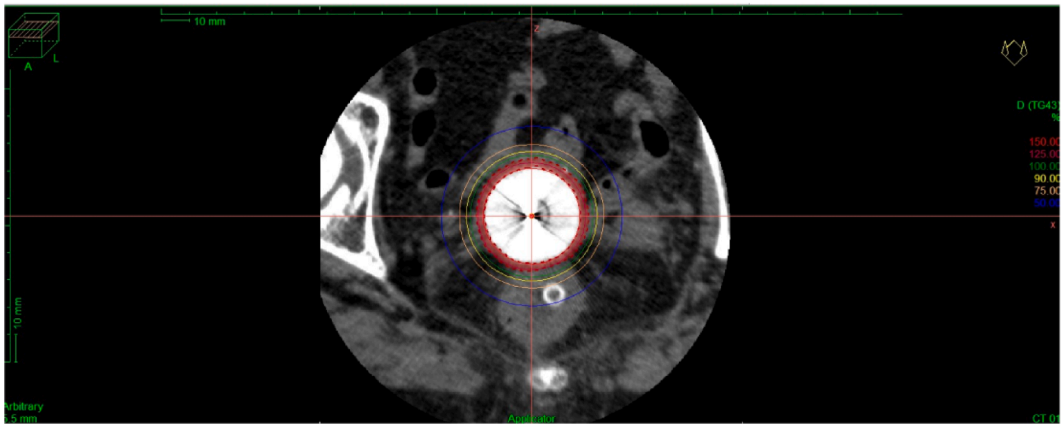


Fig. 1. (*continued*).

<8 weeks after surgery. However, the COVID pandemic and the increased number of patients received from other hospitals and the complete health of vaginal scar has increased the time interval to a mean of 9.53 weeks (SD 6.27).

Tables 2 and 3 show the characteristics of VBT. In Group-2 a 68 Gy-$EQD2_{(\alpha/\beta=3)}$ constraint was necessary in 4 patients (3/4 received 7.25 Gy×2fr and 1/4 7 Gy×2fr) and 4 patients in Group-1 received a dose > 68 Gy-$EQD2_{(\alpha/\beta=3)}$ in the most exposed 2 cm^3 of CTV. The mean $EQD2_{(\alpha/\beta=3)}$ received by the most exposed 2 cm^3 of CTV was 63.7 Gy (SD ± 10.0) in Group-1 and 60.5 Gy (SD ± 3.8) in Group-2 (p = 0.063). There were no differences between the two groups in vaginal dilator adherence, overall D90, V100 and CTV.

No patient presented rectal or bladder late toxicity or VCR. One patient in Group-1 showed pelvic lymph node relapse. In Group-2 three patients showed non-vaginal relapses: One patient had pelvic lymph node relapse, one patient showed pelvic lymph node relapse and peritoneal metastasis, and another patient presented distant recurrence in the lung, peritoneum and lymph nodes (p = 0.532).

Table 1
Clinical characteristics of the entire sample of patients and by study group.

	ALL N = 110	Group-1 N = 44	Group-2 N = 66	Difference [95% CI]	p-value	N
Mean Age (SD)	65.8 (9.1)	64.8 (8.3)	66.4 (9.5)	−1.69 [−5.18; 1.80]	0.337	110
Myometrial invasion (n, (%))						
≥50%	40 (36.4%)	17 (38.6%)	23 (34.8%)	3.8% [−16.5; 24.1]	0.690	110
<50%	70 (63.6%)	27 (61.4%)	43 (65.2%)			
Pathologic types (n, (%))						
Endometrioid	97 (88.1%)	40 (89.5%)	58 (85.3%)	2.27 [0.726; 0.10]	0.14	110
Serous	1 (0.9%)	0 (0%)	1(0.9%)			
Clear cell	2 (1.8%)	0 (0%)	2 (1.8%)			
Mixed	10 (0.9%)	4 (10.5%)	9 (8.1%)			
Histologic grade						
G1 + 2	93 (84.5%)	41 (93.2%)	52 (78.8%)	−11 [−50;050]	0.075	110
G3	17 (15.5%)	3 (6.8%)	14 (21.2%)			
Mean Tumor size (SD)	1.9 (1.5)	1.9 (1.6)	2.0 (1.5)	0.1 [−0.76; 0.53]	0.720	98
Focal VLSI (n, (%)						110
Yes	11 (10.0%)	1 (2.3%)	10 (15.1%)	−12.9% [−24.5; −1.3]	0.027	
No	99 (90%)	43 (97.7%)	56 (84.9%)			
FIGO stage: (n, %)						
IA	66 (60.0%)	27 (61.4%)	39 (59.1%)	2.3% [−18.7; 22.8]	0.318	110
IB	40 (36.4%)	17 (38.6%)	23 (34.8%)	3.8% [−16.5; 24.1]		
II	4 (3.6%)	0 (0.0%)	4 (6.1%)	−6.1% [−13.7; 1.6]		
Chemotherapy (n, (%)):						
Yes	2 (1.8%)	0 (0.0%)	2 (3.0%)	−3.03% [−9.4; 3]	0.516	110
No	108 (98.2%)		64 (97%)			
Vaginal dilator adherence (n, %)						
≥9 months	35 (31.8%)	12 (27.3%)	23 (34.8%)	−7.6% [−26.9; 11.8;]	0.415	110
<9 months	75 (68.2%)	32 (72.3%)	43 (65.2%)			

SD: Standard deviation. VLSI: vascular and lymphatic space invasion. N,n: number: CI: confidence interval.

Table 2
Brachytherapy characteristics for the entire sample of patients and by study group.

	ALL	Group-1	Group-2	P value	N
BT Technique (n, (%)):				1.000	110
Cylinders	106 (96.4%)	42 (95.5%)	64 (97.0%)		
Colpostats	4 (3.6%)	2 (4.5%)	2 (3.0%)		
Cylinder diameter (n, (%)):				0.560	106
2.5	3 (2.8%)	2 (4.7%)	1 (1.6%)		
3.0	16 (14.5%)	5 (11.4%)	11 (16.7%)		
3.5	87 (79.1%)	35 (79.5%)	52 (78.8%)		
Colpostats in cm: (n, (%))					
2.0	1 (25.0%)	1 (50.0%)	0 (0.00%)	0.333	4
2.5	1 (25.0%)	1 (50.0%)	0 (0.00%)		
3.0	2 (50.0%)	0 (0.00%)	2 (100%)		

BT: brachytherapy; n: number; cm: centimeters.

LVT appeared in 51/110 (46.4%) patients: 26/44 (59.1%) in Group-1 and 25/66 (37.9%) patients in Group-2 (p = 0.032). Among patients presenting LVT, 26/110 (23.6%) had only telangiectasia: 18/44 (40.9%) and 8/66 (12.1%) in Groups-1 and 2 respectively (p < 0.001). Vaginal stenosis/shortening was detected in 38/110 (34.5%) patients: 19/44 (43.2%) patients in Group-1 and 19/66 (28.8%) patients in Group-2 (p = 0.119). In Group-1, 13/44 (29.5%) patients showed grade-1 (5/44 (11.4%): dog ear, 8/44 (18.2%) stenosis/shortening < 1/3 of vagina), 5/44 (11.4%) grade-2 and only one patient (3%) showed grade-3 late vaginal stenosis/shortening, while in Group-2, 15/66 (22.7%) patients showed grade-1 (6/66 (9%) dog-ear, 9/66 (13.6%) stenosis/shortening < 1/3 of vagina) and 4/66 (6.1%) grade-2 (p = 0.224).

The median follow-up in Group-1 was 60 months (range 55.2–60.0) and in Group-2 51 months (range 15.9–60.0). The mean time to LVT was similar in both dose regimens, being 21.1(SD ± 14.6) months in the whole series. The mean time to G1 LVT was 21.3 months (SD ± 12.1) in Group-1 and 17.6 months (SD ± 14.7) in Group-2 (p = 0.266). The mean time to G ≥ 2 LVT was 29.6 (SD ± 18) months in Group-1 and 29.5 (SD ± 17) months in Group-2 (p = 0.999).

Fig. 2 and Table 4 indicate that despite the different number of LVT cases between the two groups, the monthly incidence rate of LVT was similar:1.5% [1;2.2] in Group-1 and 1.1% [0.7;1.6] in Group-2 (HR 1.5,

Table 3
Dosimetry parameters and vaginal toxicity.

	All	Group-1 (35)	Group-2 (66)		P-value	N
Mean $EQD2_{(\alpha/\beta=3)}$ in 2 cm^3 of CTV(SD)	61.6 (6.8)	63.7 (10.0)	60.5 (3.8)		0.063	101
Mean $EQD2_{(\alpha/\beta=3)}$ in D90(SD)	40.6 (6)	40.7 (7.5)	40.5 (5)		0.900	100
Mean V100 cc (SD)	8.0 (1.4)	8.2 (1.6)	7.9 (1.3)		0.444	101
Mean CTV volume (SD)	8.1 (1.5)	8.30 (1.7)	8.03 (1.5)	1.12 [0.86;1.45]	0.408	101
Mean $EQD2_{(\alpha/\beta=3)}$ 2 cm^3 of bladder (SD)	21.2(5.2)	21.43(5.4)	21.2(5.1)	1.08[1.91;2.40]	0.821	101
Mean $EQD2_{(\alpha/\beta=3)}$ 2 cm^3. of rectum (SD)	16.2(7.9)	24.2(7)	21.3(4.5)	1.14(0.5616:5.0987)	<0.0150	101
Late vaginal toxicity:						110
No	59 (53.6%)	18 (40.9%)	41 (62.1%)	Ref.	Ref.	
≥G1	51 (46.4%)	26 (59.1%)	25 (37.9%)	2.34 [1.08;5.21]	0.032	
Mean time to G ≥ 1 appearance (months) (SD)	21.1(14.6)	24(13.6)	19.5(15.4)	95% CI: −3.6427—2.7249	0.270	110

SD: standard deviation. EQD2: Equivalent dose to a fractionation of 2 Gy per fraction. CTV: Clinical Target volume. V100: Volume receiving the 100% of dose. D90: isodose that receives the 90% of the dose.

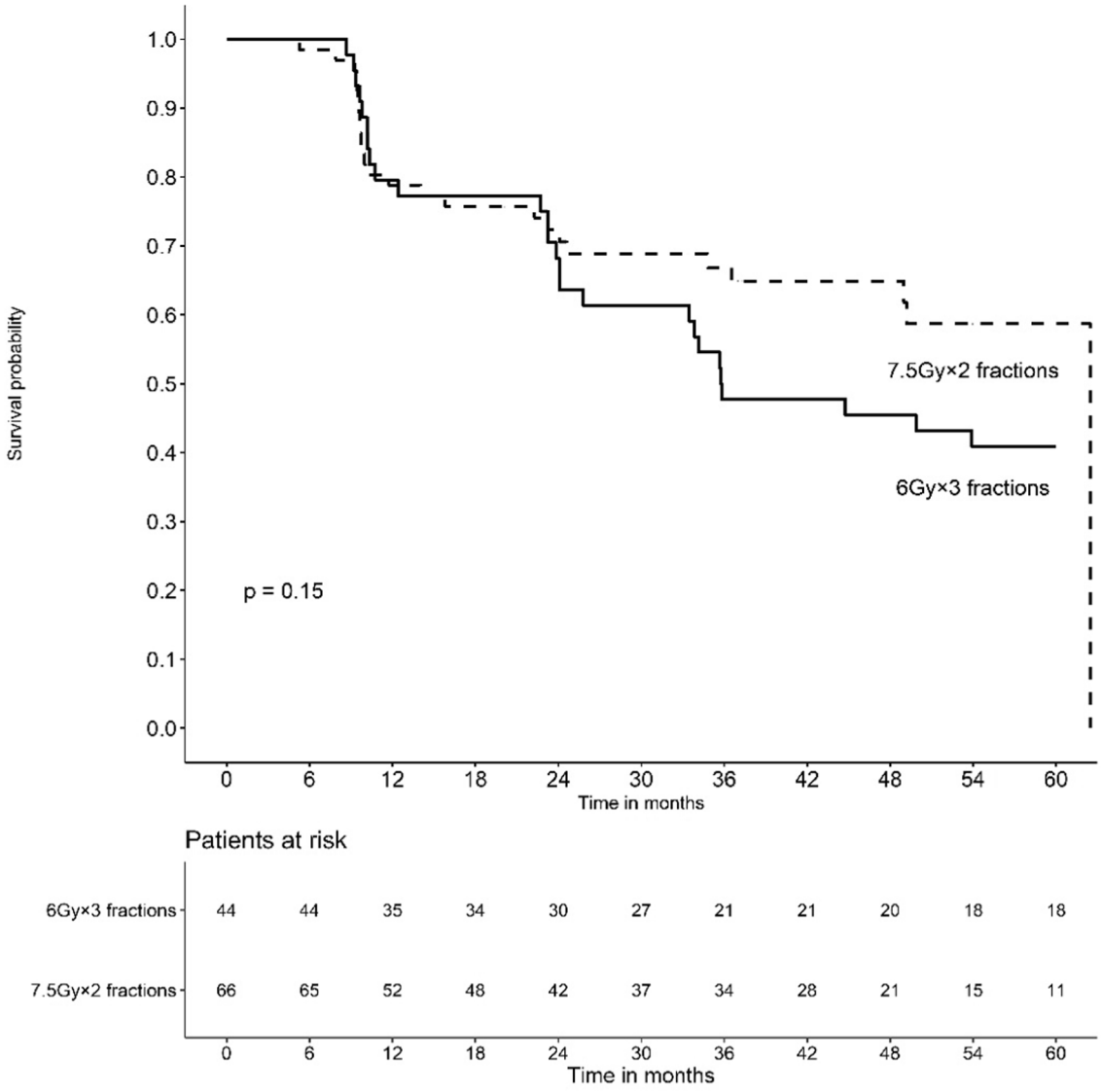


Fig. 2. Toxicity free time probability according study Groups 1 (6Gy×3 fractions) and 2 (7.5Gy×2 fractions).

Table 4
Univariate analysis of prognostic factors of late vaginal toxicity.

	[ALL] N = 110	G0 N = 59	G ≥ 1 N = 51	HR [95% CI]	p-value
Study group (n, %):					0.157
2	66 (60.0%)	41 (62.1%)	25 (37.9%)	1	
1	44 (40.0%)	18 (40.9%)	26 (59.1%)	1.49 [0.86;2.60]	
Mean age (SD)	65.8 (9.1)	64.4 (9.9)	67.4 (7.8)	1.03 [1.00;1.07]	0.031
Mean $EQD2_{(\alpha/\beta=3)}$ in 2 cm^3 of vagina (SD)	61.6 (6.8)	60.6 (4.2)	62.8 (8.8)	1.02 [0.99;1.06]	0.171
Mean $EQD2_{(\alpha/\beta=3)}$ in D90 (SD)	40.6 (6)	41.0 (4.9)	40.0 (7)	0.98 [0.93;1.03]	0.478
Mean V100cc (SD)	8 (1.4)	7.9 (1.3)	8.1 (1.5)	1.07 [0.88;1.31]	0.479
Mean CTV (cc) (SD)	8.1 (1.6)	8.0 (1.5)	8.2 (1.7)	1.09 [0.91;1.31]	0.350
Vaginal dilator use (n, (%))					
No	75 (68.2%)	36 (48.0%)	39 (52.0%)	1	
Yes	35 (31.8%)	23 (65.7%)	12 (34.3%)	0.61 [0.32;1.16]	0.134

SD: Standard deviation; HR: hazard ratio; EQD2: Equivalent dose to a fractionation of 2 Gy per fraction; CTV: Clinical Target volum; V100: Volume receiving the 100% of dose; D90: isodose that receives the 90% of the dose; n: number.

95% CI: 0.9; 2.6), suggesting the same probability of LVT occurrence over time in both groups.

The only variable related to LVT in the univariate analysis (Table 4) was age: patients presenting LVT were older than those without LVT.

Discussion

The present study compared two schedules of exclusive VBT for PEC. In previous studies by our group, 6 Gy×3fr seemed to be more efficient, considering complications and VCR, compared to a larger number of

fractions. Here, we compared this fractionation schedule with 7.5 Gy×2fr for the first time in the literature. Moreover, we previously reported a possible relationship between VBT outcomes and a 68 Gy-$EQD2_{(\alpha/\beta=3)}$ constraint in the most exposed 2 cm^3 of CTV [15,16]. Hence, we administered 2 fractions of 7.5 Gy with a 68 Gy-$EQD2_{(\alpha/\beta=3)}$ constraint in the most exposed 2 cm^3 of CTV in Group-2. There were no differences in other dosimetry parameters, such as V100, overall D90 and CTV volume, between the two groups. The conclusion is that the two series were very similar in VBT dosimetry aspects except for dose fractionation.

Most recurrences in EC are diagnosed within 3 years after primary treatment. The most common site of recurrence is the vaginal-cuff while lymph node and distant relapses represent about one-third of cases. The main factors that may influence local control are total dose administered, fractionation schedule, depth of myometrium invasion, histological type, grade, and VLSI. In this study no patient showed VCR with a median follow-up of 60 months in total, 60 months in Group-1 and 51.3 months in Group-2. Although the median follow-up was shorter in Group-2, it should not affect the detection of VCR because both were longer than the average 3 years to VCR reported in the literature [19–21].

VBT delivers a conformal dose to the vagina with less dose to surrounding normal tissues compared to EBRT. Hence, the rates of late bladder and rectum toxicities are quite low. Sorbe et al. showed that patients treated at a longer length of the vagina or who received a greater dose per fraction experienced greater bladder, rectal, and late vaginal toxicities [5,13]. Glatzer et al. reported that a significantly increased vaginal stenosis rate was associated with a deeper prescription point and longer treatment length. In the literature, the proportion of >60% of treated vagina and total dose > 14 Gy were significant independent predictors of G ≥ 1 vaginal stenosis; 71% of the experts in the multicenter European study by Glatzer administered the treatment to the upper 3 cm of the vagina [1,19,22]. In our study, both groups were treated with the same VBT characteristics except for dose fractionation. The dose was prescribed to a depth of 5 mm from applicator surface along the first 2.5 cm of the proximal cylinder. No patient in either of the two schedules analyzed showed late rectal or bladder toxicity.

The primary risk of toxicity with VBT is in the proximal (most common) and the second third of vagina resulting in vaginal atrophy, adherences, bleeding, stenosis, and/or decreased vaginal length. The incidence of Grade-1–2 LVT ranges widely in the literature (7.5%-27.7% up to 50%) and grade 3–4 is reported with ranges between 0–5.2% in different reports Include: [13,14,23-25]

In the present series, Group-1, 13/44 (29.5%) patients showed grade-1, 5/44 (11.4%) grade-2 and only one patient (3%) showed grade-3 LVT, while Group-2, 15/66 (22.7%) patients showed grade-1 and 4/66 (6%) grade-2 LVT ($p = 0.224$). Thus, the incidence of LVT was similar or lower than the literature series. The mean time to G ≥ 2 LVT was 29.6 months (SD ± 18) in Group-1 and 29.5 months (SD ± 17.0) in Group-2 ($p = 0.999$). Consequently, when using the present two schedules to analyze LVT in VBT in PEC patients, they should likely be followed at least 47 months. However, this should be confirmed in studies with a larger number of patients. The shorter follow-up of Group-2 compared to Group-1 could induce differences in LVC in Group-2. Nevertheless, considering the similar median time to the appearance of LVC suggests no differences between both groups. Indeed, Fig. 2 shows no differences over time in LVC.

Our previous results with more protracted schedules with higher doses showed a 20% incidence of ≥G2 LVT. In the present series, LVT ≥ G2 appeared in 10/110 (9%) patients. The number of G2 LVT complications was lower than that in the previous series with a larger follow-up in our center. Therefore, these 2 schedules seem to be beneficial for G2 LVT [16,26–30].

Clinically implemented VBT schedules often depend on local standards and the experience of each center. According to the American Brachytherapy Society, VBT was the preferred treatment in intermediate-risk disease with the most common schedules being 7 Gy to 0.5 cm depthx3fr and 6 Gy×5fr to the applicator surface, but over 24 different regimens were reported. Markus Glatzer reported nine different VBT regimens as monotherapy for brachytherapy in 18 experienced centers in Europe: 65% experts used fractionation regimens of 7 Gy×3fr or 5 Gy×4fr for brachytherapy as monotherapy. Two fractions of 7.5 Gy×2fr and 3 fractions of 6 Gy were used by two different centers. In the Glatzer et al. study, the $EQD2_{(\alpha/\beta=10)}$ ranged from 19.5 Gy to 37.5 Gy for brachytherapy as monotherapy. The constraints for OARs varied among the experts. Thus, it is essential to determine a fractionation that produces fewer complications and is more patient-friendly and less costly [1,5,6,14,27].

The present series is very homogeneous considering dosimetry parameters including the dose (most patients had $EQD2_{(\alpha/\beta=3)} < 68$ Gy in the most exposed 2 cm^3 of CTV) and consequently, this dose should not impact the appearance of LVT (Table 4). The dosimetry parameters were the same in patients with LVT-G ≥ 1 vs. those without LVT including $EQD2_{(\alpha/\beta=3)}$ in the most exposed 2 cm^3 of CTV, overall $EQD2_{(\alpha/\beta=3)}$ in D90, V100 and CTV. Therefore, it could be considered that these parameters, being similar in the two schedules, had no influence on LVT in the present series. Considering that only 4 patients in Group-1 received a dose > 68 Gy-$EQD2_{(\alpha/\beta=3)}$ in the most exposed 2 cm^3 of CTV and the mean $EQD2_{(\alpha/\beta=3)}$ received by the most exposed 2 cm^3 of CTV was similar in both schedules, the application of a 68 Gy-$EQD2_{(\alpha/\beta=3)}$ constraint in these two schedules does not seem necessary. Thus, dosimetry parameters seem to be a good way to compare VBT schedules in PEC.

Bahng et al. reported that the use of vaginal dilators by patient significantly reduces the incidence of vaginal atrophy. In a prospective study of vaginal dilator adherence, continued use of a vaginal dilator 6 months after pelvic radiotherapy decreased the rate of vaginal stenosis. In a previous multivariate analysis, we showed that vaginal dilator use ≥9 months is related to less G2 LVT. Thus, all patients were encouraged to use dilators ≥ 9 months. Nevertheless, in the present series only 1/3 of patients in the 2 groups reported adherence to vaginal dilators. Univariate analysis showed a non-significant difference in the use of vaginal dilators and the time of adherence between the two treatment groups. Perhaps patients with higher adherence may benefit the most from vaginal dilator use showing a lower grade of LVT [19,22,28,31–34].

Comparing patients with versus those without LVT we found that the only variable with a statistically meaningful difference was age, although the difference in age was very low: the median age was 64.4 years for no LVT vs. 67.4 years for having LTV. In a previous retrospective multivariate study, we found no influence of age on LVT [28]; consequently, the present result should be confirmed in larger prospective studies.

A limitation of this study is the number of patients included and the follow-up of Group 2. Thus, further studies including more patients with a longer follow-up are necessary to achieve more robust conclusions. Nevertheless, in the present study both fractionation schedules were safe, being similar in the dosimetry parameters analyzed and the LVT over time. This is the first study to compare 6 Gy×3fr and 7.5 Gy×2fr showing dosimetry parameters, being useful for comparing fractionation schedules.

Conclusion

Considering all the above, including the absence of vaginal relapses in both groups, similar LVT occurrence over time, $EQD2_{(\alpha/\beta=3)}$ in the most exposed 2 cm^3 of CTV and other dosimetry parameters in both groups, it can be concluded that 7.5 Gy×2fr is more cost-effective and imposes a lower burden on the health system and is also more patient-friendly. Furthermore, this study is the first to evaluate dosimetry parameters when comparing these two schedules. Larger series are needed to confirm the present results.

CRediT authorship contribution statement

Faegheh Noorian: Conceptualization, Visualization, Writing – review & editing, Data curation, Investigation, Formal analysis, Methodology. **Rosa Abellana:** Conceptualization, Resources, Methodology, Formal analysis. **Yaowen Zhang:** Writing – review & editing. **Antonio Herreros: . Clara Baltrons:** Formal analysis, Writing – review & editing. **Valentina Lancellotta:** Writing – review & editing. **Luca Tagliaferri:** Writing – review & editing. **Sebastia Sabater:** Writing – review & editing. **Aureli Torne:** Writing – review & editing. **Angeles Rovirosa:** Writing – review & editing, Conceptualization, Project administration, Supervision, Investigation, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Glatzer M, Tanderup K, Rovirosa A, Fokdal L, Ordeanu C, Tagliaferri L, et al. Role of brachytherapy in the postoperative management of endometrial cancer: decision-making analysis among experienced European radiation oncologists. Cancers 2022;14:906.

[2] Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR. Marnitz S et al ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 2021;31:12–39.

[3] Ager BJ, Francis SR, Do OA, Huang YJ, Soisson AP, Dodson MK, et al. Do vaginal recurrence rates differ among adjuvant vaginal brachytherapy regimens in early-stage endometrial cancer? Brachytherapy 2019;18:453–61.

[4] Barretina-Ginesta MP, Quindós M, Alarcón JD, Esteban C, Gaba L, Gómez C, et al. SEOM-GEICO clinical guidelines on endometrial cancer (2021). Clin Transl Oncol 2022;24:625–34.

[5] Harkenrider MM, Block AM, Alektiar KM, Gaffney DK, Jones E, Klopp A, et al. American Brachytherapy Task Group Report: Adjuvant vaginal brachytherapy for early-stage endometrial cancer: A comprehensive review. Brachytherapy 2017;16:95–108.

[6] Harkenrider MM, Grover S, Erickson BA, Viswanathan AN, Small C, Kliethermes S, et al. Vaginal brachytherapy for postoperative endometrial cancer: 2014 Survey of the American Brachytherapy Society. Brachytherapy 2015;15:23–9.

[7] Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: Multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355:1404–11.

[8] Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744–51.

[9] Nout RA, Smit VT, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): An open-label, non-inferiority, randomised trial. Lancet 2010;375:816–23.

[10] Pearcey RG, Petereit DG. Post-operative high dose rate brachytherapy in patients with low to intermediate risk endometrial cancer. Radiother Oncol 2000;56:17–22.

[11] van den Heerik ASVM, Horeweg N, Creutzberg CL, Nout RA. Vaginal brachytherapy management of stage I and II endometrial cancer. Int J Gynecol Cancer 2022;32:304–10.

[12] Koskas M, Amant F, Mirza MR, Creutzberg CL. Cancer of the corpus uteri: 2021 update. Int J Gynaecol Obstet 2021;155:45–60.

[13] Sorbe BG, Smeds AC. Postoperative vaginal irradiation with high dose rate afterloading technique in endometrial carcinoma stage. Int J Radiat Oncol Biol Phys 1990;18:305–14.

[14] Zhang Y, Fornes B, Gómez G, Bentoldrà I, Carmona C, Herreros A, et al. EQD2 (α/β=3) analyses of vaginal complications in exclusive brachytherapy for postoperative endometrial carcinoma. Cancers (Basel) 2020;12:3059.

[15] Zhang Y, Gomez G, Ascaso C, Herreros A, Fornes B, Mases J, et al. Preliminary results of a vaginal constraint for reducing G2 late vaginal complications after postoperative brachytherapy in endometrial cancer: a prospective analysis. Clin Transl Oncol 2022;24:875–81.

[16] Rovirosa Á, Herreros A, Camacho C, Ascaso C, Sánchez J, Cortés S, et al. Comparative results of three short brachytherapy schedules as exclusive treatment in postoperative endometrial carcinoma. Brachytherapy 2017;16:1169–74.

[17] Routledge JA, Burns MP, Swindell R, Khoo VS, West CM, Davidson SE. Evaluation of the LENT-SOMA scales for the prospective assessment of treatment morbidity in cervical carcinoma. Int J Radiat Oncol Biol Phys 2003;56:502–10.

[18] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341–6.

[19] Park HS, Ratner ES, Lucarelli L, Polizzi S, Higgins SA, Damast S. Predictors of vaginal stenosis after intravaginal high-dose-rate brachytherapy for endometrial carcinoma. Brachytherapy 2015;14:464–70.

[20] Delishaj D, Barcellini A, D'Amico R, Ursino S, Pasqualetti F, Fumagalli IC, et al. Vaginal toxicity after high-dose-rate endovaginal brachytherapy: 20 years of results. J Contemp Brachytherapy 2018;10:559–66.

[21] Nieto K, Levine B, Brown D, Lanier C, Carriere P, McGinnis H, et al. Pilot study to assess sexual function, quality of life (QOL) and change in vaginal dimensions following vaginal brachytherapy (VBT). 30Brachytherapy 2022;21:283–90.

[22] Guy CL, Fields EC, Quinn BA, Fisher CM, Ladbury CJ, Romano KD, et al. The vaginal cylinder: Misunderstood, misused, or trivial? An in-depth dosimetric and multiinstitutional outcome investigation. Brachytherapy 2019;18:763–70.

[23] Sorbe B, Straumits A, Karlsso L. Intravaginal high-doserate brachytherapy for Stage I endometrial cancer: A randomized study of two dose-per-fraction levels. Int J Radiat Oncol Biol Phys 2005;62:1385–9.

[24] Ríos I, Rovirosa A, Ascaso C, Valduvieco I, Herreros A, Castilla L, et al. Vaginal-cuff control and toxicity results of a daily HDR brachytherapy schedule in endometrial cancer patients. ClinTrans Oncol 2016;18:925–30.

[25] Lancellotta V, Macchia G, Dinapoli N, Autorino R, Campitelli M, Nardangeli A, et al. EROS 2.0 study: evaluation of two interventional radiotherapy (brachytherapy) schedules for endometrial cancer: a comparison of late vaginal toxicity rates. Radiol Med 2022;127:341–8.

[26] Zhang Y, Ascaso C, Herreros A, Sánchez J, Del Pino M, Torné A, et al. Is one brachytherapy fraction of 7 Gy similar to more fractions after external beam irradiation in postoperative endometrial carcinoma? Clin Transl Oncol 2020;22:1295–302.

[27] Zhang Y, Rovirosa A, Ascaso C, Herreros A, Torne A, Li Y, et al. Economic impact of decreasing the fraction number in vaginal cuff brachytherapy: A direct cost analysis. Brachytherapy 2020;19:60–5.

[28] Zhang Y, Noorian F, Abellana R, Rochera J, Herreros A, Antelo G, et al. Vaginal dilator use more than 9 months is a main prognostic factor for reducing G2–late vaginal complications in 3D–vaginal–cuff brachytherapy (interventional radiotherapy)? Clin Transl Oncol 2023. https://doi.org/10.1007/s12094-023-03099-4 [in press].

[29] Amagami W, Mikami M, Nagase S, Tabata T, Kobayashi Y, Kaneuchi M, et al. Japan Society of Gynecologic Oncology 2018 guidelines for treatment of uterine body neoplasms. J Gynecol Oncol 2020;31:e18.

[30] Harkenrider MM, Abu-Rustum N, Albuquerque K, Bradfield L, Bradley K, Dolinar, et al. Radiation Therapy for Endometrial Cancer: An ASTRO clinical practice guideline. Practical Radiat Oncol 2023;13:41–65.

[31] Zhang H, Gopalakrishnan M, Lee P, Kang Z, Sathiaseelan V. Dosimetric impact of cylinder size in high-dose rate vaginal cuff brachytherapy (VCBT) for primary endometrial cancer. J Appl Clin Med Phys 2016;17:262–72.

[32] Bahng AY, Dagan A, Bruner DW, Lin L. Determination of prognostic factors for vaginal mucosal toxicity associated with intravaginal high-dose rate brachytherapy in patients with endometrial cancer. Int J Radiat Oncol Biol Phys 2012;82:667–73.

[33] Law E, Kelvin JF, Thom B, Riedel E, Tom A, Carter J, et al. Prospective study of vaginal dilator use adherence and efficacy following radiotherapy. Radiother Oncol 2015;116:149–55.

[34] Son CH, Law E, Oh JH, Apte AP, Yang TJ, Riedel E, et al. Dosimetric predictors of radiation-induced vaginal stenosis after pelvic radiation therapy for rectal and anal cancer. Int J Radiat Oncol Biol Phys 2015;92:548–54.