

# Venezia applicator with oblique needles improves clinical target volume coverage in distal parametrial tumor residue compared to parallel needles only

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## Abstract

**Purpose:** Residual distal parametrial involvement after radiochemotherapy is a true challenge for brachytherapists since the width and asymmetry of high-risk clinical target volume (HR-CTV) are difficult to cover properly with a standard implant.

**Material and methods:** Dosimetric plans of five patients treated with Venezia advanced gynecological applicator at our institution were reviewed. For each patient, we compared the original plan with a new plan where oblique needles were removed and re-optimized manually. Optimization process was halted when EQD<sub>2</sub><sub>10</sub> D<sub>90</sub> HR-CTV reached 90 Gy, when one hard constraint to organs at risk (OARs) was reached according to the EMBRACE II protocol, or when dose-rate of one of OARs exceeded 0.6 Gy/h.

**Results:** Tumors were large; median HR-CTV volume was 64 cc and median distance between tandem and outer contour of HR-CTV was 40 mm. For the five patients, HR-CTV EQD<sub>2</sub><sub>10</sub> D<sub>90</sub> was superior in the plan using oblique needles, with a median difference of 6.5 Gy (range, 1.7-8.5 Gy). Median D<sub>90</sub> HR-CTV and intermediate-risk CTV (IR-CTV) were significantly increased with oblique needles: 85.9 Gy (range, 83.2-90.3 Gy) vs. 81.5 Gy (range, 77.4-84 Gy), and 68.7 Gy (range, 66.3-72.3 Gy) vs. 67 Gy (range, 64.3-69.1 Gy),  $p = 0.006$  for both. There were no significant differences in the dose to OARs. Plans with only parallel needles had less favorable dose distribution, with cold spots on the outer parametria and higher vaginal activation to compensate parametrial coverage in its inferior part.

**Conclusions:** Venezia<sup>TM</sup> applicator permits reproducible application to increase CTV coverage in patients with distal parametrial tumor residue during brachytherapy, while maintaining acceptable dose to OARs.

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**Key words:** brachytherapy, cervix cancer, interstitial, parametrium, Venezia, applicator.

## Purpose

External beam radiation therapy (EBRT) with concurrent platinum-based chemotherapy, followed by brachytherapy is the standard treatment of locally advanced cervical cancer. In the last decades, major advances have been made in the field of brachytherapy, with image-guided brachytherapy development (2D, 3D, then magnetic resonance imaging (MRI)-based) or standardized delineation and dose prescription [1,2]. The interstitial adjunct to intracavitary brachytherapy in large tumors has been shown to improve local control of 2-3% per each Gray delivered [3,4,5], and to be the best modality to treat parametrial extent. EBRT parametrial boosts have been shown to increase severe bowel morbidity and deliver inferior doses than brachytherapy, therefore they should be definitely abandoned in routine practice [6,7,8].

Patients with a distal parametrial residue after radiochemotherapy have a dismal prognosis, partly because dose escalation is quite difficult in such cases, even with brachytherapy. This kind of tumors is classified as group 5 in an analysis of EMBRACE (image-guided intensity-modulated external beam radiochemotherapy and MRI-based adaptive brachytherapy in locally advanced cervical cancer) prospective cohort, corresponding to poor response. This group was characterized by a significantly lower dose to high-risk clinical target volume (HR-CTV) (mean D<sub>90</sub>, 88.4 Gy in this group versus > 90 Gy in groups 1 to 3, corresponding to small tumors with good or moderate response,  $p < 0.001$ ). Recent data from the EMBRACE study show that this situation is not infrequent: 16% of patients have a distal parametrial residue after radiochemotherapy [9]. Furthermore, retrospective data suggest that tumors with poor volumetric response

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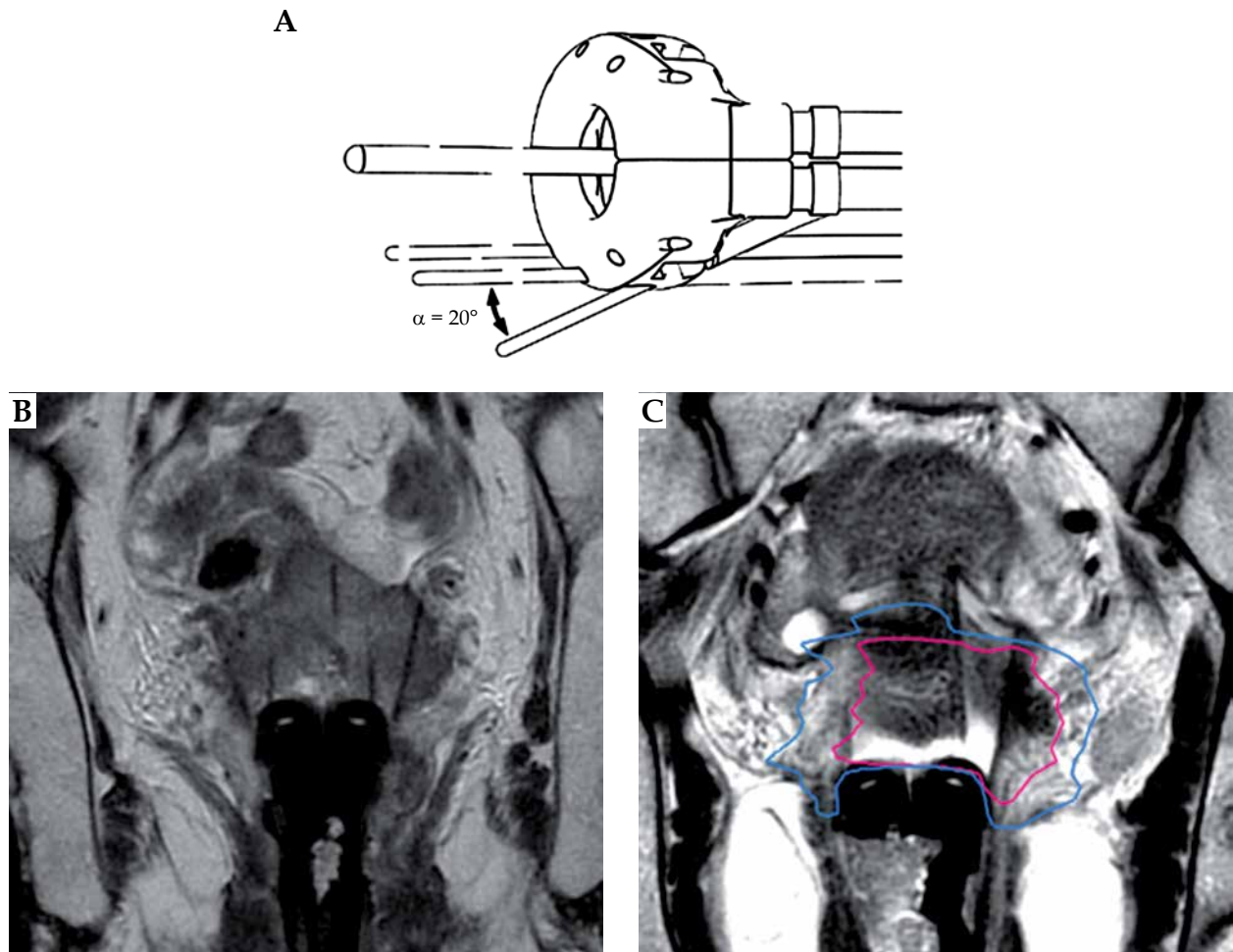
after EBRT (< 90%) require higher doses to be eradicated, as compared to tumors with good shrinkage [10].

Distal parametrial extension is a true challenge for brachytherapists. Historically, free-hand needles' insertion or perineal templates were used to implant needles in the outer third of parametria. Perineal templates, such as Syed-Neblett or MUPIT (multiple site perineal applicator), seem superior to intracavitary brachytherapy alone to treat the most lateral part of parametria [11]. However, parallelism is usually maintained only in the proximal part of the needles, there is a risk of divergence or convergence when these kinds of templates are used to treat the parametrium, especially its upper part, because of the distance between the template and the region of interest [12]. Using free-hand technique, one has no possibility to precisely control clinically the path of needle. Fluoroscopy may be helpful in the left-right direction, but not in the anterior-posterior direction [12]. Furthermore, distal parametrial regions are characterized by proximity of fragile structures, such as uterine arteries, ureters, rectum, and bladder, which are not visible on fluoroscopy. Peroperative MRI or ultrasound guidance in this context seem to be precise, but are not yet a routine practice in all

centers [13,14,15]. The risks of vascular or bowel injuries, though relatively low, need to be also considered [16].

While reducing the distance between the point of insertion and the target, the use of a vaginal applicator to implant parametrial regions seems to be particularly relevant. Some commercial hybrid applicators have been developed in this perspective, combining intracavitary and interstitial components, where the interstitial component originated from vaginal fornices, the two major ones used in clinical practice being the Vienna™ and the Utrecht™ applicators. The Vienna™ applicator is a ring applicator allowing for insertion of at most 9 parallel needles through the ring acting as a template [4]. The Utrecht™ applicator is a Fletcher design-based tandem, where each ovoid is a template for three to five needles in one or two parallel planes [5]. Both applicators allow for parallel needles only and may treat inner third to half of the parametria.

The recently developed Venezia™ advanced gynecological applicator (Elekta®, Stockholm, Sweden) combines two lunar-shaped ovoids, forming a ring through which, parallel and oblique interstitial needles can be inserted (22 mm ring diameter: up to 6 parallel and 6 oblique needles, 26 mm and 30 mm ring diameters: up to 8 parallel



**Fig. 1.** A) Venezia™ applicator and its oblique needles (design drawn from the Venezia user guide with a permission from Elekta France), B) Coronal MRI view of Venezia implant, C) Coronal MRI view of Venezia implant with corresponding brachytherapy contours (pink line: HR-CTV, blue line: IR-CTV)

and 8 oblique needles) [17]. The divergent needles span out and may treat a larger part of the parametria.

Here, we report five cases of Venezia™ use as a way to treat distal parametrial extensions with brachytherapy.

## Material and methods

Plans of the first five patients treated with the Venezia™ applicator using oblique needles at our institution were reviewed. Patients were considered for inclusion if they had a distal parametrial residue after radiochemotherapy for a locally advanced cervical cancer. At 40-45 Gy, all patients had a clinical examination, and 4 patients additionally underwent MRI to guide the choice of applicator.

The Venezia™ applicator with a 26 mm diameter ring was used, combined with blunt-end plastic tubes (ProGuide round needles, 6F × 294 mm, Nucletron) inserted through straight holes and oblique holes angled at 20°. The number, position, and depth of needles were determined by a radiation oncologist considering the size and shape of residual tumor after radiochemotherapy. For each patient, MRI was performed with the applicator in situ for delineation and dosimetry (Figure 1). HR-CTV, intermediate-risk CTV (IR-CTV), rectum, bladder, sigmoid colon, and small intestines were delineated on MRI according to Groupe Européen de Curiothérapie – the European Society for Radiotherapy and Oncology (GEC-ESTRO) recommendations, using Oncentra Brachy treatment planning software (version 4.6.0, Elekta) [2]. Pulsed-dose-rate (PDR) brachytherapy was exclusively used. Total prescription dose including EBRT was 85 Gy (EQD<sub>2,10</sub>) to HR-CTV. Brachytherapy prescription dose to IR-CTV was 15 Gy. The number of pulses depended on the dose delivered per hour, constrained by the limitation of 0.6 Gy/h on organs at risk (OARs). The equivalent dose in 2 Gy fractions (EQD<sub>2</sub>) sum of brachytherapy and EBRT was calculated, assuming  $\alpha/\beta$  value of 10 Gy for target volume and  $\alpha/\beta$  value of 3 Gy for OARs, according to linear quadratic model and considering repair half-time of 1.5 h for PDR [18].

For each patient, we performed a comparative dosimetry using the parallel needles only (Vienna plan) and both the parallel and oblique needles (Venezia plan). In order to do so, the Venezia plan was duplicated and all activation in the oblique needles was shut down. The contours and number of pulses were unaltered between both plans for each patient. Then, manual dwell time optimization was made jointly by experienced pair of radiation oncologist (MK) and physicist (NF). Dwell time positions could be increased on the tandem, on the parallel needles, and on the free-hand needles (in some cases free-hand needles were inserted besides the applicator) in the way deemed to be optimal. Optimization was made in the fairest conditions possible, aiming to deliver the maximum possible dose to the target, while respecting a classical repartition for PDR in terms of needle contribution relative to total activation. The portion of the needles remaining inside the vagina was not activated, since vaginal caps cannot be used with oblique needles in the Venezia applicator. The most proximal dwell position was always above the superior plane of the ring to avoid any overdosage at the

vaginal mucosa level. For both plans, the optimization process was halted when HR-CTV EQD<sub>2,10</sub> D<sub>90</sub> reached 90 Gy, when a hard constraint on OARs was reached according to the EMBRACE II protocol (D<sub>2cc</sub> bladder ≥ 90 Gy, D<sub>2cc</sub> rectum ≥ 75 Gy, D<sub>2cc</sub> sigmoid ≥ 75 Gy, D<sub>2cc</sub> bowel ≥ 75 Gy) [19], or when dose-rate on an OAR exceeded 0.6 Gy/h [20]. Conformation number (CN) was calculated for each plan using the following formula:

$$CN = \frac{HR-CTV\ RI}{HR-CTV} \times \frac{HR-CTV\ RI}{VRI}$$

where VRI is the volume encompassed by the prescription isodose, HR-CTV is the HR volume in cc, and HR-CTV RI is the target volume covered by the prescription isodose [21]. We considered the EQD<sub>2,10</sub> 85 Gy isodose as the prescription dose. The CN evaluated how well the prescription isodose line matches the HR-CTV volume, with “1” representing the best possible match and “0” indicating no overlap.

In order to obtain a graphic representation of dosimetric comparison between plans, Raystation® treatment planning software (RaySearch Laboratories, Stockholm, Sweden) was used.

Dose comparison between the two sets of plans for each patient was performed by Student's *t*-test for matched data. A *p* value of 0.05 was considered significant. Statistical analyses were performed using R software, version 4.0.2.

The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and did not require further ethical committee approval.

## Results

Five patients were retrospectively included in the present study. All patients had a locally advanced cervical cancer, staged as T3b or T4a disease at diagnosis, and had at least a unilateral distal parametrial residue at brachytherapy. All patients had received radiochemotherapy with weekly cisplatin 40 mg/m<sup>2</sup>. EBRT doses were 45 Gy in 25 fractions for all but one patient (50.4 Gy in 28 fractions delivered in Kuwait), who was referred to our institution for a brachytherapy boost. An EBRT boost on involved nodes was delivered when appropriate, up to EQD<sub>2,10</sub> dose of 60 Gy, taking into consideration the planned brachytherapy dose [22]. Patients' and treatments' characteristics are reported in Table 1.

A median of 6 parallel needles and 7 oblique needles were inserted. Additional free-hand needles were implanted in three patients to cover para-vaginal or peri-urethral invasion. No complication occurred during or following the procedures. Median HR-CTV volume was 64 cc, and median distance between tandem and outer lateral contour of HR-CTV was 40 mm.

Median follow-up was 3 months. One patient developed an asymptomatic rectal ulceration, which was found during clinical examination 3 months after brachytherapy. No grade 2 or higher toxicity occurred to last follow-up date. At last follow-up, three patients achieved complete response and one patient achieved good partial response (one patient had not been re-evaluated yet).

For the five patients, HR-CTV  $D_{90}$  EQD<sub>2</sub><sub>10</sub> was superior in the plan using the oblique needles, with a median difference of 6.5 Gy (range, 1.7-8.5 Gy) (Table 2). Median  $D_{90}$  HR-CTV was significantly higher in the Venezia™ plans, with 85.9 Gy (range, 83.2-90.3 Gy) vs. 81.5 Gy in the ring plans (range, 77.4-84 Gy),  $p = 0.006$  (Table 2 and Figure 2). Median IR-CTV  $D_{90}$  was also significantly superior in the Venezia™ plans, with 68.7 Gy (range, 66.3-72.3 Gy) vs. 67 Gy (range, 64.3-69.1 Gy),  $p = 0.006$ . For one patient (Pt No. 2), the gain on HR-CTV with oblique needles was lower because there was a large part of residual tumor lying in the upper and posterior part of the uterine body, invading the myometrium almost up to serosa, and the maximum dose to bowel was quickly reached. There were no significant differences in the dose to OARs (Table 2). In the ring plans, median EQD<sub>2</sub>  $D_{2cc}$  to rectum, bladder, sigmoid, and bowel were 68.1 Gy, 83.7 Gy, 56.9 Gy, and 72.7 Gy, respectively. In the Venezia™ plans, median  $D_{2cc}$  to rectum, bladder, sigmoid, and bowel were 72.5 Gy, 80.8 Gy, 57.2 Gy, and 73.6 Gy, respectively ( $p = 0.20, 0.89, 0.62, \text{ and } 0.37$ , respectively). Median total reference air-kerma (TRAK) was 2.55 cGy/m<sup>2</sup> in the ring plans, and 2.64 cGy/m<sup>2</sup> in the Venezia™ plans ( $p = 0.17$ ).

The dose to CTV was definitely numerically superior with Venezia™ but dose distribution was quite different between the plans with oblique needles and the ones without. For most patients, in the plans using only the parallel needles, ring activation had to be markedly increased to compensate for the absence of oblique needles, and still attempting to cover the inferior part of parametria (Figure 3). As a consequence, the vaginal/TRAK ratio was statistically higher in the plans with parallel needles only (34% vs. 28% in the Venezia plans,  $p = 0.01$ ), and in two cases exceeding the recommended 40%, as a secondary objective in the EMBRACE II protocol (Table 2). Moreover, all plans using parallel needles only had cold spots in the distal parametrial area compared with the plan with oblique needles. The oblique needles “extended” the dose to the side, thus allowing to treat correctly very asymmetrical tumors, provided a correct implantation (Figure 3). Median conformation number was 0.52 in the ring-like plans and 0.58 in the Venezia™ plans. The difference was at the limit of significance ( $p = 0.09$ ).

### Discussion

As recently reported in literature, we showed that Venezia™ applicator is a safe way to increase CTV coverage while maintaining dose to OARs [23]. Our study demonstrated a clinically meaningful gain of more than 6 Gy in terms of HR-CTV coverage with oblique needles in patients with distal parametrial residue after radiochemotherapy. Moreover, a crucial advantage on the topographic repartition of the dose in the distal parametrial areas was observed.

The association of intracavitary and interstitial (IC/IS) approach has already been shown to improve local control by 10% in “large” (> 30 cm<sup>3</sup>) or poorly responding tumors with acceptable toxicity [24]. Here, we report on 5 patients with very large tumors; in our cases (Tables 1

**Table 1.** Patients’ characteristics and technical data

Characteristic	n Median (min.-max.)	N
Age (years)	50 (36-79)	5
T stage		5
T3b	2	
T4a		
Bladder	1	
Rectum	1	
Sigmoid	1	
EBRT dose (Gy)	45 (45-50.4)	5
Number of pulses	60 (40-60)	5
Maximal distance between tandem and outer contour of HR-CTV (mm)	40 (30-44)	5
Number of straight needles	6 (3-8)	5
Number of oblique needles	7 (6-8)	5
Number of free-hand needles	2 (0-3)	5
HR-CTV volume (cc)	64 (57-96)	5
IR-CTV volume (cc)	135 (110-171)	5

and 2), HR-CTVs were at least twice or even three times larger than 30 cm<sup>3</sup>. In the literature, the addition of interstitial component escalated target coverage without increasing doses to OARs, and enhanced a therapeutic window by an average of 4 to 8 Gy EQD<sub>2</sub> [4,5,25]. This has been confirmed recently in the large prospective trial EMBRACE I, where for a HR-CTV volume of 60 cm<sup>3</sup>, which is comparable to the patients included in our study, mean HR-CTV  $D_{90\%}$  was 5.4 Gy (95% CI: 2.7-8.1) higher for ovoids-IC/IS compared with ovoids-IC centers, and 8.9 Gy (95% CI: 7.0-10.7) higher for ring-IC/IS compared with ring-IC centers [26].

The Utrecht applicator is widely appreciated for its ability to treat parametrial involvements, especially when large ovoids can be used. Indeed, ovoids ≥ 20 mm allow for two planes of parametrial needles, but both remaining generally in the proximal parametrium. Ring applicators were shown to have better target dose and dose conformity than ovoids applicators [26]. If 95% of tumors are estimated to be correctly covered by Vienna™-type applicator [27], the remaining 5% of patients will require an oblique implant to reach acceptable target coverage.

The first published report on a commercially available applicator with transvaginal oblique implants was the modified Vienna™ ring applicator described by Berger *et al.* in 2010 [28]. A specially designed removable semi-template bearing clockwise oblique holes could be fixed to the ring. This applicator was tested in 6 patients with distal parametrial disease at the time of brachytherapy. Needle

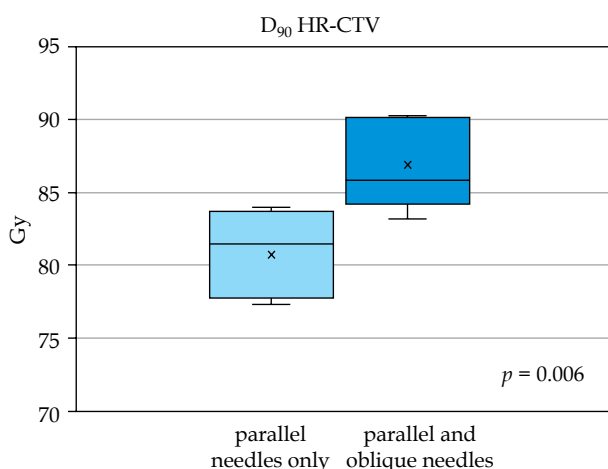
**Table 2.** Dosimetric comparison of Vienna-type plan using only parallel needles versus Venezia plan using both parallel and oblique needles

EQD <sub>2</sub> (Gy)	Patient no. 1		Patient no. 2		Patient no. 3		Patient no. 4		Patient no. 5		P-value
	HR-CTV = 61 cc IR-CTV = 116 cc		HR-CTV = 96 cc IR-CTV = 171 cc		HR-CTV = 57 cc IR-CTV = 110 cc		HR-CTV = 64 cc IR-CTV = 135 cc		HR-CTV = 92 cc IR-CTV = 158 cc		
	Parallel needles	Parallel and oblique needles	Parallel needles	Parallel and oblique needles	Parallel needles	Parallel and oblique needles	Parallel needles	Parallel and oblique needles	Parallel needles	Parallel and oblique needles	
D <sub>90</sub> HR-CTV (EQD <sub>2,10</sub> , Gy)	84.0	90.3	81.5	83.2	77.4	85.9	83.5	90.0	78.1	85.3	0.006
D <sub>90</sub> IR-CTV (EQD <sub>2,10</sub> , Gy)	68.4	72.3	67.0	68.7	69.1	70.6	64.3	67.1	64.4	66.3	0.006
D <sub>2cc</sub> rectum (EQD <sub>2,3</sub> , Gy)	68.1	74.7	72.0	72.5	66.0	67.6	74.5	73.9	67.6	68.7	NS
D <sub>2cc</sub> bladder (EQD <sub>2,3</sub> , Gy)	90.1	87.5	84.1	87.9	<i>Dose rate limit 0.6 Gy/h</i>	<i>Dose rate limit 0.6 Gy/h</i>	76.4	77.4	<i>Dose rate limit 0.6 Gy/h</i>	<i>Dose rate limit 0.6 Gy/h</i>	NS
D <sub>2cc</sub> sigmoid (EQD <sub>2,3</sub> , Gy)	51.4	53.1	52.4	52.3	56.9	57.2	61.7	61.7	75.1	74.3	NS
D <sub>2cc</sub> bowel (EQD <sub>2,3</sub> , Gy)	72.7	73.6	74.8	75.1	57.6	57.7	75.0	74.7	55.6	55.6	NS
Vaginal TRAK/total TRAK ratio	54%	44%	32%	28%	34%	28%	13%	11%	45%	34%	0.01
TRAK (cGy/m <sup>2</sup> )	2.51	2.64	2.88	2.94	1.55	1.74	2.55	2.56	2.88	2.83	NS
Conformation number	0.50	0.51	0.59	0.58	0.52	0.61	0.54	0.61	0.50	0.54	0.09

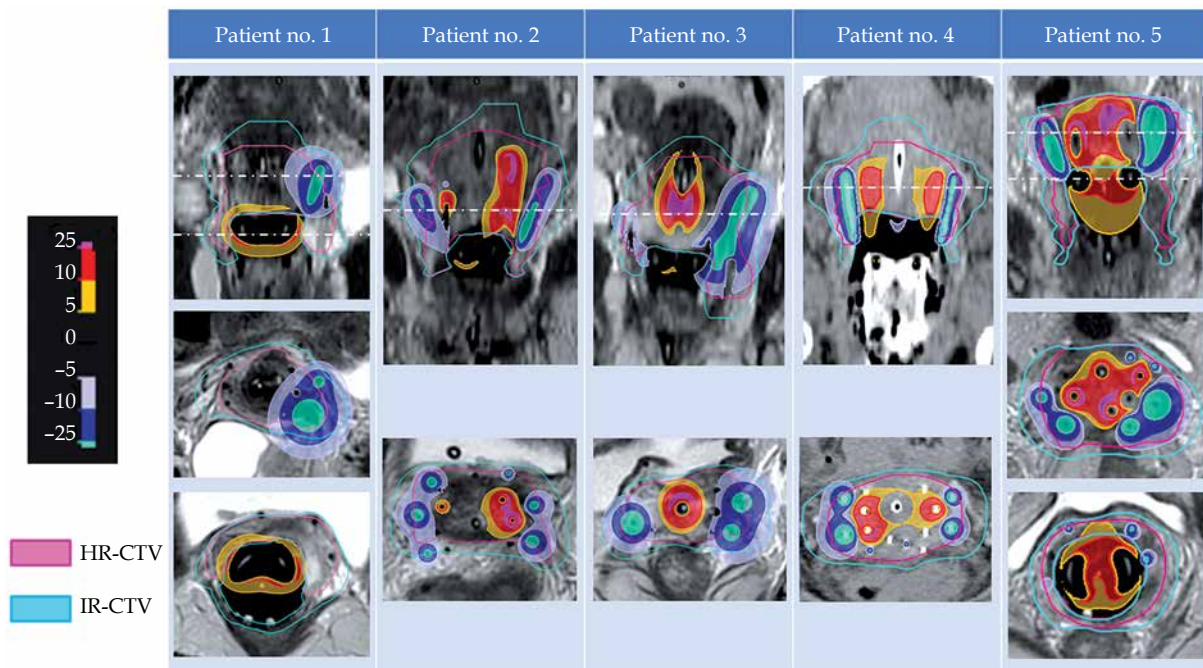
*Italic characters represent dosimetric factor that reached pre-established constraint first during optimization process, NS – not significant*

loading was maximum 20% of intracavitary contribution. With HR-CTVs of mean 50 cm<sup>3</sup>, mean EQD<sub>2,10</sub> D<sub>90</sub> was 86 Gy. Mean EQD<sub>2,3</sub> D<sub>2cc</sub> for OARs were 79 Gy, 61 Gy, and 67 Gy for bladder, rectum, and sigmoid, respectively. Aarhus also published their experience with oblique

transvaginal implants in 2012, where a 3D-printed needle cap was attached to a commercially available tandem-ring applicator [29,30]. A good coverage was achieved with this technique in patients with large tumors. For example, in 27 patients with a mean HR-CTV volume of 53 cc, a mean D<sub>90</sub> HR-CTV of 87 ±6 Gy was delivered [29]. In another publication, in 23 patients with a mean HR-CTV volume of 48 cc, a mean D<sub>90</sub> HR-CTV of 89 ±3.4 Gy was reported [6]. The largest experience ever reported was with the Vienna II applicator, which is a Vienna™ applicator with an add-on cap allowing for additional oblique needles into the distal parametrium [31]. Mean distance between tandem and outer contour of HR-CTV was 38 mm, and mean HR-CTV (±SD) volume was 69 ±32 cm<sup>3</sup>, which is comparable to the patients in our cohort. Among 69 patients with distal parametrium residue after radiochemotherapy, a mean (±SD) EQD<sub>2,10</sub> D<sub>90</sub> HR-CTV was 86 ±7 Gy and a mean EQD<sub>2,3</sub> D<sub>2cc</sub> for bladder, rectum and sigmoid were 86 ±12, 68 ±7 and 68 ±9 Gy, respectively. This is consistent with what we obtained in the plans using oblique needles. However, intra-operative utero-vaginal complications or arterial bleeding during removal occurred in 14 patients in this study (20%), and long-term high-grade toxicity were high compared to existing literature, since 20% of the patients had at least one grade 3/4 toxicity [32,33].



**Fig. 2.** Box plot representing EQD<sub>2,10</sub> D<sub>90</sub> HR-CTV in plans using parallel needles only (Vienna plan) vs. parallel and oblique needles (Venezia™ plan)



**Fig. 3.** Graphical representation of dosimetric advantage of oblique needles in Venezia™ plans compared to ring plans. For each patient, graphic representation of dosimetric differences (warm colors for overdosage and blue colors for underdosage in Vienna plan compared with Venezia plan). The dotted line(s) on the coronal view represent(s) the level of the axial plane(s) displayed below, passing through the cervix and through the upper vagina for patients no. 1 and no. 5

Another recent study reported on differences in dosimetry of high-dose-rate (HDR) brachytherapy treatments between plans using advanced multichannel applicators and their simplified base versions [34]. For Venezia™, the simplified plan had all interstitial needles deleted, whereas in our study, only the oblique ones were shut down. The simplified applicator plans each utilized the same inverse planning optimization parameters from their original advanced applicator plan to generate a new dose distribution. After optimization, each simplified plan was renormalized to match  $D_{90}$  HR-CTV of original advanced plan within 0.4%. By doing this, they compared critical structure doses for similarly effective plans, while our approach was to remain clinically acceptable on OARs, and to see how the advanced applicator could increase CTV coverage. Comparing simplified to advanced Venezia plans in their study, the doses to all organs were significantly lower with the exception of rectum, with an average percent differences in EQD<sub>2</sub> to 2 cm<sup>3</sup> of 101.7 ±85.9%, 147.8 ±76.7%, 95.3 ±61.6%, and 44.0 ±12.4% for rectum, bladder, sigmoid, and bowel, respectively. Conformation number was better by 0.251 ( $p < 0.05$ ), while in our study, the gain was naturally lower (0.06,  $p = 0.07$ ), since the only difference between both plans in our study was the presence of oblique needles. Vaginal de-escalation was not addressed in this study but vaginal stenosis is a frequent late side effect that can impact quality of life after brachytherapy. In our study, in order to treat very large tumors without oblique needles, the ring activation was mathematically increased to cover the inferior parts of parametrial involvement. However, as promoted in the EMBRACE II trial, vaginal dose de-escalation

is a challenge for modern brachytherapy without compromising local control, since toxicity is highly correlated with vaginal brachytherapy dose [35,36].

The limitation of our study is its small size and retrospective nature. However, it is of importance to show how the use of oblique needles as designed in the Venezia applicator could lead to a good coverage of very large tumors while avoiding a detrimental overdosage of the vagina wall. The dose difference patterns between the Venezia and the parallel-only needles plans, plotted in Figure 3, demonstrate where the oblique needles were needed within the target volume (cold blue colored areas), and how much the dose increase in the vagina wall may have occurred without them (warm red colored areas).

Similarly, PDR is not perfectly reproducible with HDR, since dose-rate in PDR is limited to 0.6 Gy/h on OARs but on the other hand, the differential between OARs and EQD<sub>2</sub> to HR-CTV is greater in HDR. The drawback of the Venezia applicator is its high cost, which can limit its wider use in low- or middle-income countries with high prevalence of cases with cervical cancer, especially large tumors. The other technical limitation is that the brachytherapists have to choose between the vaginal caps and oblique needles (the former clogging the oblique holes once in place) when performing the Venezia implant. As a consequence, a tumor presenting with both distal parametrial and lower vaginal tumor residue may be a challenge to cover properly without additional free-hand needles. Even though different semi-lunar ovoids diameter, uterine tandem angle, and length are available, commercial applicators do not always fit all anatomies, especially narrow or massively invaded vaginas. 3D print-

ing is a very interesting line of research that could allow for a custom-made and inexpensive way of further tailoring brachytherapy dose distribution for patients with intricate anatomies or wide/asymmetrical/complex tumor residues after radiochemotherapy [37]. The personalized vaginal mould applicator may also be used to complete the treatment at the level of vagina or to provide personalized interstitial application; however, the number of needles that can be used is quite limited [38].

To conclude, we showed how the Venezia™ applicator may be a safe and effective way to treat distal parametrial extensions during brachytherapy. In our study, the mean gain by adding oblique needles to an IC/parallel IS implant on HR-CTV was 6.5 Gy without raising the dose to OARs, which is in line with what can be expected when adding an interstitial component to an intracavitary implant. The EMBRACE II study is currently recording brachytherapy techniques using oblique needles, and may definitely validate their relevance in terms of local control and long-term toxicity.

## Disclosure

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The remaining authors report no conflict of interest.

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