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Original Article

Vienna-II ring applicator for distal parametrial/pelvic wall disease in cervical cancer brachytherapy: An experience from two institutions: Clinical feasibility and outcome

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ABSTRACT

Purpose: Recent evidence from EMBRACE shows that around 16% patients with locally advanced cervical cancer (LACC) have residual tumor in distal parametrium (DP) and pelvic wall disease (LPW) after concurrent radio-chemotherapy (CCRT). Adequate target coverage with standard brachytherapy approaches represents a challenge. Therefore, we modified the Vienna I applicator with an add-on cap allowing for additional oblique needles into the DP/LPW (Vienna II). We report here the feasibility and clinical outcomes using Vienna II applicator in LACC patients treated in 2 institutions.

Methods and materials: 69 patients with residual disease in DP/LPW after CCRT were accrued. FIGO (2009) stage was 26% IIB, 52% III, 15% IVA, 7% IVB (para-aortic nodes). At diagnosis 91% had disease involving DP/LPW. After CCRT, patients underwent image guided adaptive brachytherapy (IGABT) using Vienna II applicator. IGABT details, acute complications, dose volume parameters and clinical outcome variables were compiled and analyzed.

Results: Residual DP/LPW disease at BT was found in 90% patients. Median total number of needles were 7 [3–15], oblique 4 [1–7]. Manageable intraoperative utero-vaginal complications occurred in 8 patients and manageable arterial bleeding in 6 patients during removal. Mean distance between tandem and outer contour of CTV_{HR} was 38 mm and mean CTV_{HR} (±SD) volume was 69 ± 32 cm^3. The mean D_{90} CTV_{HR} was 86 ± 7 Gy (EQD2) and mean (±SD) D^3_{2cm} (Gy, EQD2) 86 ± 12, 68 ± 7, 68 ± 9 for bladder, rectum and sigmoid respectively. Actuarial LC, PFS, OS at 3/5 years was 76/72%, 56/50%, 62/54% and G3-4 late toxicities (n = 23) were observed in 14 patients (20%).

Conclusions: IGABT using Vienna II applicator allows for appropriate target coverage in tumors extending into DP/LPW at the time of BT. Clinical use is feasible and results in good local control, DFS and OS with moderate rate of acute and late ≥G3 toxicity.

Brachytherapy (BT) is a mandatory part of curative treatment for locally advanced cervical cancer (LACC). In order to decide on optimum BT techniques, the tumor topography at BT may be classified into following categories: tumors limited to cervix at the time of BT with cconventional intracavitary BT techniques providing sufficient dose distribution (category 0); tumors with up to medial half parametrial infiltration (category I) may benefit from additional parallel interstitial needles [1,2]; tumors in the distal parametrium or beyond (category II) and tumors with significant (more than 2–3 cm) vaginal infiltration (category III). In general, interstitial brachytherapy (ISBT) has been generally considered in category II and III tumors. Historically, free-hand and transperineal approaches with fixed geometry templates have been used [3–5]. However, these methods had technical limitations

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including challenges to achieve parallelism (long distance between insertion points and target) and required specific gynaecologic experience with a significant learning curve, and implied a considerable additional workload.

In recent past, straightforward combined intracavitary–interstitial brachytherapy (IC/IS BT) applicators have been developed that enables trans-vaginal placement of parametrial needles parallel to the tandem through the modified vaginal ring (Vienna Applicator) [1] or ovoids (Utrecht applicator) [2] and were successfully implemented into practice [6–8]. The point of needle insertion being in the upper vagina and close to the target, allows for a safe, fast, precise and reproducible needle location and enables target dose coverage up to the middle third of the parametrium. The current evidence suggests excellent clinical outcome [2,6,9–12] using these IC/IS applicators in terms of long-term local control, especially in large tumors >5 cm [8], with 3–5% gastrointestinal and 2–4% urinary bladder grade 3–5 toxicities [10,11].

However, in more advanced disease the pattern of clinical tumor regression after CCRT suggests a considerable proportion (even up to 45%) of patients have residual disease in distal parametrium (category II) [13]. A recent report in 481 EMBRACE study patients with stage IIB–IIIB disease, showed 180 patients (37.4%) with primarily distal parametrium/lateral pelvic wall disease (DP/LPW), and 75 patients (15.6%) residual DP/LPW disease at BT [14].

In such clinical situations, even with the use of IC/IS applications (Vienna I/Utrecht [1,2]), the target coverage is inadequate and limits the target dose to <75 Gy with underdosage of periphery of target resulting in poor local control [15].

Taking into account the clinical success of the Vienna/Utrecht IC/IS applicator systems based on a vaginal approach using a template fixed to the axis of the cervix/uterus [8,11] an analog applicator system has been designed. The newly designed modified Vienna I applicator (original "Vienna Applicator") now called "Vienna II Applicator" of which the technical and physical characteristics are described in detail (Fig. 1), has an additional cap fixed to the vaginal ring. This cap allows guided positioning of interstitial needles into the DP in oblique direction of 20° relative to the tandem direction for sufficient dose coverage of residual DP/LPW disease (category II tumors). Here, we present the clinical feasibility and outcome using the Vienna II Applicator for advanced IC/IS BT applications clinically introduced at two institutions.

Methods and materials

Patient selection

Patients with clinical FIGO (2009) stage IIB–IVB (IVB: para-aortic nodal disease) were evaluated for BT after CCRT. At the time of BT, patients with residual disease in the DP or beyond were considered for advanced IC/IS BT technique using the Vienna II applicator (Fig. 1). Another indication was the presence of unfavorable topography between an asymmetrical target and organs at risk as identified during first application or pre-planning to achieve an optimal IC/IS implant geometry.

Clinical brachytherapy procedure details

All patients after obtaining the written informed consent, were hospitalized one or two days prior BT. After pre-anesthetic assessment, counseling, bowel preparation, adjustment of anticoagulation, lower limb pressure stockings whenever indicated, preparation of perineum, and anxiolytics if required was given. The procedure was performed under general or spinal anesthesia with the patient in low-dorsal lithotomy position. The bladder was catheterized and retained with 7 cm^3 saline in the Foley catheter balloon. A thorough gynecological examination and mapping of tumor topography was done. The presumed number of needles and their position in the ring and the cap and their tissue depth was determined based on clinical examination and MRI performed prior to BT (if available).

The principles of BT procedure included insertion of appropriate uterine tandem after cervical canal dilatation and insertion of the Vienna-I ring with add on cap fixed to the ring (Vienna II). The straight holes allowed for needle insertion parallel to the tandem (Vienna I) using 20–24 cm long titanium needles pre bent at 4–5 cm from the tip to 60°. The oblique holes on the add-on-cap were used for insertion of the divergent needles with 20–24 cm long straight titanium needles with round tip. The number of needles and positions were selected based on the configuration of the CTV_{HR} in relation to the cervical canal and latero-cranial distance from the vaginal ring (Fig. 1). The planned depth of needle insertion in the parametrium was determined by the cranial extent of CTV_{HR}, usually up to 3–4 cm above the upper ring surface, with additional margin of 0.8–1 cm to account for the needle offset (approximately: 4–5 cm). Optimal needle implantation was facilitated by digital rectal examination and/or real time trans-rectal ultrasonography (TRUS). Vaginal packing was performed to fix and stabilize the application. A rectal tube was placed into the rectum for continuous drainage of flatus/secretions and as a channel allowing for in vivo dosimetry. The applicator assembly was secured to the perineum with the help of T-bandage.

MR/CT imaging with applicator in situ was performed. Delineation of target volume (CTV_{HR} and/or Intermediate risk-CTV) and OARs was done according to Gynecological Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (GYN GEC-ESTRO)/ICRU 89 recommendations [16,17]. Treatment planning was performed in a manual iterative procedure to achieve the planning aims and to limit the loading in the interstitial needles to an extent which provides optimal coverage but does not change the overall dose gradients typical for an intracavitary treatment. To understand the laterality of the target in relation to the central tandem, we measured the maximum radial distance and the cranial position to the edge of CTV_{HR} MRD (r, z), respectively and recorded for each patient. *(more details see corresponding Physics paper.)*

The HDR BT was scheduled as two applications, one week apart with two fractions 12–15 h apart delivered with each application. Planning aims for target and dose constraints for OAR followed institutional guidelines. The dose volume histogram (DVH) parameters for target and OARs were defined as recommended by GYN GEC-ESTRO/ICRU 89 recommendations [17,18]. The cumulative EBRT and BT equivalent doses in 2 Gy fractions (EQD2) was calculated using the equi-effective dose concept based on the linear quadratic model assuming α/β of 10 Gy for tumor ($EQD2_{10}$) and 3 Gy for OARs ($EQD2_3$). The planning aim was to achieve total D_{90} for the CTV_{HR} of at least 85 Gy $EQD2_{10}$, which corresponds to 45 Gy of EBRT plus 4 sessions of 7 Gy HDR BT and limiting the OARs to a $EQD2_3$ of total 90, 70 and 75 Gy for the bladder, rectum and sigmoid, respectively, which were lowered in the later phase according to the EMBRACE II protocol [19] Fig. 1]. Patients with bilateral pelvic and low para-aortic nodal disease treated with 3D conformal external radiation techniques usually receive 50.4 Gy @ 1.8 Gy per fraction in one centre. BT treatment was delivered with remote after-loading Nucletron microSelectron® high-dose-rate (HDR) system using Iridium-192 (^{192}Ir) source. After completion of BT treatment, the applicator removal was done under sedation or anesthesia. The principles of removal included removal of the tandem first and then individual stepwise removal of oblique needles, followed by the vaginal ring with the add-on cap, together with the parallel needles. Patients were observed for removal associated complications, stabilized and discharged. Applicator

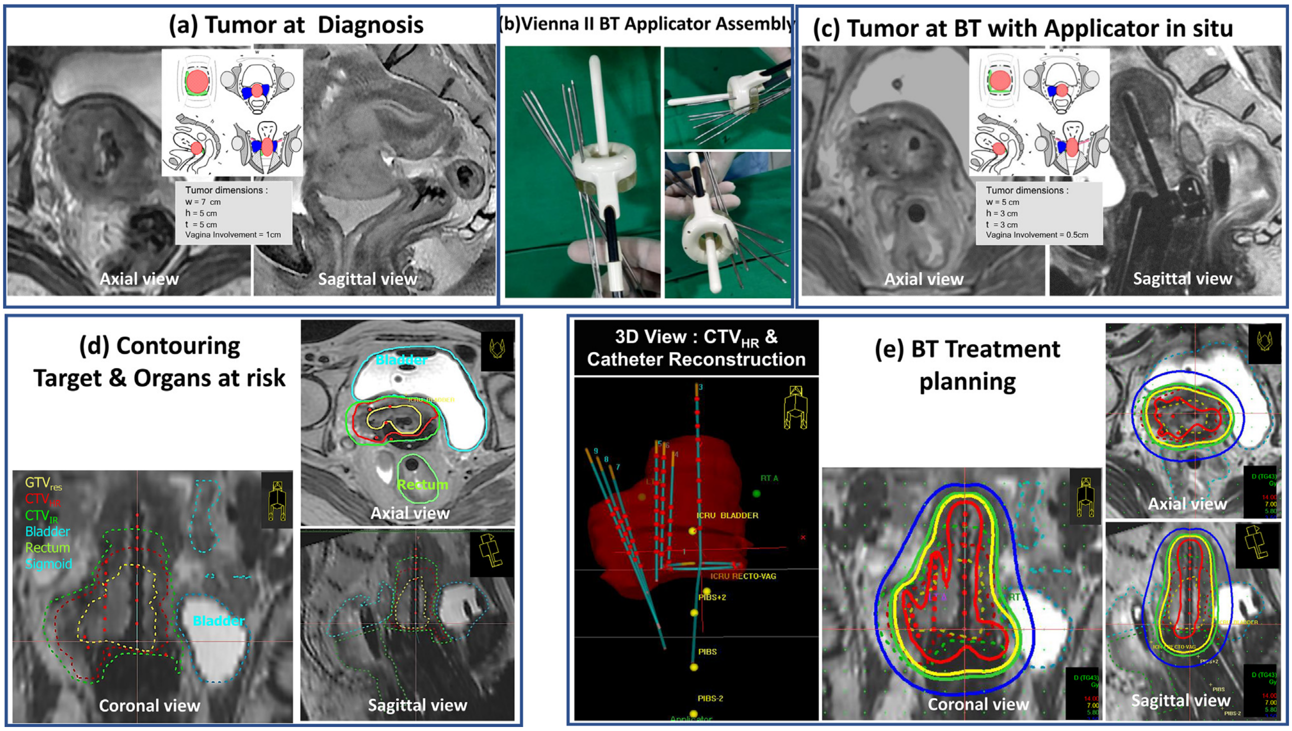


Fig. 1. A typical case of Vienna II BT application showing: (a) MRI and clinical drawings at the time of diagnosis; (b) in vitro assembly of the Vienna I applicator with an add on cap to transform into Vienna II; (c) MRI and clinical drawings at the time of brachytherapy with Vienna II applicator to encompass the residual disease in distal parametrium on right; (d) contouring the target and the organs at risk; (e) BT Treatment Planning showing 3D view of the applicator with straight and oblique needle reconstruction and final plan showing isodose distribution in different views.

removal associated complications e.g. excessive bleeding were documented and appropriately managed.

After completion of treatment, all patients underwent regular follow-up with pelvic examination every 3–4 months in first 2 years and 6 monthly thereafter. Depending on the symptoms and clinical findings, appropriate investigations including imaging (MRI to assess response) were performed to define disease status/-toxicities. Acute (<3 months) and late (≥3 months) toxicities were scored using Common Terminology Criteria for Adverse Events (CTCAE v3.0) [20].

Statistical analyses

Statistical analysis was performed using Statistical Programme for Social Sciences software for Windows (SPSS Inc., Version 22, Chicago, IL). Kaplan–Meier curves were used to generate various time to event curves indicating overall survival (OS), progression free survival (PFS), and local control (LC) estimates. PFS was defined as freedom of local, regional and distant failure from the date of diagnosis (biopsy confirmation) to date of first documented relapse Patients who were alive at last follow-up and progress free were censored.

Results

Patient and tumor characteristics

A total of 69 histologically proven LACC patients from two institutions (39 and 30) treated with "Vienna II" between March 2011 and January 2017 were analyzed. Table 1 shows baseline patient and tumor characteristics in detail. All patients underwent volumetric imaging at diagnosis [MR (n = 55) and CT (n = 14)] with 63 (91%) patients showing DP or LPW disease while 6 (9%) had proximal parametrial disease at the time of BT. Of note, 22/35 patients with stage IIIB cervical cancer had hydronephrosis, of which, 8 had both hydronephrosis and pelvic wall involvement.

Treatment characteristics

All 69 patients received pelvic EBRT with conformal/IMRT technique to a dose of 45–50.4 Gy (median 46 Gy) at 1.8–2 Gy per fraction. At first BT, persistent DP disease was found in 62 (90%) patients with 52 (75%) patients having bilateral and 17 (25%) unilateral parametrial involvement (Table 2). Fifty-six (82%) patients received 2 applications one week apart with 2 fractions delivered with each, while 13 (18%) patients had one application with 2 fractions provided, aiming at a total dose of over 80 Gy EQD2. Vienna II BT applicator was used in both applications in 51 patients (74%) and in only one application in 18 patients (26%). In one institution, 26 mm diameter ring was used in all patients while in the other, ring diameters of 26 mm in 5 patients, 30 mm in 19 and 34 mm in 15 patients.

Median number of needles was overall 7 [3–15] of which oblique needles were 4 [1–7]. The mean (±SD) CTV_{HR} width and height at the time of BT was 54 (±12) mm and 44 (±12) mm respectively. The mean (±SD) needle insertion depth was 50 (±15) mm. Maximum Radial Distance MRD (r, z) of the CTV_{HR} edge from the tandem was mean $r = 38 \pm 4$ mm laterally at level of point 'A' and at a distance of mean $z = 20 \pm 9$ mm from the upper ring surface.

Additional treatment characteristics for BT and dose volume parameters are detailed in the physics paper (Berger et al. 2018). In short, the mean volume of CTV_{HR} at the first BT was 69 ± 32 cm^3, the mean CTV_{HR} D_{90} and D98 CTV_{HR} cumulative $EQD2_{10}$ of combined EBRT and IC/ISBT were 86 ± 7 Gy and 76 ± 6 Gy respectively. Similarly, cumulative mean $EQD2_3$ for bladder, rectum and sigmoid D2cm^3 was 86 ± 12 Gy, 68 ± 7 Gy and 68 ± 9 Gy respectively. Overall, mean (±SD) duration (EBRT + BT) was 56 days (±21 days).

Table 1
Baseline patient and tumor characteristics.

Parameters		Classification		Centre I (n = 39) *N* (%)	Centre II (n = 30) *N* (%)	Total (n = 69) N (%)
Age (years)		Median (range)		45 (23–74)	47.5 (27–61)	47 (23–74)
Histology		Squamous cell carcinoma		37 (95)	30 (100)	67 (97)
		Adenocarcinoma		2 (5)	0 (0)	2 (3)
Primary staging as per FIGO 2009		Stage IIB		14 (36)	4 (13.3)	18 (26)
		Stage IIIA		0 (0)	1 (3.3)	1 (1.4)
		Stage IIIB		17 (44)	18 (60)	35 (50.8)
		Stage IVA		5 (13)	5 (16.7)	10 (14.5)
		Stage IVB (PA node)		3 (8)	2 (6.7)	5 (7.3)
Nodal involvement		Involved		24 (62)	19 (63.3)	43 (62.3)
		Uninvolved		15 (38)	11 (36.7)	25 (37.7)
Parametrial involvement at diagnosis	Laterality	Bilateral		35 (90)	26 (86.7)	61 (88.4)
		Unilateral		4 (10)	4 (13.3)	8 (11.6)
	Degree	Proximal		5 (13)	1 (3.3)	6 (8.7)
		Distal or to LPW*		34 (87)	29 (96.7)	63 (91.3)
	Side and degree	*Right parametrium*	Proximal	9 (23)	4 (13.3)	13 (18.8)
			Distal/LPW	27 (69)	24 (80)	51 (73.9)
			Uninvolved	3 (8)	2 (6.7)	5 (7.3)
		Left parametrium	Proximal	13 (33)	8 (26.7)	21 (30.4)
			Distal/LPW	23 (59)	20 (66.6)	43 (62.3)
			Uninvolved	3 (8)	2 (6.7)	5 (7.3)
GTV_D dimensions on baseline MRI, Mean (±1SD)				(***n* = 39**)	(***n* = 16**)	(***n* = 55**)
		Volume (cm^3)		66 (±59)	89 (±47)	73 (±56)
		Height (mm)		43 (±14)	49 (±10)	45 (±13)
		Width (mm)		56 (±14)	62 (±41)	58 (±13)
		Thickness (mm)		43 (±13)	50 (±11.5)	45 (±13)

Abbreviations: *LPW = lateral pelvic wall; GTV_D = Gross tumor volume at diagnosis.

Table 2
Tumor and treatment characteristics at the time of brachytherapy.

Parameters		Classification		Centre I (n = 39) *N* (%)	Centre II (n = 30) *N* (%)	Total (n = 69) *N* (%)
Parametrial disease at the time of BT	Laterality	Bilateral		31 (79)	21 (70)	52 (75.4)
		Unilateral		8 (21)	9 (30)	17 (24.6)
	Degree	Proximal		6 (15)	1 (3.3)	7 (10)
		Distal/LPW		33 (85)	29 (96.7)	62 (90)
	Side and degree	*Right parametrium*	Proximal	14 (36)	8 (26.7)	22 (31.9)
			Distal/LPW	20 (51)	18 (60)	38 (55.1)
			Uninvolved	5 (13)	4 (13.3)	9 (13)
		Left parametrium	Proximal	15 (38)	9 (30)	24 (34.8)
			Distal/LPW	20 (51)	16 (53.3)	36 (52.2)
			Uninvolved	4 (11)	5 (16.7)	9 (13)
BT planning imaging		MRI		39 (100)	27 (90)	66 (95.7)
		CT		0 (0)	3 (10)	3 (4.3)
Amount of residual gray zone on T2-MRI imaging at first implant		<25%		5 (13)	3 (10)	8 (11.6)
		25–49%		24 (62)	9 (30)	33 (47.8)
		50–75%		10 (26)	11 (36.7)	21 (30.4)
		>75%		0 (0)	4 (13.3)	4 (5.8)
		NA		0 (0)	3 (10)	3 (4.3)
Distance between tandem and lateral edge of HR-CTV		≥30–35 mm		19 (48)	10 (33.3)	29 (42)
		>35–40 mm		10 (26)	15 (50)	25 (36.7)
		≥40 mm		10 (26)	5 (16.7)	15 (21.8)
EQD2 total dose D_{90}		Mean (1SD)		87 (5)	85 (9)	86 (7)
CTV_{HR} dimensions on planning MRI mean (±1SD)		Volume (cm^3)		77 (±41)	63 (±21)	71 (±34)
		Height (mm)		39 (±12.5)	51 (±6)	44 (±12)
		Width (mm)		52 (±17)	59 (±8)	54 (±12)
		Thickness (mm)		35 (±11)	39 (±6)	37 (±9)

Procedure related complications[2]

The insertion of the applicator, including the additional cap was technically feasible in all the patients. The insertion of the oblique needle was possible in all patients, and the whole applicator was stable and did not pose problems during the patient transfer to the MRI room or BT after loader.

During BT application utero-vaginal complications were seen in 8 patients (11.5%); with uterine wall perforations in 5 patients independent of the application of the Vienna II ring with cap while vaginal lacerations in 3 patients which related to use of Vienna II ring with cap. The tandem was re-positioned or left unchanged, with a caution not to load the extra-uterine part while the vaginal lacerations were managed by suturing.

During applicator removal, active bleeding was observed in 19 patients (27.5%). These were classified into arterial in 6 patients [ring diameter 34 mm (3 pts), 30 mm (2 pts) 26 mm (1 pt)], venous in 12 patients [severe: 2 pts and moderate: 10 pts] and arterial bleeding due to myoma rupture in 1 patient. The patients with

[2] Appendix: Management of Procedure Related Complications.

arterial and venous bleeding were managed by the radiation oncology team, conservatively with continuous compression for at least 6–10 min, blood transfusion if required, observed overnight and discharged after stabilization. The patient with the myoma rupture underwent surgical intervention and discharged later.

Treatment outcome

Complete response was achieved in 62/69 patients (90%). With a median follow up of 35 months (range 7–105), overall 33 (42%) patients developed failures with 6 (9%) local alone, 15 (22%) systemic alone and 12 as combination of failure sites (Table 3). Overall, 16 (23%) patients had local failure either alone ($n = 6$) or in combination with other sites ($n = 10$).

The actuarial estimates for local control, PFS and OS at 3 and 5 years were 76/72%, 56/50%, and 62/54%, respectively (Fig. 2).

Late toxicity

G3-4 late toxicities were observed in 14 patients (20%): G3-4 bladder toxicities in 8 patients (11.6%) [incontinence (3), frequency (3), hematuria (1), vesico-vaginal fistula (1)]; G3-4 recto-sigmoid toxicities in 6 patients (8.7%) [proctitis (2), recto-vaginal fistula (3), sigmoid fistula (1)], G3 vaginal in 3 patients (4.3%) [stenosis (2), necrosis (1)] and others in 7 patients [G3 ureteric stenosis (5), G3 lymphoedema (1), G4 small bowel perforation (1)]. Rectum D2cc in patients with recto-vaginal fistula was between 88.8 and 107 Gy EQD2, bladder D2cc bladder was between 88.8 and 95.7 Gy EQD2 for those with vesico-vaginal fistula, the one patient with sigmoid and bowel perforation had a sigmoid D2cc of 55.3 Gy EQD2 and a bowel D2cc of 72.6 Gy EQD2.

Table 3
Comparison of outcomes in the two centres.

Parameter	Centre I ($n = 39$) *N* (range/%)	Centre II ($n = 30$) *N* (range/%)	Total ($n = 69$) *N* (range/%)
Median follow-up cohort – months	37 (7–105)	30 (9–78)	35 (7–105)
Median follow-up alive patients – months	62 (9–105)	62 (9–78)	62 (9–105)
Median follow-up dead patients – months	19 (7–45)	14 (9–49)	16 (7–49)
Complete remission	37 (95)	25 (83)	62 (90)
Local failure alone	2 (5.1)	4 (13.3)	6 (8.7)
Local + pelvis	–	1 (3.3)	1 (1.4)
Local + systemic failure	4 (10.3)	3 (10)	7 (10.1)
Local + pelvis + systemic	2 (5.1)	–	2 (2.9)
Regional + systemic	–	2 (6.7)	2 (2.9)
Systemic only	11 (28.2)	4 (13.3)	15 (21.7)
Total local failure	8 (20.5)	8 (27)	16 (23)
Total failures	19 (49)	14 (47)	33 (48)
No failure	20 (51)	16 (53)	36 (52)
Alive disease free	19 (49)	15 (50)	34 (49)
Death of disease	15 (5)	10 (33)	25 (38)
Total death	16 (41)	11 (37)	27 (39)
OS (absolute)	23 (59)	19 (63)	42 (61)
LC (actuarial) at 3/5 years %/%	79/75	73/73	76/72
OS (actuarial) at 3/5 years %/%	64/54	60/56	62/54
PFS (actuarial) at 3/5 years %/%	60/54	56/50	56/50

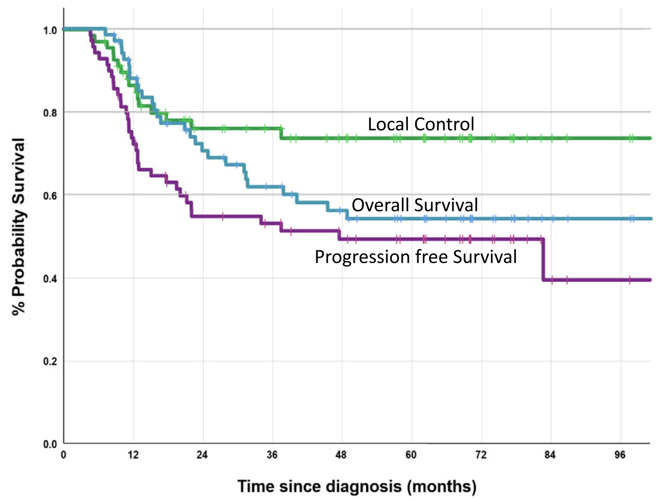
Discussion

In LACC, DP and LPW disease (category II) pose a major challenge for BT and is usually associated with dismal outcome. In the past, initial disease extension has been usually treated with EBRT parametrial boost or in highly selected centers with perineal implant brachytherapy boost [4–6,21,22]. In IGABT, target for BT is adapted according to the response to CCRT. DP/LPW disease at diagnosis and residual DP disease at BT (category II) is seen in 37.4% and 15.6% of EMBRACE stage IIB/IIIB patients [14]. These disease patterns would be higher in the developing world where advanced disease is common [23]. In these clinical settings, the IGABT target concept with dose prescription to the CTV_{HR} requires widely applicable specific BT applicator systems to achieve an appropriate BT application with adequate target coverage and sparing of OAR's. A system allowing for transvaginal needle application linked to the vaginal and the uterine intracavitary applicator for distal parametrium was not commercially available in the past. Vienna II has been developed as in house-prototype and was clinically tested in two institutions. This is the first cohort of patients with LACC and DP/LPW disease (category II) at BT treated by placement of additional oblique needles through an add-on cap to the existing Vienna I applicator ("Vienna II").

The Vienna II applicator design, its physical characteristics, treatment planning details and dosimetric comparison with the standard IC/IS approach (Vienna I) has been described in detail (Fig. 1). Beside the dosimetric advantages, the main advantage of the Vienna II applicator is that a simple add-on cap to the commercially available Vienna ring allows for a safe, standardized, fast and reproducible insertion of parallel and additional oblique needles to adapt and optimize the BT application. In comparison to conventional perineal interstitial techniques, Vienna-II is less tissue penetrating (~5cm versus ~13 cm), uses fewer needles (median 7 versus 24 for interstitial [21]), is not related to any pubic arch interference and is fixed to the cervix and upper vagina facilitating precise and reproducible needle positioning. In addition, through the use of MRD (r, z) we ascertained a quantified clinical measure of the maximum asymmetry and tumor-extension in relation to the applicator. This method allows preplanning of the implant, preferably on a pre-brachytherapy MRI. These features make Vienna II relatively less operator dependent resulting in a steeper and faster learning curve and allowing for a more reliable wide spread practice.

Our cohort included large tumors with FIGO stage IIB (26%), IIIB (51%) and IVA (15%) with 75% bilateral parametrial involvement and residual disease in the DP in 90%. This new method of an adaptive transvaginal interstitial boost technique to the DP/LPW for LACC with moderate to poor response can hardly be directly compared to literature as reports on such cohorts of patients are missing so far. The reports on perineal template interstitial procedures are addressing advanced disease at diagnosis and these cohorts comprise large proportions of IIB and bulky IB patients [4–6,21,24]. Our cohort, however, refers only to those who represent with large CTV_{HR} at the time of BT and is – according to EMBRACE experience - less than half of those presenting with involvement of DP/LPW at diagnosis (15.6% versus 37.4% stage IIB/IIIB patients [14]. Therefore, in the following the major highlights of our findings are summarized and can only be briefly discussed in the literature frame.

Our results underline that the advanced IC/IS application ("Vienna II") with additional cap and insertion of needles in oblique direction is clinically feasible and reproducible across institutions with clinical experience in gynecologic brachytherapy. An optimal implantation is facilitated through trans-rectal ultrasonography (TRUS) which has been increasingly used during this study by both the teams and is nowadays recommended [25,26]. In our cohort, the mean CTV_{HR} volume was 69 cm^3 and unilateral width measured from the central tandem was mean 38 mm. The CTV_{HR} is about two times compared to what has been described from mono-center and multicenter experience with mean 30–35 cm^3 [1,10,11] and also much larger compared to mean 45 cm^3 reported from a cancer center in India [12].



Survival	3 year	5 year
LC	76%	72%
OS	62%	54%
PFS	56%	50%

Number at risk											Total no of events
	LC	69	54	38	34	28	22	18	12	3	16
	OS	69	58	42	34	28	22	12	5	3	27
	PFS	69	48	33	30	25	21	12	4	2	33

Fig. 2. Kaplan-Meier estimates for local control (LC), progression free survival (PFS), overall survival (OS) ($n = 69$).

With the advanced IC/IS application through Vienna II, a mean total D_{90} of 86 Gy EQD2 could be achieved which forms the basis for an excellent complete response rate (90%) and considerable local control rate of 76% at 3 years. Only six isolated local recurrences occurred (9%), one failure was loco-regional only (1%) and 9 local failures had a systemic component (14%) (Table 3). This local control rate is slightly inferior to what has been reported for patient cohorts treated through perineal templates. However, as stated before, direct comparison is not straightforward as those cohorts address a more favorable patient selection [4,5,21,22,24]. Systemic recurrence was predominant (26/33) with 15 systemic failures only (22%) (Table 3). Actuarial PFS and OS at 3/5 years was 56/50%, and 62/54%, respectively, after median 35 months, which can be regarded as ‘considerable for this poor prognostic group’ and compares well with cohorts of IIIB and IVA (at diagnosis) [5,21].

The use of the Vienna II applicator with oblique needles could be associated with procedure related complications. This included bleeding during applicator insertion due to vaginal wall laceration ($n = 3$), related to the ring and cap (most likely due to a bulkier applicator), and unrelated uterine perforation ($n = 5$) through the tandem. Also, the removal of the applicator resulted in bleeding in 19 cases, which was classified as arterial (6 pts), venous (12 pts) and one bleeding from a ruptured myoma (1 pt). The patient with myoma rupture had to undergo an open abdominal uncomplicated surgery. The arterial bleeds were more in patients with larger ring size which possibly increases the chance of uterine vessel perforation. This could be avoided with the use of real time Doppler US during BT application [27]. In older historical series intraoperative complications or removal of application were reported to be low, in MUPIT 5.4% (2/37), Martinez et al. [28] or with Vienna I IC/IS technique 2% (4/22), (1 perforation and 3 mucosal lacerations) [6]. Altogether there seems to be a higher risk of arterial/venous bleeding associated with use of oblique needles and these findings need attention.

Late toxicity (G3-4) occurred in 20% of patients with respecting the corresponding planning aims at that time for OAR DVHs in the majority of these patients. This crude rate is above what has been reported so far for unselected patient cohorts treated with IGABT of 8–13% [10,11] and 10.2% (excluding vagina toxicity) in a recent mono-institutional experience with perineal templates [21]. When comparing large unselected patient cohorts after IC or combined IC/IS brachytherapy in RetroEMBRACE and EMBRACE no significant differences were reported for late toxicities (G3-5) with an overall crude rate of 14–17% [8,29]. However, as stated before, our cohort represents an unfavorable patient selection with more advanced disease and more intensive treatment.

In summary, Advanced IC/IS applications based on “Vienna II” was implemented at two institutions with highly dedicated and skilled teams experienced in IGABT and proved to be clinically feasible. We report here patients with quite an advanced disease at diagnosis and at BT and performing BT boost with a simple modifications in the existing Advanced BT Applicator System Vienna-I (Vienna Applicator) with add-on cap, and placement of divergent needles into distal parametrium, and achieve decent doses to the target even with extensive disease at BT with reasonably good outcome.

These advanced BT applications are associated with some acute bleeding either during insertion or removal procedures. This is due to the presence of extensive disease and placement of needles into lateral parametrium where vessel injury probability is higher. This could be reduced with the use of real time US/trans-rectal US and/or Doppler [27]. So, these advanced BT applications be done after gaining some experience or in centers with some BT experience and capable of handling the complications. Hence the complexity of such cases and the advanced treatment techniques applied may favor treatment in experienced and high volume IGABT centres.

A new applicator (“Venezia”) based on Vienna I/II and Utrecht applicators has been recently introduced commercially which may further contribute to the successful dissemination of the transvaginal interstitial IGABT approach for category II and III tumors [30].

In conclusion, IGABT using Vienna II applicator in experienced centres allows for dose escalation and appropriate target coverage in tumors extending into/beyond distal parametrium at the time of BT. The clinical use is feasible and results in high local control and considerable DFS and OS while maintaining a moderate rate of acute and late toxicity $\geq$G3 in unfavorable locally advanced cervical cancers.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.08.004.

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