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Original Research Article

High-dose-rate brachytherapy boost for locally advanced cervical cancer: Oncological outcome and toxicity analysis of 4 fractionation schemes

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ABSTRACT

Purpose: Brachytherapy (BT) boost after radio-chemotherapy (RCT) is a standard of care in the management of locally advanced cervical cancer (LACC). As there is no consensus on high-dose-rate (HDR) BT fractionation schemes, our aim was to report the oncological outcome and toxicity profile of four different schemes using twice-a-day (BID) HDR-BT.

Patients and methods: This was an observational, retrospective, single institution study for patients with LACC receiving a HDR-BT boost. The latter was performed with a single implant and single imaging done on day 1. The different fractionation schemes were: 7 Gy + 4x3.5 Gy (group 1); 7 Gy + 4x4.5 Gy (group 2); 3x7Gy (group 3) and 3x8Gy (group 4). Local (LFS), nodal (NFS) and metastatic (MFS) recurrence-free survival as well as progression-free survival (PFS) and overall survival (OS) were analyzed. Acute (≤6 months) and late toxicities (>6 months) were reported.

Results: From 2007 to 2018, 191 patients were included. Median follow-up was 57 months [45–132] and median $EQD2_{10}D_{90}CTV_{HR}$ was 84, 82 and 90 Gy for groups 2, 3 and 4 respectively (dosimetric data missing for group 1). The 5-year LFS, NFS, MFS, PFS and OS were 85% [81–90], 83% [79–86], 70% [67–73], 61% [57–64] and 75% [69–78] respectively, with no significant difference between the groups. $EQD2_{10}D_{90}CTV_{HR} < 85$ Gy was a prognostic factor for local recurrence in univariate analysis ($p = 0.045$). The rates of acute/late grade ≥ 2 urinary, digestive and gynecological toxicities were 9%/15%, 3%/15% and 9%/25% respectively.

Conclusion: Bi-fractionated HDR-BT boost seems feasible with good oncological outcome and slightly more toxicity after dose escalation.

Introduction

Worldwide, cervical cancer is the fourth most common cancer among women in terms of incidence and mortality [1,2]. In 2040, the estimated number of cervical cancers and related deaths will increase by 34% and 44% respectively, making it a major public health problem [3].

Abbreviations: BED, biologically effective dose; BID, twice-a-day; BMI, body-mass index; BT, brachytherapy; CT, computerized tomography; CTCAE, common terminology criteria for adverse events; CTV, clinical target volume; EBRT, external beam radiotherapy; EMBRACE, image guided intensity modulated External beam radiochemotherapy and MRI based Adaptative BRAchytherapy in locally advanced CErvical cancer; ESTRO, European Society for Radiotherapy and Oncology; $EQD2_{Gy}$, equivalent dose at 2 Gy; FIGO, International Federation of Gynecology and Obstetrics; GEC, groupe européen de curiethérapie; GTV, gross tumor volume; HDR, high-dose-rate; HIV, human immunodeficiency virus; HR, high-risk; ICRU, International Commission on Radiation Units and measurements; IGABT, image-guided adaptative brachytherapy; IMRT, intensity modulated radiotherapy; IR, intermediate-risk; LACC, locally advanced cervical cancer; LDR, low-dose-rate; LFS, local recurrence-free survival; LQ, linear quadratic; MFU, median follow up; MFS, metastatic recurrence-free survival; MRI, magnetic resonance imaging; NA, not available; NCI, national cancer institute; NFS, nodal recurrence-free survival; OAR, organs at risk; OS, overall survival; OTT, overall treatment time; PDR, pulsed-dose-rate; PET, positron emission tomography; PFS, progression-free survival; pt, patient; pts, patients; PTV, planning target volume; RCT, radio-chemotherapy; SCC, squamous cell cancer; SEER, surveillance, epidemiology and end results.

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According to the SEER database, 35.5% of cervical cancers are locally advanced at diagnosis. The standard of care treatment for locally advanced cervical cancer (LACC) is concurrent radio-chemotherapy (RCT) followed by brachytherapy (BT) [4-7].

Image-guided adaptive brachytherapy (IGABT) boost is now well-known to be associated with improved pelvic control and overall survival [8-11]. Different BT implants exist (intra-cavitary with or without interstitial implant) and different dose-rate regimens are used. Low-dose-rate (LDR) BT was the mainstay treatment but was progressively replaced by pulsed-dose-rate (PDR) and high-dose-rate (HDR) BT [12-18]. While PDR-BT is well defined with a single implant and imaging (CT and/or MRI) the day of the implant, there is no clear consensus for HDR-BT boost schemes [19-22]. The number of HDR-BT implant procedures, fractions per implant session and imaging are not standardized, either with multiple implants performed during external beam radiotherapy (EBRT) or afterwards [23]. The most commonly used HDR-BT fractionation scheme is 28 Gy in 4 fractions, using 2–4 implants and imaging is often done for each fraction or every two fractions [24-27]. However, due to anesthesiology human resources and operative room availability, hospitalization duration and imaging resources (MRI), BT organization remains a major issue and there is therefore a need to simplify this procedure as much as possible.

In order to tailor treatment to the organizational constraints of our institution, a twice-a-day (BID) HDR-BT boost scheme has been implemented, based on a single implant and imaging only on day 1. Fractionation schemes have evolved with published data but preservation of patient (pt) comfort during treatment remains crucial while considering local organizational constraints and optimal dose escalation [28,29]. The purpose of this study was to assess the impact of 4 different HDR-BT fractionation schemes on oncological outcome and toxicity in LACC.

Material and methods

This was an observational, retrospective, single institution study, performed in the Antoine Lacassagne Cancer Center in Nice (France) for patients with LACC receiving a HDR-BT boost after RCT. This study was approved by the Gynecologic Board of Antoine Lacassagne Cancer Center. Before data collection, the consent of all patients was obtained. In accordance with current legislation, data collection was registered at the National Health Data Hub under the number I11200801202020.

Patient features

Patients with a histologically proven LACC stage IB2 to IVA according to FIGO 2018 or stage IB1 to IVA according to FIGO 2009, were retrospectively analyzed in terms of dosimetric data, oncological outcome and toxicity [30,31]. At diagnosis, patients had undergone clinical cervical, vaginal and rectal examination. Biological test (full blood count, serum SCC antigen), computed tomography scan (CT), pelvic magnetic resonance imaging (MRI) and 18 fluoro-deoxy-glucose positron emission tomography (PET) were performed. Para-aortic lymph node dissection was done for staging at the discretion of physicians. Tumor size was determined either on MRI (maximum width on axial T2-weigthed sequence) or on conization (size of histological tumor if no residual tumor on MRI).

Exclusion criteria were metastasis at time of diagnosis (FIGO 2018 stage IVB), hysterectomy prior to RCT, no concomitant chemotherapy to EBRT and isolated BT schedules.

Treatment features

Concomitant radio-chemotherapy

All patients first received EBRT with concurrent platin-based chemotherapy weekly (minimum 5 courses). EBRT delivered 45/46 Gy (ICRU point) in 25/23 fractions, based on a 3-dimensional conformal technique, with or without modulated intensity, using 6 or 10 MV X-photons.

Since 2013, intensity modulated radiotherapy (IMRT) has been used. Target volumes included the whole cervix with the tumor, uterus, bilateral parametrial tissue, upper or whole vagina (for stage IIIA disease), broad and utero-sacral ligaments. All pelvic lymph nodes were included in the clinical target volume (CTV). Suspicious lymph nodes were considered for concomitant or sequential boost with total equivalent dose (EQD2) of 60 Gy. Some patients were referred to our center and EBRT could be performed in multiple centers. For these patients, clinical and EBRT dosimetric parameters were collected before HDR-BT boost.

High-dose rate brachytherapy boost

HDR-BT was performed in our center at the end of RCT to complete the overall treatment in <63 days [10]. Under general anesthesia, a gynecological examination was performed in order to evaluate the clinical response after RCT.

The procedure used a combined uterine tandem and vaginal cylinder with 8 interstitial needles for all patients for the whole period of time [32]. In case of parametrial invasion, the same applicator was associated with a perineal implant as previously described [33]. After patient recovery, a post-implant planning CT-scan was performed. Since 2014, a post-implant MRI was added to CT-scan to improve the delineation of target volumes as recommended by GYN GEC-ESTRO working group [34].

Dose-volume adaptation was manually achieved using graphical optimization (OncentraBrachy, Elekta Company, Elekta AB, Stockholm, Sweden) by dwell location and time variation. Dose volume parameters for CTV_{HR} and organs at risk (OARs) were calculated and reported according to GYN GEC-ESTRO working group recommendations [35].

From 2007 to 2018, fractionation schemes have evolved according to our experience, organizational constraints and the goal of dose escalation of at least 85 Gy (EQD2) to CTV_{HR} in accordance with published data [28,29,36]. Four HDR-BT groups were defined as described in Fig. 1.

Patients was treated in bed, after transfer from a non-shielded room to the brachytherapy bunker. After the last BT session, the applicator was removed after analgesic pre-medication, paying attention to the risk of vaginal and perineal bleeding. The patient was discharged from hospital the following day in the absence of early complications.

Total dose EQD2 (EBRT and BT)

Summation of EBRT and BT was performed by calculation of a biologically equivalent dose in 2 Gy (EQD2) using the linear-quadratic model with α/β ratios of 10 Gy for tumor effects and 3 Gy for late normal tissue damage. As HDR-BT boost schemes evolved (number of fractions, dose per fraction and overall BT time), we also calculated the EQD2(t) taking into account the time factor for $D_{90}CTV_{HR}$ and D_{2cc} of OARs for the different HDR-BT fractionation schemes [37-39]. Dosimetric results were analyzed by comparing EQD2 with and without time factor of BT alone in order to evaluate the potential impact of a BID treatment on oncological outcome and toxicity.

Follow up and evaluation

Immediate bleeding after withdrawal of the interstitial implant was recorded. MRI and PET-CT were combined with clinical examination 2 months after HDR-BT to evaluate tumor response and acute toxicities. Patients were then followed every 3 months for the first 2 years and every 6 months during at least 5 years by the radiation oncologist and the gynecologic surgeon alternatively.

Oncological outcome was analyzed based on local, nodal and metastatic recurrence. Local recurrence occurred in central pelvis (cervix, vagina, parametria) and was confirmed by successive imaging (MRI and/or PET-CT) or biopsy. Nodal recurrence was defined as nodal failure confirmed by imaging, in the pelvis (in or out field) and *para*-aortic area.

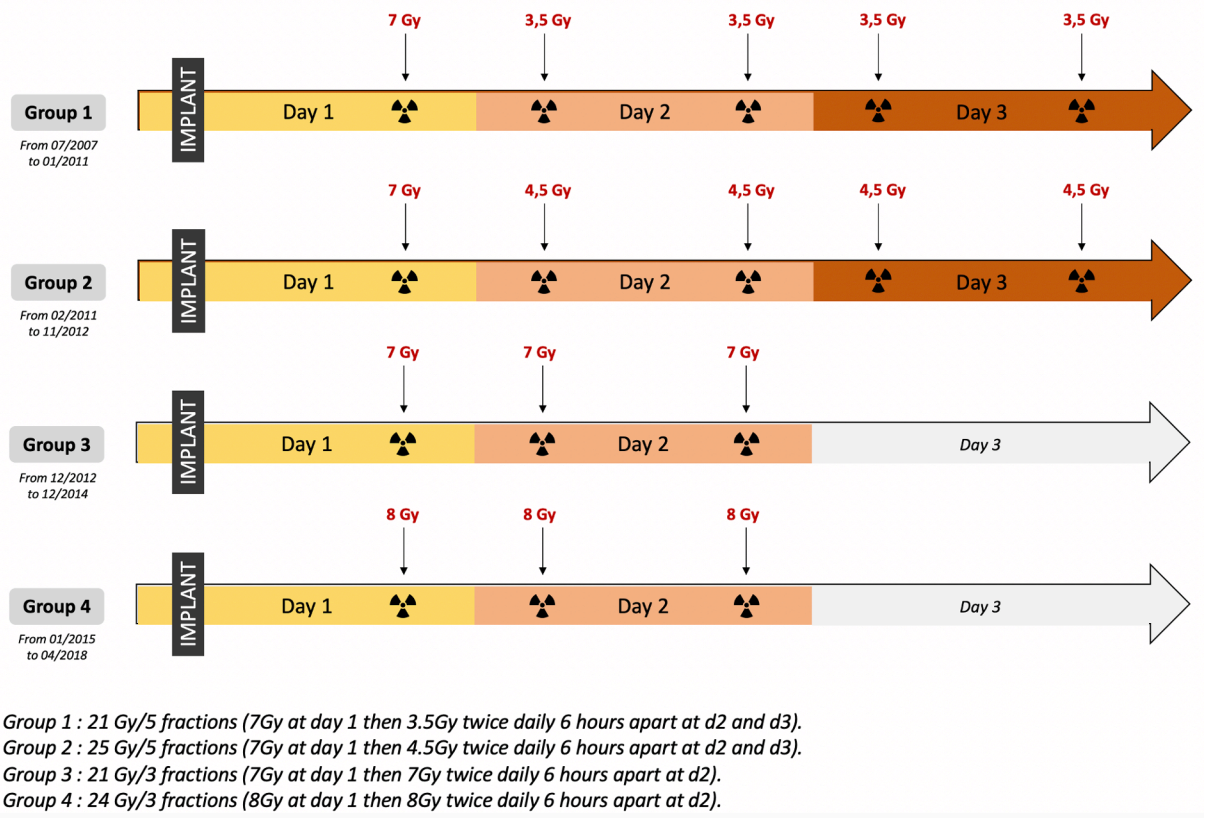

Fig. 1. Evolution of dose prescription through time and fractionation groups.

Metastatic recurrence was defined as distant failure confirmed on PET-CT.

Toxicity comprised bleeding during hospitalization, urinary, gastro-intestinal and gynecological events. Acute toxicities (within 6 months after treatment) and late toxicities (>6 months after treatment) were recorded using the NCI-Common Toxicity Criteria version 3.0 and 4.0 (CTCAE3.0 and 4.0).

Statistical analysis

Qualitative data are presented as absolute frequency and relative frequency and are compared using Chi2 test or Fisher exact test when necessary.

Quantitative data are presented as median and range. These quantitative data are compared using variance analysis (ANOVA) or Kruskal-Wallis test when needed.

Univariate and multivariate analyses were performed using the Cox regression model to identify prognosis factors for local, nodal and metastatic relapse.

Survival data are presented as Kaplan-Meier curve and survival rate with corresponding 95% CI. These data are compared according to LogRank test.

Local recurrence-free survival (LFS) was defined as the time between date of diagnosis (date of biopsy) and date of first local event. Nodal recurrence-free survival (NFS) was defined as the time between date of diagnosis and date of first nodal event. Metastatic recurrence-free survival (MFS) was defined as the time between date of diagnosis and date of first distant event. Progression free survival (PFS) was defined as the time between date of diagnosis and date of first progression (local, nodal or distant) or death. Overall survival (OS) was defined as the period from the date of diagnosis until date of death.

All statistical analyses were performed at 5% alpha risk in bilateral hypothesis using R.3.6.1 Software for windows.

Results

Patient and treatment features

Between 07/2007 and 04/2018, 191pts were included in this study (Fig. 2). Patient and treatment characteristics are reported in Table 1. Median age was 53 years (27–83), median tumor size at diagnosis was 45 mm (10–84) and most patients had T2b stage cancer (64%). EBRT was mainly performed with IMRT (91%) and median overall treatment time (OTT-from the first session of EBRT to the last session of BT) was 51 days (42–110).

Dosimetric analysis

HDR-BT dosimetric data combined with EBRT according to the different fractionation schemes groups are reported in Table 2 (BT dosimetric data missing for group 1). Median volume CTV_{HR} was 38 cc in group 2, 45 cc in group 3 and 31 cc in group 4 ($p < 0.001$). Median $D_{90}CTV_{HR}$ was comparable between groups. Median $EQD2_{10}D_{90}CTV_{HR}$ were 84, 82 and 90 Gy for group 2, 3 and 4 respectively. In group 4, $EQD2_{10}D_{90}CTV_{HR} \geq 85$ Gy was achieved for 91% of patients versus 25% and 6% for groups 2 and 3 respectively. Dose constraints to OARs were significantly higher in group 4 for bladder ($p = 0.009$) and sigmoid ($p = 0.041$). When taking into account the overall BT time, an increase of 8 to 9% was observed for $EQD2_{10}D_{90}CTV_{HR}$ while this increase was 5 to 10% for OARs $EQD2_3D_{2cc}$ (Table 2 **and Supplementary data 1**).

Oncological outcome

With a MFU of 57 months (45–132), 5-year oncological outcomes for the whole cohort were: local recurrence-free survival (LFS): 85% [95% IC, 80–91%], nodal recurrence-free survival (NFS): 83% [95%IC, 78–89%], metastatic recurrence-free survival (MFS): 70% [95%IC,

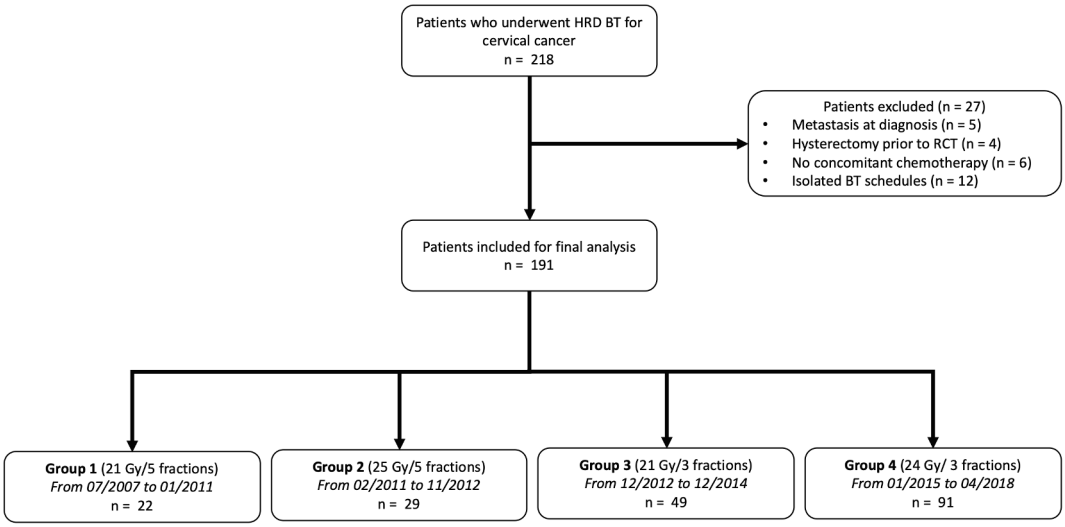

Fig. 2. Flowchart.

Table 1
Patient and tumor characteristics according to the different HDR-BT schemes.

Data	Whole cohortn/ %/min–max	Group 1n/ %/min–max	Group 2n/ %/min–max	Group 3n/ %/min–max	Group 4n/ %/min–max	*p* value
Number of pts	191 (100)	22 (11)	29 (15)	49 (26)	91 (48)	
Age (years)	53 (27–83)	52 (37–65)	45 (27–78)	56 (33–82)	56 (27–83)	0.035
Comorbidities						0.103
HIV	3 (2)	1 (4)	0 (0)	2 (4)	0 (0)	0.103
Diabetes	7 (4)	1 (4)	0 (0)	1 (2)	5 (5)	0.584
Smoker	46 (24)	4 (18)	5 (17)	18 (37)	19 (21)	0.193
Median BMI (kg/m^2)	23 (16–38)	21 (16–34)	24 (16–37)	24 (16–38)	23 (16–33)	0.468
Histology types						0.872
SCC	151 (79)	19 (86)	23 (79)	38 (78)	71 (78)	
Adenocarcinoma	37 (19)	3 (14)	6 (21)	9 (18)	19 (21)	
Others	3 (2)	0 (0)	0 (0)	2 (4)	1 (1)	
Median tumor size at diagnosis (mm)[†]	45 (10–84)	43 (10–65)	41 (18–70)	48 (16–84)	46 (10–72)	0.157
Lymph node involvement	94 (49)	7 (32)	9 (31)	29 (59)	49 (54)	0.026
TNM (7th edition)						NA
T1b1	14 (7)	3 (14)	0 (0)	4 (8)	7 (8)	
T1b2	22 (11)	4 (18)	8 (28)	3 (6)	7 (8)	
T2a1	6 (3)	0 (0)	4 (14)	0 (0)	2 (2)	
T2a2	8 (4)	2 (9)	0 (0)	1 (2)	5 (5)	
T2b	123 (64)	13 (59)	13 (45)	37 (75)	60 (66)	
T3a	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (1)	
T3b	12 (6)	0 (0)	4 (14)	1 (2)	7 (8)	
T4a	5 (3)	0 (0)	0 (0)	3 (6)	2 (2)	
$FIGO_{2018}$						NA
FIGO IB2	4 (2)	1 (5)	0 (0)	1 (2)	2 (2)	
FIGO IB3	17 (9)	4 (18)	7 (24)	2 (4)	4 (4)	
FIGO IIA1	2 (1)	0 (0)	1 (3)	0 (0)	1 (1)	
FIGO IIA2	5 (3)	0 (0)	0 (0)	0 (0)	5 (5)	
FIGO IIB	61 (32)	9 (41)	10 (34)	15 (31)	27 (30)	
FIGO IIIA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
FIGO IIIB	3 (2)	0 (0)	1 (3)	0 (0)	2 (2)	
FIGO IIIC1	74 (39)	8 (36)	7 (24)	21 (43)	38 (42)	
FIGO IIIC2	20 (10)	0 (0)	3 (10)	7 (14)	10 (11)	
FIGO IVA	5 (3)	0 (0)	0 (0)	3 (6)	2 (2)	
Median EBRT total dose (Gy)	46 (43–50)	46 (45–50)	46 (44–50)	46 (44–50)	45 (43–50)	0.006
BT dose (Gy)/#F		21/5	25/5	21/3	24/3	
Median OTT (days)	51 (42–110)	51 (42–110)	52 (43–100)	56 (43–92)	50 (43–92)	<0.001

Group 1: 7 Gy + 4 × 3.5 Gy/Group 2: 7 Gy + 4 × 4.5 Gy/Group 3: 3 × 7 Gy/Group 4: 3 × 8 Gy
BMI: body mass index; SCC: squamous cell carcinoma; EBRT: external beam radiation therapy; BT: brachytherapy; #F: number of fractions; OTT: overall treatment time.
[†]Tumor size was defined on MRI at diagnosis. If conization was performed before MRI, tumor size was calculated by adding tumor size on MRI and conization.
[°]Lymph node status was determined by MRI, PET TDM and lymph node dissection at diagnosis. Status N + was predicated on at least one positive finding.

Table 2
Report of median dosimetric data and Equivalent dose at 2 Gy (EQD2) with or without the time factor according to the different HDR-BT fractionation schemes.

Data	Group 1Median/ min–max	Group 2Median/ min–max	Group 3Median/ min–max	Group 4Median/ min–max	p value
BT aloneCTV_{HR} (cc)$D_{90}CTV_{HR}$ (%)$V_{100}CTV_{HR}$ (%)$V_{150}CTV_{HR}$ (%)$V_{200}CTV_{HR}$ (%)	NA	38 (29–40)115 (110–127)99 (97–100)48 (22–64) 14 (8–23)	45 (29–82)116 (91–130)99 (84–100) 57 (34–67)23 (12–33)	31 (13–69)117 (88–128)98 (78–100)64 (36–75) 28 (9–44)	<0.0010.4750.037<0.001<0.001
∑BT/EBRT (time factor -)[1]$EQD2_{10}D_{90}CTV_{HR}$ (Gy)$EQD2_3D_{2cc}$bladder (Gy) $EQD2_3D_{2cc}$rectum (Gy)$EQD2_3D_{2cc}$sigmoid (Gy)	NA	84 (82–90)71 (66–81) 61 (55–69)59 (54–67)	82 (72–89)73 (61–79)62 (54–78)60 (49–76)	90 (77–98)76 (58–85)61 (47–79) 66 (50–79)	<0.0010.0090.3760.041
∑BT/EBRT (time factor +)[2]EQD2 $(t)_{10}D_{90}CTV_{HR}$ (Gy)$EQD2(t)_3D_{2cc}$bladder (Gy) $EQD2(t)_3D_{2cc}$rectum (Gy)EQD2 $(t)_3D_{2cc}$sigmoid (Gy)	NA	91 (88–96)76 (71–85) 65 (59–73)65 (59–72)	89 (79–96)78 (65–84)67 (58–81)66 (54–81)	98 (82–104)80 (64–89)66 (53–83) 69 (52–81)	NA*

Group 1: 7 Gy + 4 × 3.5 Gy/Group 2: 7 Gy + 4 × 4.5 Gy/Group 3: 3 × 7 Gy/Group 4: 3 × 8 Gy
Dosimetric data missing for group 1. p value estimated for group 2, 3 and 4.
CTV_{HR}: high-risk clinical target volume; $D_{90\%}$: minimal dose to 90% of the clinical target volume; EBRT: external beam radiotherapy; $EQD2_{10}$: equivalent dose at 2 Gy per fraction for $\alpha/\beta = 10$ Gy; D_{2cc}: minimal dose to the most exposed 2 cc of the respective organ at risk; $EQD2_3$: equivalent dose at 2 Gy per fraction for $\alpha/\beta = 3$ Gy.
[1 & 2]∑BT/EBRT: Brachytherapy and external beam radiation therapy sum; EQD2 is reported without (1) and with (2) the time factor.
*EQD2 including time factor was calculated for the median, minimum and maximum dose per dose constraint target volume and OAR. The p value is not available for the data thus calculated, according to the formula described (supplementary data).

63–77%], progression-free survival (PFS): 61% [95%IC, 54–69%] and overall survival (OS): 75% [95%IC, 69–82%]. No statistical difference was observed in oncological outcome between the different fractionation schemes as shown in Table 3 and Fig. 3.

In univariate analysis, $EQD2_{10}D_{90}CTV_{HR}$ < 85 Gy (p = 0.045), adenocarcinoma histological type (p = 0.019) and OTT ≥ 50 days (p = 0.014) were prognostic factors for local recurrence. $EQD2_{10}D_{90}CTV_{HR}$ < 85 Gy (p = 0.011) was a prognostic factor for nodal recurrence while tumor size (≥5cm) (p = 0.001) was a prognostic factor for metastatic recurrence. In multivariate analysis, independent prognostic factors were adenocarcinoma histological type (p = 0.024) and OTT ≥ 50 days (p = 0.035) for local recurrence, $EQD2_{10}D_{90}CTV_{HR}$ < 85 Gy (p = 0.044) for nodal recurrence and tumor size (≥5cm) (p = 0.003) for metastatic recurrence (**Supplementary data 2**).

Toxicity

Eight patients (4%) presented vaginal bleeding after withdrawal of the applicator, requiring prolonged manual compression with absorbent hemostat. Three of them (2%) required blood transfusion.

Acute (≤6months) and late toxicities (>6months) were reported in Table 4 (and **supplementary data 4**). Thirty-nine patients (20%) presented acute toxicities grade ≥ 2: 18pts (9%) urinary, 6pts (3%) digestive and 18pts (9%) gynecological. Among them, 7 (4%) presented acute grade 3 toxicities: 3 (2%) urinary, 1 (0.5%) digestive and 5 (3%) gynecological.

Seventy-five (39%) patients presented late toxicities grade ≥ 2: 28pts (15%) urinary, 28pts (15%) digestive and 47pts (25%) gynecological. Among them, 35 (18%) presented late grade 3 toxicities: 14 (7%) urinary, 12 (6%) digestive and 22 (11%) gynecological. Two late grade 4 toxicities were observed (both in group 4): 1pt presented a sigmoid perforation and 1pt presented a sigmoid stenosis. No grade 5 acute and late toxicities were observed. No significant differences were observed between the 4 treatment groups in terms of acute and late toxicities apart from late grade 3 gynecological toxicity (p = 0.037) and a tendency towards higher acute grade ≥ 2 toxicities in group 4 (p = 0.061).

Discussion

BT allows dose escalation leading to improved local control, using either PDR or HDR-BT as LDR is currently no longer used [17]. However, there is no standard HDR-BT scheme in terms of total dose, dose per fraction and time irradiation schedule.

Oncological outcomes reported in this study are comparable to those

Table 3
Oncological outcome according to the different HDR-BT fractionation schemes.

Data	Whole cohort	Group 1	Group 2	Group 3	Group 4	*p* value
	n/%/min–max	n/%/min–max	n/%/min–max	n/%/min–max	n/%/min–max	
Number of pts	191 (100)	22 (11)	29 (15)	49 (26)	91 (48)	
MFU (months)	57 (45–132)	92 (74–132)	81 (71–118)	63 (60–76)	48 (45–52)	<0.001
Recurrence rates						
Local	27 (14)	4 (18)	7 (24)	8 (16)	8 (9)	0.141
Nodal	30 (16)	5 (23)	5 (17)	10 (20)	10 (11)	0.302
Metastatic	54 (28)	9 (41)	9 (31)	14 (29)	22 (24)	0.458
5y-survival rates (95%CI)						
LFS	85 (80–91)	84 (69–100)	81 (68–98)	81 (70–94)	90 (83–97)	0.429
NFS	83 (78–89)	81 (66–100)	81 (67–98)	79 (68–91)	86 (77–95)	0.407
MFS	70 (63–77)	67 (49–90)	67 (51–87)	69 (57–84)	73 (64–84)	0.821
PFS	61 (54–69)	58 (40–83)	57 (41–79)	64 (52–79)	63 (53–74)	0.855
OS	75 (69–82)	76 (60–97)	76 (60–95)	69 (57–84)	78 (70–88)	0.688

Group 1: 7 Gy + 4 × 3.5 Gy/Group 2: 7 Gy + 4 × 4.5 Gy/Group 3: 3 × 7 Gy/Group 4: 3 × 8 Gy
MFU: median follow up; LFS: local recurrence-free survival; NFS: nodal recurrence-free survival; MFS: metastatic recurrence-free survival; PFS: progression-free survival; OS: overall survival.

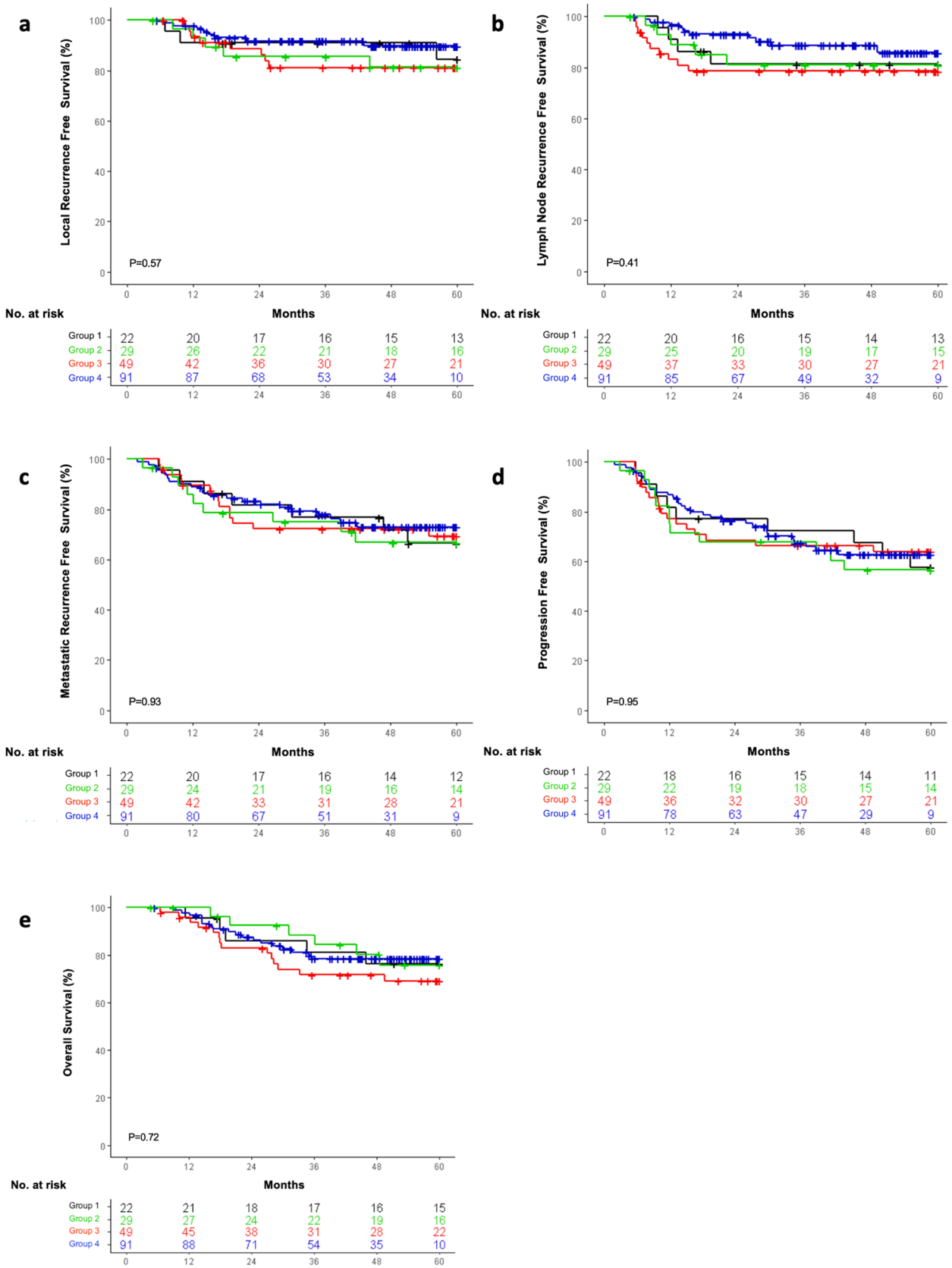

Fig. 3. Survival rates according to high dose rate brachytherapy fractionation schemes: (a) local recurrence free survival, (b) lymph node recurrence free survival, (c) metastatic recurrence free survival, (d) progression free survival, (e) overall survival.

Table 4
Toxicities according to HDR-BT schemes.

Toxicities*	Whole cohort	Group 1	Group 2	Group 3	Group 4	p value
	n/%	n/%	n/%	n/%	n/%	
Grade ≥ 2	89 (47)	13 (59)	14 (48)	15 (31)	47 (52)	0.061
Acute	39 (20)	4 (18)	6 (21)	4 (8)	25 (27)	0.061
Urinary	18 (9)	1 (4)	4 (14)	2 (4)	11 (12)	0.319
Gastro-intestinal	6 (3)	0 (0)	1 (3)	0 (0)	5 (5)	0.332
Gynecological	18 (9)	3 (14)	2 (7)	1 (2)	12 (13)	0.111
Late	75 (39)	12 (54)	13 (45)	14 (29)	36 (40)	0.181
Urinary	28 (15)	5 (23)	5 (17)	5 (10)	13 (14)	0.519
Gastro-intestinal	28 (15)	5 (23)	1 (3)	8 (16)	14 (15)	0.205
Gynecological	47 (25)	8 (36)	9 (31)	7 (14)	23 (25)	0.163
Grade 3	39 (20)	7 (32)	8 (28)	6 (12)	18 (20)	0.194
Acute	7 (4)	2 (9)	0 (0)	0 (0)	5 (5)	0.114
Urinary	3 (2)	0 (0)	0 (0)	0 (0)	3 (3)	0.711
Gastro-intestinal	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (1)	1
Gynecological	5 (3)	2 (9)	0 (0)	0 (0)	3 (3)	0.12
Late	35 (18)	6 (27)	8 (28)	6 (12)	15 (16)	0.235
Urinary	14 (7)	2 (9)	3 (10)	3 (6)	6 (7)	0.794
Gastro-intestinal	12 (6)	2 (9)	0 (0)	5 (10)	5 (5)	0.282
Gynecological	22 (11)	5 (23)	6 (21)	2 (4)	9 (10)	0.037

Group 1: 7 Gy + 4 × 3.5 Gy/Group 2: 7 Gy + 4 × 4.5 Gy/Group3: 3 × 7 Gy/ Group 4: 3 × 8 Gy
*Presented as the number of patients in whom at least one toxicity occurred

reported in mono-institutional studies (**Supplementary data 3 – p5**), with a 3-y LFS: 88% (89–97%), 3-y PFS: 70% (61–80%) and 3-y OS: 78% (64–86%) [25,26,40-43]. Five-year oncological outcomes reported in EMBRACE-I study were 92%, 87%, 68% and 74% for local and nodal control, PFS and OS respectively [11]. Even though we did not observe any statistical difference in terms of efficacy between BT groups, there was a trend towards better local control in group 4 (5y-LFS: 90%) as most patients reached the required GYN GEC-ESTRO dose recommendation of $EQD2_{10}D_{90}CTV_{HR} \geq 85$ Gy ($p < 0.001$) [29,36]. The absence of statistical difference between the different groups may be due to the relatively small number of patients. Furthermore, group 4 pts have the shortest follow-up.

In our study, there was a tendency towards higher acute grade ≥ 2 toxicities in group 4 ($p = 0.061$) and the two late grade 4 toxicities were also in this group. A higher rate of late grade 3 gynecological toxicities were observed in group 1 and 2 ($p = 0.037$). After review of the BT dosimetric data, all OARs dosimetric constraints were respected. When comparing toxicities to the literature, patients presenting late grade 3 toxicities in our study versus EMBRACE-1 study were 7% versus 4.7% (urinary), 6% versus 4.3% (gastro-intestinal) and 11% versus 4% (gynecological) respectively [11]. The possible explanations for these differences are:

1- In group 4, the dose per fraction was 8 Gy and the goal for $EQD2_{10}D_{90}CTV_{HR} \geq 85$ Gy. This meant that $D_{90}CTV_{HR}$ needed to be at least 115% of the prescribed dose. This increase in the prescribed dose for tumor control was detrimental in terms of the dose delivered to OARs because of the difference in α/β ratios. Furthermore, according to the literature, a dose higher than 7 Gy/fraction may result in higher toxicity for HDR-BT [44].
2- In our BT procedure, imaging was done only the first day after implant insertion. During the BT treatment time, displacement of the applicator may occur and not appear clinically observable. Shukla et al. reported mean caudal displacement of 17.4 mm in the case of multifractionated interstitial BT for cervical cancers [45]. These implant movements can impact CTV_{HR} coverage and dose to OARs, explaining the higher toxicity rate [46].
3- We did not take into account the recto-vaginal reference point in our dose optimization and the upper vagina was often part of the target volume delineation with CT scan only used in groups 1 and 2; this could lead to a higher rate of vaginal stenosis [47]. However, this toxicity may be overestimated as it was retrospectively recorded and poorly reported according to CTCAE 3.0 and 4.0.
4- Our BID BT scheme respected a 6-hour interval between fractions, based on general radiobiological principles (repair halftime for normal tissues around 2.5 h) [5]. However, several EBRT studies reported more toxicities with BID schemes and the 6-hour interval between fractions may be insufficient [48,49]. Therefore, with dose escalation in cervical cancer, this time interval of 6 h may also be too short for tissue repair [50].
5- General calculations of EQD2 and dose constraint recommendations do not take into account an accelerated scheme. When we calculated the EQD2 dose delivered to OARs considering the time factor (Table 2), we observed that the delivered dose was in fact 5 to 10% higher than initially planned. Therefore, more careful consideration is to be taken of dosimetric constraints with BID schemes and these dose constraints to OARs can even be lowered as proposed in EMBRACE-2 protocol [29].

There are several weaknesses in our study. It was a retrospective data collection over a long period of time (from 2007 to 2018), whence some missing data, especially for referred patients from other centers. There were also disparities between treatment delivery (EBRT using 3D technique versus IMRT; use of MRI and dose escalation for BT) and staging (the use of PET-CT and/or *para*-aortic lymph node dissection) as recommendations and classifications changed during this time lapse. Meanwhile, in our study, calculation of EQD2 including the time factor only considered the time of BT boost and not OTT including EBRT, which is known to be a key prognosis factor [51]. We chose to consider that all patients had similar total treatment time for EBRT to only analyze the impact of variation of BT time. However, EBRT time could vary as some centers used sequential boost for pathological lymph nodes. Multiple variables have been tested for multiple outcome events. However, the number of patients is not that high and especially the numbers for the two first groups are quite low. Such an imbalance bares the probability of influencing the power of the statistical analysis and the strengths of the conclusions.

Nevertheless, the strength of our study is to mimic LDR or PDR-BT for multi-fractionated HDR-BT with a single implant and a single imaging on the first day. Our aim was to strike a balance between achieving optimal dosimetric constraints while improving patient comfort (limiting invasive procedure and hospitalization time) and complying with limited human (anesthesiologists, radiation oncologists, nurses and hospitalization teams) and material resources (imaging, implants and catheters) in addition to the local organizational constraints of our institution. To our knowledge, this is the first study reporting clinical outcomes of different fractionation schemes using a single implant and BID HDR-BT scheme for LACC.

To maintain, and enhance, our local organization on the strength of these results, we modified our HDR-BT protocol in 4 main ways. First, we changed our protocol to 28 Gy in 4 fractions, decreasing dose per fraction to 7 Gy. Second, we increased time interval to 8 h between the BID sessions on day 2 (7 Gy + 2x7Gy + 7 Gy). Third, we systematically checked implant position on day 2 by means of an additional CT-scan done before the 3rd fraction (fusion facilitated by gold seed markers implanted during BT procedure on first day) [52]. Finally, we lowered our dose constraints to OARs as proposed in the EMBRACE-2 protocol while paying more attention to vaginal delineation and constraints.

Conclusion

BID HDR-BT boost seems feasible with good oncological outcome after dose escalation. While achieving these dosimetric constraints

should be a mainstay for tumor control, patient comfort and local organizational constraints in terms of human and material resources must be taken into account.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.10.005.

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