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 Adaptive BRACHytherapy in locally advanced CErvical cancer; ESTRO, European Society for Radiotherapy and Oncology; EQD2γy, equivalent dose at 2 Gy; FIGO, International Federation of Gynecology and Obstetrics; GEC, groupe européen de curietherapie; 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 adaptive 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; NPS, 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.

* Corresponding author at: Department of Radiation Oncology, Antoine Lacassagne Cancer Center, University of Côte d’Azur, 33 Avenue Valombrose, 06189 Nice Cedex 2, Nice, France

E-mail address: jean-michel.hannoun-levi@nice.unicanter.fr (J.-M. Hannoun-Levi).

https://doi.org/10.1016/j.ctro.2021.10.005
Received 31 August 2021; Received in revised form 15 October 2021; Accepted 15 October 2021
Available online 6 November 2021
2405-6308/© 2021 The Author(s). Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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-weighed 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 CTVHR 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 CTVHR 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 $\alpha/\beta$ 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 $D_{50,CTVHR}$ and $D_{2cc}$ of OARs for the different HDR-BT fractionation schemes [37-39]. Dosiometric 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.
Metastatic recurrence was defined as distant failure confirmed on PET-CT.

Toxicity comprised bleeding during hospitalization, urinary, gastrointestinal 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, 191 pts 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} ≥ 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_{3}D_{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 cohort/ %/min-max | Group 1/ %/min-max | Group 2/ %/min-max | Group 3/ %/min-max | Group 4/ %/min-max | p value |
|-----------------------------|-------------------------|--------------------|--------------------|--------------------|--------------------|---------|
| Number of pts               | 191 (100)               | 22 (11)            | 29 (15)            | 49 (26)            | 91 (48)            | 0.035   |
| Age (years)                 | 53 (27-83)              | 52 (37-65)         | 45 (27-78)         | 56 (33-82)         | 56 (27-83)         | 0.005   |
| Comorbidities               |                         | 0.103              |                     | 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/m²)          | 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)              |         |
| FIGO2018                    |                         |                    | 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 IIIIC1                 | 74 (39)                 | 8 (36)             | 7 (24)             | 21 (43)            | 38 (42)            |         |
| FIGO IIIIC2                 | 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.
was observed in oncological outcome between the different fractionation schemes as shown in Table 3 and Fig. 3.

In univariate analysis, EQD2₀EQD₂0CTVinh < 85 Gy (p = 0.045), adenocarcinoma histological type (p = 0.019) and OTT ≥ 50 days (p = 0.014) were prognostic factors for local recurrence. EQD2₀EQD₂0CTVinh < 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, EQD2₀EQD₂0CTVinh < 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 3 (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 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 1 | Group 2 | Group 3 | Group 4 | p value |
|-----------------------------|---------|---------|---------|---------|---------|
| Median/ min-max             |         |         |         |         |         |
| BT aloneCTVinh (cc)D₀EQD₂0CTVinh (%)/V₁₀₀₀CTVinh (cc)D₀EQD₂0CTVinh (%)        | NA      | 38 (29-40)/115 | 45 (29-82)/116 | 31 (13-69)/117 | <0.0010.4750.037<0.001<0.001 |
| CTVinh: high-risk clinical target volume; D₀: minimal dose to 90% of the clinical target volume; EQD2: equivalent dose at 2 Gy per fraction for α/β = 10 Gy; D₀2cc: minimal dose to the most exposed 2 cc of the respective organ at risk; EQD2c: equivalent dose at 2 Gy per fraction for α/β = 3 Gy. | | | | | |
| 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  |
| Sy-survival rates (%/Cl)    |         |         |         |         |         |
| 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 x 3.5 Gy/Group 2: 7 Gy + 4 x 4.5 Gy/Group 3: 3 x 7 Gy/Group 4: 3 x 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.
Clinical and Translational Radiation Oncology 32 (2022) 15–23

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)  | 0.532   |
| 1- Gynecological | 18 (9)       | 3 (14)| 2 (7) | 1 (2) | 12 (13)| 0.111   |
| Late        | 75 (39)      | 12 (54)| 14 (45)| 14 (29)| 36 (40)| 0.181   |
| Urinary     | 28 (15)      | 5 (23)| 5 (17)| 10 (13)| 14 (15)| 0.154   |
| Gastro-
  intestinal | 28 (15)      | 5 (23)| 1 (3) | 8 (16)| 14 (15)| 0.132   |
| 1- 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)  | 0.001   |
| 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) | 7 (7)  | 0.794   |
| Gastro-
  intestinal | 12 (6)       | 2 (9) | 0 (0) | 5 (10)| 5 (5)  | 0.282   |
| 1- Gynecological | 22 (11)      | 5 (23)| 6 (21)| 2 (4) | 9 (10) | 0.037   |

*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-γ LFS: 88% (89–97%), 3-γ PFS: 70% (61–80%) and 3-γ OS: 78% (64–86%). In 5-years outcome analysis reported in EMBRACE-1 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 (Sy-LFS: 90%) as most patients reached the required GYN GEC-ESTRO dose recommendation of EQD2, 3YD (D0, CTVHR ≥ 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% (gynecologically) 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, 3YD (D0, CTVHR ≥ 85 Gy). This meant that D0, CTVHR 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 CTVHR 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.

We did 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 BT 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
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.

References

[1] World Health Organization. International Agency for Research on Cancer 2021 – GLOBOCAN 2020. Cancer Today n.d. http://gco.iarc.fr.
[2] Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. The Lancet 2019;393(10167):69–82. https://doi.org/10.1016/s0140-6736(18)32470-5.
[3] World Health Organization. International Agency for Research on Cancer 2021 – GLOBOCAN 2020. Cancer Tomorrow n.d. https://gco.iarc.fr/tomorrow.
[4] Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340(15):144–53.
[5] Vreventhan AN, Bolos S, de Los Santos JF, Demanes DJ, Gaffney D, Hansen J, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. Brachytherapy 2012;11(1):47–52. https://doi.org/10.1016/j.brachy.2011.07.002.
[6] Cibula D, Potter R, Fokdal LU, Haie-Meder C, Tan LT, Mazeron R, et al. Image guided brachytherapy in locally advanced cervical cancer: improved pelvic control and survival in RETROEMBRACE, a multicenter cohort study. Radiother Oncol 2016;120(3):428–33. https://doi.org/10.1016/j.radonc.2016.03.011.
[7] Charrati G, Deutsch E, Blanchard P, Gouy S, Martelli H, Guerin F, et al. Brachytherapy: an overview for clinicians. CA Cancer J Clin 2019;69(5):386–401. https://doi.org/10.3322/caac.21578.
[8] Holzscheiner CH, Peteret DG, Chu C, Hsu I-C, Ioffe YJ, Klomp AH, et al. Brachytherapy: a critical component of primary radiation therapy for cervical cancer. Brachytherapy 2019;18(2):123–32. https://doi.org/10.1016/j.brachy.2018.11.009.
[9] Peteret DG, Tandrerup K, Schmid MP, Jürgenleitner-Schulz I, Haie-Meder C, Fokdal LU, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. Lancet Oncol 2021;22(4):338–47. https://doi.org/10.1016/s1470-2045(20)70510-1.
[10] Charrart C, Harter V, Delamoine M, Haie-Meder C, Quetin P, Kerr C, et al. Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: results of the french STIC prospective study. Radiother Oncol 2012;103(3):205–13. https://doi.org/10.1016/j.radonc.2012.04.007.
[11] Charrat C, Magne N, Dumas I, Messai T, Vicien L, Gillion N, et al. Physics contributions and clinical outcome with 3D-MRI-based pulsed-dose-rate intracavitary brachytherapy in cervical cancer patients. Int J Radiat Oncol Biol Phys 2009;74(1):113–9. https://doi.org/10.1016/j.ijrobp.2008.06.1912.
[12] Bremner DJ, Hall EJ. Conditions for the equivalence of continuous to pulsed low dose rate brachytherapy. Int J Radiat Oncol Biol Phys 1991;21(1):181–90. https://doi.org/10.1016/0360-3016(91)90158-Z.
[13] Granger K, van Dijk S, Bernshaw D, Rajasooriyar C, Kondalsamy-Chennakesavan S. Comparative study of LDR (Manchester System) and HDR image-guided conformal brachytherapy of cervical cancer: patterns of failure late complications, and survival. Int J Radiat Oncol Biol Phys 2009;74(5):1529–35. https://doi.org/10.1016/j.ijrobp.2008.07.005.
[14] Lin AJ, Samson P, Zoberi J, Garcia-Ramirez J, Williamson JF, Markovina S, et al. Concurrent chemoradiation for cervical cancer: comparison of LDR and HDR brachytherapy. Brachytherapy 2019;18(3):353–60. https://doi.org/10.1016/j.brachy.2018.11.008.
[15] Peiffert D, Hannoun-Levi J-M. Evolution de la curiethérapie en France: résultats de l’étude Prospective Multicentrique de Curiethérapie (EMBRACE). Radiother Oncol 2013;107(1):69–74. https://doi.org/10.1016/j.radonc.2013.04.006.
[16] Jamalladin Z, Min UN, Ibsan WZM, Malik RA. Preliminary experience on the implementation of computed tomography (CT)-based image guided brachytherapy (IGBT) of cervical cancer using high-dose-rate (HDR) Cobalt-60 source in University of Malaya Medical Centre (UMMC). J Phys Conf Ser 2016;694:012016. https://doi.org/10.1088/1742-6596/694/1/012016.
[17] Tandrerup K, Fokdal LU, Stürza A, Haie-Meder C, Mazeron R, van Limbergen E, et al. Effect of tumor dose, volume and overall treatment time on local control after radiochemotherapy including MRI guided brachytherapy of locally advanced cervical cancer. Radiother Oncol 2016;120(3):441–6. https://doi.org/10.1016/j.radonc.2016.05.014.
[18] Peteret R, Tandrerup K, Kirisits C, de Leeuw A, Kirchehein K, Nout R, et al. The EMBRACE II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. Clin Transl Radiat Oncol 2019;8:48–60. https://doi.org/10.1016/j.ctro.2018.10.001.
[19] Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. Int J Gynecol Obstet 2009;105(2):107–8. https://doi.org/10.1016/j.ijgo.2008.09.009.
[20] Bhutla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri – FIGO 2018 report. Int J Gynecol Obstet 2018;143:22–36. https://doi.org/10.1016/j.ijgo.2016.11.001.
[21] Hannoun-Levi J-M, Chand-Fouche M-E, Gautier M, Dejean C, Marcy M, Fouche V. Intestinal preoperative high-dose-rate brachytherapy for early stage cervical cancer: dose-volume histogram parameters, pathologic response and early clinical outcome. Brachytherapy 2013;12(2):148–55. https://doi.org/10.1016/j.brachy.2012.04.007.
[22] Ballieux C, Falk AT, Chand-Fouche M-E, Gautier M, Barranger E, Hannoun-Levi J-M. Concomitant cervical and transperineal parametrial high-dose-rate brachytherapy boost for locally advanced cervical cancer. Jcb 2016;4:23–31. https://doi.org/10.6004/jcb.2016.57535.
[23] Haie-Meder C, Peteret R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J, et al. Recommendations from gynaecological (GYN) GEC-ESTRO Working Group☆: concepts and terms in 3D image based 3D treatment planning in cervical cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 2005;74(3):235–45. https://doi.org/10.1016/j.radonc.2004.12.015.
[24] Peteret R, Haie-Meder C, Limbergen EV, Barillot I, Bebrabandere MD, Dimopoulos J, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO working group☆: concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy –3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 2006;78(1):67–77. https://doi.org/10.1016/j.radonc.2006.02.004.
[25] Dimopoulos JCA, Peteret R, Lang S, Fidarova E, Georg P, Dörr W, et al. Dose-effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy. Radiother Oncol 2009;93(2):311–5. https://doi.org/10.1016/j.radonc.2009.07.007.
[26] Beskov C, Ägren-Cronqvist A-K, Lewensohn R, Toma-Dansu I. Clinical Investigations Biological effective dose evaluation and assessment of rectal and bladder complications for cervical cancer treated with radiotherapy and surgery. Jcb 2012;4:205–12. https://doi.org/10.6004/jcb.2012.32554.
van Leeuwen CM, Oei AL, Crezee J, Bel A, Franken NAP, Stalpers LJA, et al. The α and β of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. Radiat Oncol 2018;13(1). https://doi.org/10.1186/s13014-018-1040-z.

Gasinska A, Fowler JF, Lind BK, Urbanski K. Influence of overall treatment time and radiobiological parameters on biologically effective doses in cervical cancer patients treated with radiation therapy alone. Acta Oncol 2004;43(7):657–66. https://doi.org/10.1080/02841860410018511.

Tinkle CL, Weinberg V, Chen L-M, Littell R, Cunha JAM, Sethi RA, et al. Inverse planned high-dose-rate brachytherapy for locoregionally advanced cervical cancer: 4-year outcomes. Int J Radiat Oncol Biol Phys 2015;92(5):1093–100. https://doi.org/10.1016/j.ijrobp.2015.04.018.

Hallock A, Surry K, Batchelor D, VanderSpek L, Yuen J, Hammond A, et al. An early report on outcomes from computed tomographic-based high-dose-rate brachytherapy for locally advanced cervix cancer: a single institution experience. Pract Radiat Oncol 2011;1(3):173-81. https://doi.org/10.1016/j.prro.2011.01.004.

Kang H-C, Shin KH, Park S-Y, Kim J-Y. 3D CT-based high-dose-rate brachytherapy for cervical cancer: clinical impact on late rectal bleeding and local control. Radiother Oncol 2010;97(3):507–13. https://doi.org/10.1016/j.radonc.2010.10.002.

Gill BS, Kim H, Houzer CJ, Kelley JL, Sukumvanich P, Edwards RP, et al. MRI-guided high-dose-rate intracavitary brachytherapy for treatment of cervical cancer: the University of Pittsburgh Experience. Int J Radiat Oncol Biol Phys 2015;91(3):540–7. https://doi.org/10.1016/j.ijrobp.2014.10.053.

Orton CG. High-dose-rate brachytherapy may be radiobiologically superior to low-dose rate due to slow repair of late-responding normal tissue cells. Int J Radiat Oncol Biol Phys 2001;49(1):183–9. https://doi.org/10.1016/S0360-3016(00)00810-5.

Sturdza ME, Potter R, Kosmeier M, Kirchheiner K, Mahantshetty U, Haie-Meder C, et al. Nomogram predicting overall survival in patients with locally advanced cervical cancer treated with radiochemotherapy including image-guided brachytherapy: a retro-EMBRACE study. Int J Radiat Oncol Biol Phys 2021;111(1):168–77. https://doi.org/10.1016/j.ijrobp.2021.04.022.

Ostyn M, Burke AM, Fields E, Todor D. Inter-fractional variation of markers and applicators in single-implant high-dose-rate interstitial brachytherapy for gynecologic malignancies. Brachytherapy 2021;20(4):771–80. https://doi.org/10.1016/j.brachy.2021.03.011.