original reports abstract

Point-Based Brachytherapy in Cervical Cancer With Limited Residual Disease: A Low- and Middle-Income Country Experience in the Era of Magnetic Resonance–Guided Adaptive Brachytherapy

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PURPOSE To evaluate the clinical outcomes in patients with cervical cancer with limited residual disease at brachytherapy (BT) treated with point-based dose prescription.

METHODS Patients with locally advanced squamous cell carcinoma of the cervix treated with computed tomography (CT)-based intracavitary BT were considered for analysis. Patients with good response to external beam radiotherapy and limited residual disease suitable for intracavitary BT alone were included. Post-application CT scans were performed before each fraction and individual plans were made for each session. The dose per fraction was 9Gy high dose rate, prescribed to point-A. Two sessions were planned, 1 week apart. The organs at risk were contoured, and cumulative dose-volume histograms were computed. Local control, pelvic control, disease-free survival, and overall survival were evaluated and late toxicities were documented.

RESULTS Four hundred ninety patients were included. Overall, 79.8% had International Federation of Gynecology and Obstetrics (FIGO) stage IB2 to IIB disease and 20.2% had stage III to IVA disease. Median dose at point A ($EQD2_{10Gy}$) was 74.4 Gy (interquartile range [IQR] 72.3-74.5 Gy) and median D_{2cc} ($EQD2_{3Gy}$) for bladder, rectum, and sigmoid were 82.5 Gy (IQR, 65.5-90.8 Gy), 66.5 Gy (IQR, 60.7-75.7 Gy), and 54.1 Gy (IQR, 50.5-77.3 Gy), respectively. At a median follow-up of 62 (IQR, 33-87) months, the 5-year local and pelvic control rates were 90.1% and 88.3%, respectively. The 5-year disease-free survival was 80% and overall survival was 88%. Rates of grade 3-4 bladder and rectosigmoid toxicities were 6.93% and 4.08%, respectively.

CONCLUSION In patients with limited residual disease at BT, point-based dose prescription with CT planning results in good local control and acceptable toxicity. In a resource-constrained setting, patients may be triaged to receive point-based BT or magnetic resonance imaging–guided adaptive BT depending on the extent of residual disease.

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INTRODUCTION

Concurrent chemoradiation (CRT) and brachytherapy (BT) represent the standard treatment for locally advanced cervical cancer (LACC).[1,2] BT is a vital component of the curative treatment of locally advanced disease.

In recent years, 3-dimensional (3D) image-guided adaptive brachytherapy (IGABT) using magnetic resonance imaging (MRI) is being increasingly advocated as the gold standard in cervical cancers. Prospective image-guided studies including the recently published results from the IntErnational study on MRI-guided BRAchytherapy in CErvical cancer (EMBRACE-I) study group have demonstrated improved local control and favorable toxicity profile.[3-5] MRI allows for improved delineation of the tumor and clinical target volume while maintaining accurate contouring of the organs at risk (OARs) and also facilitates dose optimization.[4,6]

Although transitioning from point-based to advanced MRI-guided and volume-based BT techniques may be applicable in settings with adequate resources, the existing disparities within low- and middle-income countries (LMICs) may create unique implementation difficulties with the long patient waiting lists, suboptimal number of BT units, lack of MRI in radiation oncology departments, and limited access to

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CONTEXT

Key Objective

Utilization of image-guided adaptive brachytherapy as the standard of care in locally advanced cervical cancer is limited in resource-constrained settings of low and middle-income countries. Here, we report the long-term outcomes in patients with locally advanced cervical cancer with limited residual disease, treated with computed tomography–based intracavitary brachytherapy (BT) using dose prescription at point A and dose-volume reporting for the organs at risk.

Knowledge Generated

Our results show that in well-selected patients, this approach results in good local control (92.9 and 90.1% at 3 and 5 years, respectively) with acceptable toxicity.

Relevance

Rational implementation of point-based intracavitary BT in patients with good response and limited residual disease at BT can help in allocating the limited available resources to patients requiring dose optimization with advanced BT techniques. A structured approach can, hence, be implemented wherein dose prescription and resource allocation can be optimized based upon the volume of disease and organ at risk doses at BT.

diagnostic MRI.[7-9] Efforts to implement advanced image-guided BT for all patients in these centers may result in increase in patient waiting lists that would be deleterious to local control because of increased overall treatment time.

According to a survey conducted in 2017, a majority of practitioners in Indian centers still use computed tomography (CT) or X-ray–based point-A prescription for cervical BT.[10] Dedicated CT simulators are now widely available in most radiotherapy centers. CT for treatment planning allows for visualization of OARs as well as the applicators. The OARs can be delineated as volumetric structures rather than arbitrary reference points, whereas the definition of high risk-clinical target volume remains challenging.[11,12]

Numerous studies have demonstrated improved outcomes with IGABT relative to historical 2D BT.[4,13-15] However, there is paucity of published data from studies of CT-based intracavitary brachytherapy (ICBT) with dose prescribed and reported at point A.[16,17] In this analysis, we present the clinical outcomes in patients with LACC with limited residual disease, who were treated with CT-based ICBT using dose prescription at Point A.

METHODS

Clinical and dosimetric records of patients with locally advanced squamous cell carcinoma of the cervix (stages IB2-IVA, International Federation of Gynecology and Obstetrics [FIGO], 2009) who underwent CT-based ICBT between years 2012 and 2019 at our institute were reviewed. The study was conducted with approval from the departmental ethics committee. Patients with limited and well-responding tumors treated with high-dose-rate (HDR) ICBT alone were included. The categorization of limited disease was based on clinical assessment and included only those tumors that were expected to be adequately covered with standard point-A prescription, ie, no residual disease, or residual disease at the cervix or limited to medial parametrium and/or upper vagina. Patients with poor response to external beam radiotherapy (EBRT) and those with large residual disease at BT were excluded. These comprised patients who were treated with combined intracavitary and interstitial applications (IC-IS), interstitial BT alone, and those who received EBRT boost. Also, patients treated with medium-dose-rate BT and those who received neoadjuvant chemotherapy, postoperative, salvage, or palliative radiation, or were referred for BT alone from other institutions were excluded.

All patients received EBRT. A dose of 45 Gy-50 Gy in 23-25 fractions over 4 1/2-5 weeks with concurrent weekly cisplatin (40 mg/m^2) was prescribed and treatment was delivered using four-field box technique with 2-D conventional or 3-D conformal radiotherapy (3DCRT). Patients with pelvic lymph nodes at diagnosis were treated with intensity-modulated radiotherapy and those with para-aortic lymph nodes received extended-field radiation.

BT was planned after completion of EBRT after a detailed clinical assessment, and patients with limited disease and good response suitable for ICBT were taken up for the procedure. Intracavitary application was done under general or spinal anesthesia with the patient in lithotomy position. Transabdominal ultrasound was used to guide applicator insertion. The applicators used were either tandem and two symmetric ovoids or tandem and ring. Adequate vaginal packing was done to keep the rectum and bladder away to avoid high dose to the critical organs.

A post-application CT scan was performed before each BT fraction and individual plans were made for each session. Standardized institutional protocols were followed for the bladder and rectum. The dose per fraction was 9 Gy HDR and two fractions were planned 1 week apart. The dose was prescribed to point A[18,19] (total dose at point A: 74.5-79.5 Gy, $EQD2_{10Gy}$) and the OARs, ie, bladder, rectum, and sigmoid, were contoured in both sessions. Cumulative

dose-volume histogram was computed for the OARs, and doses to 2 cc volumes of bladder, rectum, and sigmoid were recorded. The planning constraints were D_{2cc} rectum $<$ 75 Gy, D_{2cc} sigmoid $<$ 75 Gy, and D_{2cc} bladder $<$ 90 Gy (EBRT plus BT, all $EQD2_{3Gy}$), on the basis of the American Brachytherapy Society (ABS) and Groupe Européen de Curiethérapie European Society for Radiation Oncology (GEC-ESTRO) guidelines.[20,21] Plans were optimized whenever required. Treatment planning was performed on the Oncentra microSelectron HDR (Nucletron, Netherlands) or HDR BEBIG (Eckert and Zeigler, Germany) treatment planning system.

Follow-up examinations were scheduled every 3 months during the first year, every 6 months throughout the next 2 years, and once a year thereafter. If relapse was suspected, a biopsy was obtained from the lesion.

Local, pelvic, and distant control rates, overall survival (OS), and disease-free survival (DFS) were evaluated. Treatment failures were classified as local (cervix, parametria, uterine corpus, and vagina), pelvic (local or pelvic nodes) or distant (lymph nodes outside pelvis, bones, or viscera). DFS was defined by the interval between the time of diagnosis to date of recurrence or death from any cause. OS was calculated from the date of diagnosis till death from any cause. Toxicities were assessed at each follow-up and documented using the Common Terminology Criteria for Adverse Events (CTCAE) v4.

Statistical Analysis

Descriptive statistics were used to describe patient, disease, and treatment characteristics. Medians and interquartile ranges (IQRs) were calculated for age and dosimetric parameters (EQD2 for Point A and the OARs), and frequencies were computed for stage and treatment variables. Any local, regional, or distant relapse (first event) was calculated as an event toward DFS calculation. Estimates of DFS and OS were calculated using Kaplan-Meier method and compared using log-rank test.

All statistical analyses were performed using Statistical Package for Social Sciences, version 23 (SPSS, Chicago, IL).

RESULTS

Patient and Treatment Characteristics

A total of 2,604 patients with LACC were treated during the study period. Patients who received palliative treatment (n = 231), neoadjuvant chemotherapy (n = 31), or post-

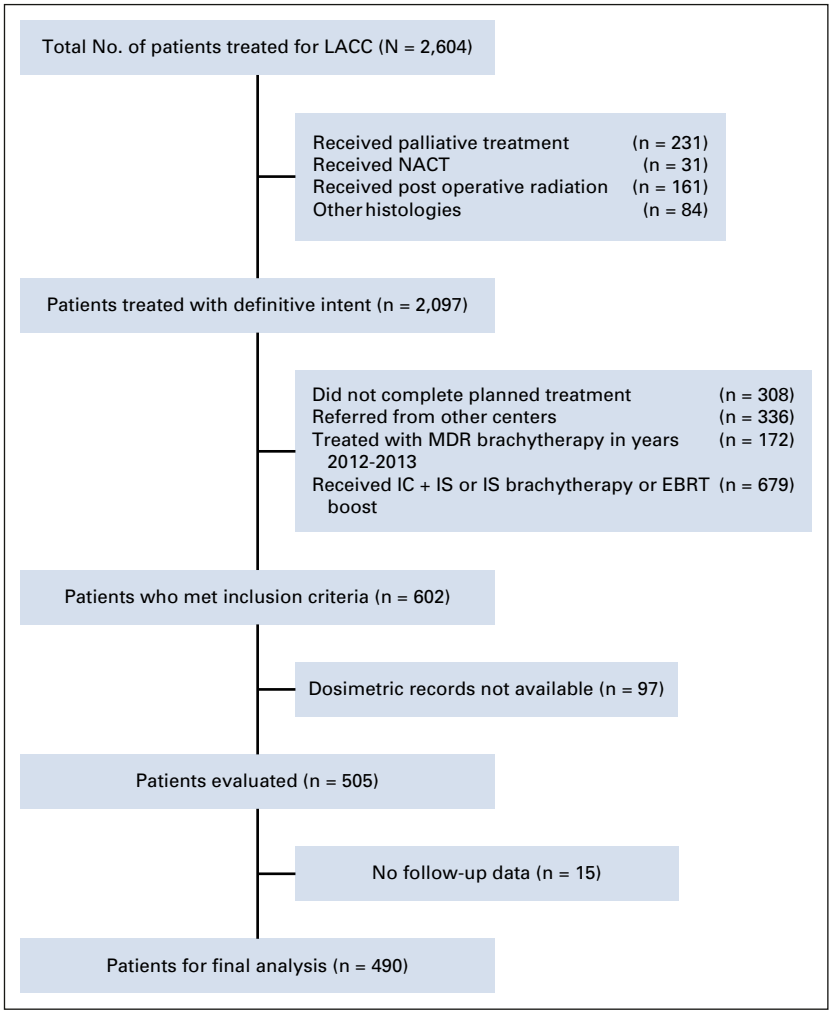

FIG 1. Study population. EBRT, external beam radiotherapy; IC, intracavitary; ICBT, intracavitary brachytherapy; IS, interstitial; LACC, locally advanced cervical cancer; MDR, medium dose rate; NACT, neoadjuvant chemotherapy.

TABLE 1. Patient and Treatment Characteristics (n = 490)

Characteristics	N = 490
Age, years, median (IQR)	52 (44-60)
Stage (FIGO 2009), No. (%)	
IB2	27 (5.5)
IIA	37 (7.5)
IIB	327 (66.8)
IIIA	3 (0.6)
IIIB	95 (19.4)
IVA	1 (0.2)
EBRT technique, No. (%)	
Conformal (3D-CRT or IMRT)	462 (94.3)
2-D conventional	28 (5.7)
Total EBRT dose, Gy, No. (%)	
45	20 (4.1)
46	457 (93.2)
50	13 (2.7)
Concurrent cisplatin, No. (%)	
Yes	462 (94.3)
No	28 (5.7)
Overall treatment time, days, median (IQR)	58 (53-67)

Abbreviations: CRT, concurrent chemoradiation; EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; IMRT, intensity-modulated radiotherapy; IQR, interquartile range.

operative radiation (n = 161), or had other histologies (n = 84) were excluded. Of the remaining 2,097 patients treated with definitive intent, 308 did not complete the planned treatment, 336 patients were referred from other centers for ICBT, 172 were treated with medium-dose-rate ICBT in years 2012-2013, and 679 patients were given IC plus IS/IS BT or EBRT boost. Six hundred two patients met the inclusion criteria, and complete clinical and dosimetric records were available for 505 patients. Fifteen patients were excluded because of lack of follow-up data and the remaining 490 patients were included for analysis (Fig 1). Patient, disease, and treatment characteristics are listed in Table 1. The median age of the study cohort was 52 years (IQR, 44-60 years). Overall, 79.8% had stage IB2-IIB disease and 20.2% had stage III-IVA disease (FIGO 2009). Four hundred sixty-two (94.3%) patients were treated with conformal radiation (3D-CRT or intensity-modulated radiotherapy), whereas the remaining (5.7%) received 2-D conventional radiotherapy using four-field box technique. The most common radiotherapy schedule for EBRT was 46 Gy in 23 fractions over 4.5 weeks (93.2%). 94.3% patients received concurrent chemotherapy. The median number of chemotherapy cycles was 4 (IQR, 3-5), and the median overall treatment time was 58 days (IQR, 53-67 days). The median dose at point A ($EQD2_{10Gy}$) was 74.4 Gy (IQR, 72.3-74.5 Gy). For OARs, median D_{2cc} for bladder, rectum, and sigmoid were 82.5 Gy (IQR, 65.5-90.8 Gy), 66.5 Gy (IQR, 60.7-75.7 Gy), and 54.1 Gy (IQR, 50.5-77.3 Gy), respectively. The dosimetric parameters are listed in Table 2.

TABLE 2. Dosimetric Parameters of Treated Patients

EQD2	Median (IQR), Gy
Point-A	74.4 (72.3-74.5)
Bladder (D_{2cc})	82.5 (65.5-90.8)
Rectum (D_{2cc})	66.5 (60.7-75.7)
Sigmoid (D_{2cc})	54.1 (50.5-77.3)

Abbreviations: EBRT, external beam radiotherapy; EQD2, equieffective dose in 2 Gy per fraction (EBRT plus brachytherapy); IQR, interquartile range.

Disease Outcomes and Patterns of Failure

At a median follow-up of 62 months (IQR, 33-87 months), 82 patients had relapsed. Thirty-seven patients developed local recurrence and 35 developed distant metastases, the most common sites being the lung (62.5%) followed by the liver (25.6%), brain (11.9%), and para-aortic lymph nodes (11.4%). Ten patients relapsed in the pelvic lymph nodes.

Local control at 3 and 5 years was 92.9 and 90.1%, respectively (92.6% and 90.6% for stage 1B2 and II and 93.9% and 89.5% for stage III and IVA, respectively, $P = .85$; Fig 2A). Pelvic control at 3 and 5 years was 91.6% and 88.3%, respectively (91.2% and 89.2% for stage IB2 and II and 92.7% and 87.1% for stage III and IVA, respectively, $P = .39$; Fig 2B). The distant control rate at 3 and 5 years was 94.1% and 90.7%, respectively (95.3% and 91.8% for stage IB2 and II and 90% and 87.2% for stage III and IVA, respectively). There was a significant difference in the distant control rates between stages IB2-II and III-IVA ($P = .05$).

The overall 3- and 5-year DFS was 86.2% and 80%, respectively (87% and 81.9% for stage IB2 and II and 83.4% and 75.9% for stage III and IVA, respectively; Fig 3A). Forty-five patients died during follow-up. The 5-year OS was 88% (89.4% for stage IB2 and II and 84.1% for stage III and IVA; Fig 3B). Significant differences were found in DFS and OS between stages IB-II and III-IVA ($P = .05$ and .02, respectively).

Late Toxicity

Grade 3-4 bladder toxicity was seen in 34 (6.93%) patients, and 20 (4.08%) patients experienced grade 3-4 rectosigmoid toxicity. One patient developed vesicovaginal fistula. Complete vaginal stenosis was documented in 25 (5.1%) patients.

DISCUSSION

In this analysis, we report the clinical outcome with CT-based ICBT using dose prescription at point A and dose-volume reporting for the OARs, in patients with limited disease at BT. Our results show that in well-selected patients, this approach results in good local control (92.9%

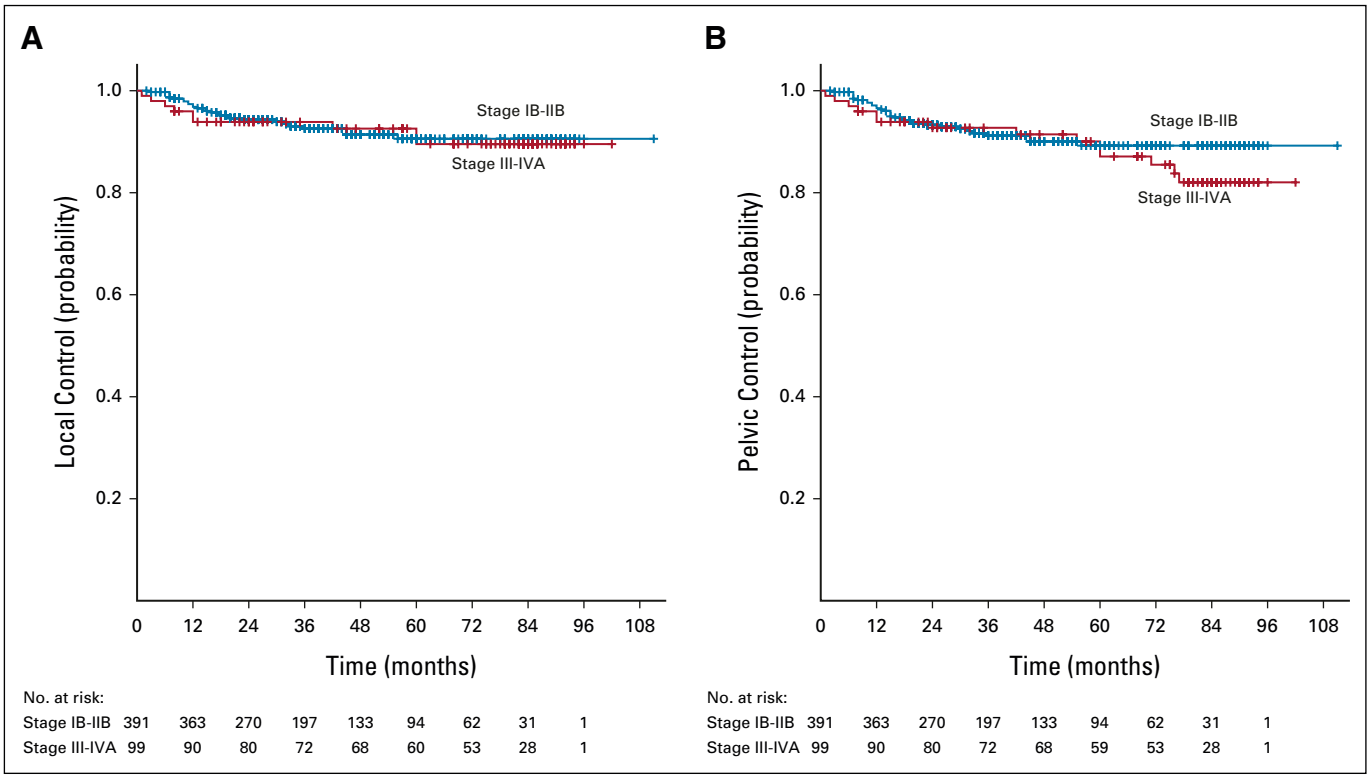

FIG 2. Kaplan-Meier survival plots for (A) local control and (B) pelvic control for FIGO stage IB-IIB (blue) and stage III-IVA (red), log-rank $P = .85$ and .39, respectively.

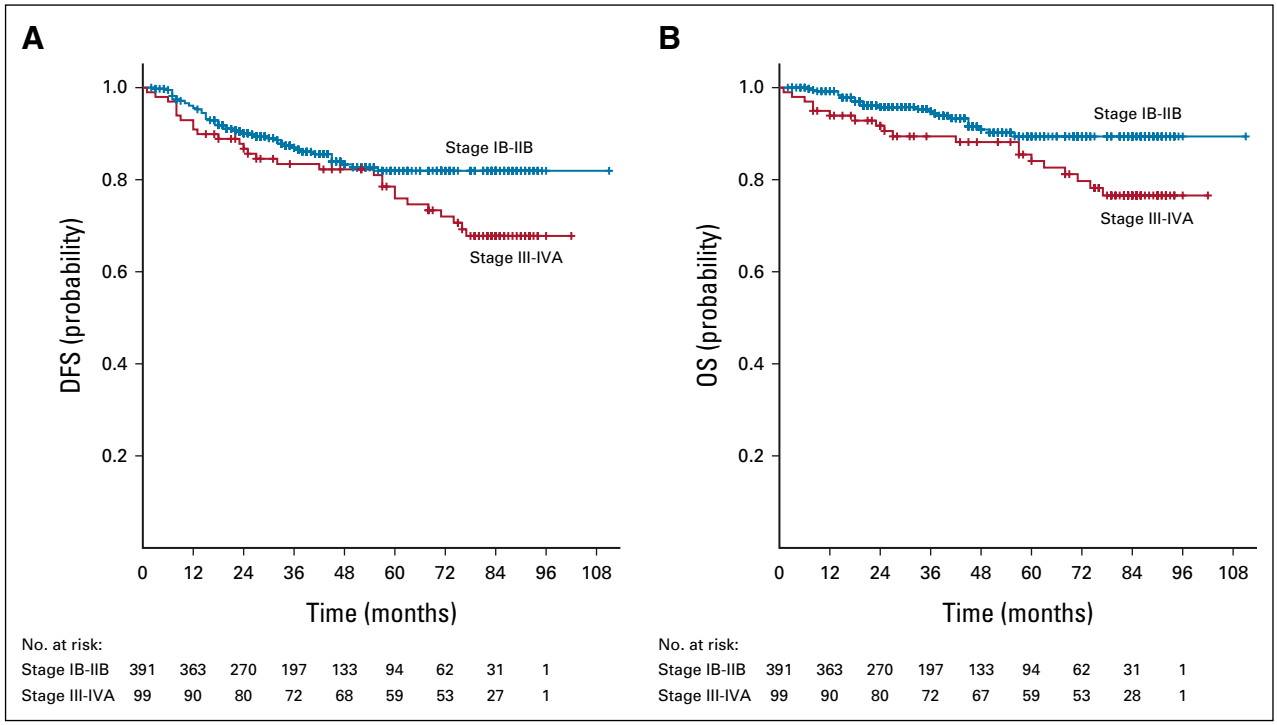

FIG 3. Kaplan-Meier survival plots for (A) DFS and (B) OS for FIGO stage IB-IIB (blue) and stage III-IVA (red), log-rank $P = .05$ and .02, respectively. DFS, disease-free survival; OS, overall survival.

and 90.1% at 3 and 5 years, respectively) with acceptable toxicity. When compared with large historical series of standard 2-D BT including the previously published results from our institute, this study shows favorable outcomes.[22-25] However, there is scarcity of clinical data from similar studies for comparison with our results.

Our outcomes are also comparable with those from RetroEMBRACE and other monoinstitutional studies of IGABT.[4,13,14] The 3-year local control rates in the above studies ranged from 98%-100% for FIGO stage IB disease and 93%-96% for stage IIB disease. For the RetroEMBRACE cohort, the 3- and 5-year local control was 91% and 89%, respectively.[14] Notably, in 23% patients of the RetroEMBRACE cohort, a combined intracavitary-interstitial approach was used in at least one BT fraction, whereas our study included patients with good response and limited disease suitable for ICBT alone.

In patients with small HR-CTV volumes (< 31cc), Tanderup et al demonstrated that standard point A plans adequately covered the target volume with mean HR-CTV D_{90} of 123 ± 20% of point A dose. In this group of patients, the overall effect of IGABT was a significant decrease in OAR doses. However, in patients with poorly responding tumors and larger HR-CTV volumes, MRI-based dose optimization significantly improved dose coverage and outcome both in terms of local control and morbidity.[26,27] They also stated that point A provides a reasonable estimate of the median HR-CTV D_{90} and is a good representation of an average extension of the tumor or cervix. Additionally, ICRU 89 also recommends absorbed-dose reporting to point A as a minimum standard requirement for any BT treatment, although volumetric assessment is recognized as the method of choice. Reporting of point A dose is not dependent on target-volume contouring and allows a direct comparison of the effects of dose delivered to different patients in different departments with variable fractionation schedules and absorbed-dose rates.[28]

The recently published clinical outcome data from EMBRACE-I have demonstrated superior rates of local and pelvic control as well as improved OS with MRI-guided adaptive BT across all stages of LACC. This was accompanied by limited severe organ-related morbidity. These results have provided high-quality clinical evidence in favor of MRI-guided adaptive BT as the gold standard in LACC to be implemented worldwide. Improved target dose was obtained through multiparametric three-dimensional treatment planning and application of combined intracavitary and interstitial techniques (43% patients). Actuarial 5-year local control was 92% and ranged from 92% to 98% in stage IB, 89% to 91% in stage II, 92% to 100% in stage III, and 91% in stage IVA disease.[5] Of notable interest within this patient cohort was that 41% of the patients (with limited and well-responding tumors) were treated with volumes (V85 Gy) smaller than those of standard plans receiving 75 Gy at point A, while maintaining excellent control rates with dose de-escalation.[5,29] On the basis of these results, de-escalation of treatment in low-risk patients (EMBRACE-III) has been proposed.[5] The doses used in our study ($EQD2_{10Gy}$ 74.5 Gy), although lower in terms of the minimum recommended doses for standard ICBT, are akin to those suggested for de-escalation in well-responding tumors with limited disease at BT.

Therefore, in a resource-constrained setting, it seems reasonable to use CT-based ICBT with standard point-A prescription in patients with good response and limited residual disease at BT as long as dose volume histogram constraints are respected for the OARs. By contrast, utilization of MRI-based IGABT can be justified and reserved for patients with tumors requiring dose escalation using combined IC-IS and IS approaches.

In this study, we have demonstrated favorable outcomes with the use of CT-based ICBT in a large cohort of patients with limited disease in an LMIC setting. Acceptable D_{2cc} doses for all OARs were achieved along with limited late morbidity. CT-based plans enable adequate delineation of all OARs while allowing 3-D assessment of dose distribution and its relation to the tumor, parametria, and pelvic sidewalls, while also enabling dose optimization. A structured approach can, hence, be implemented wherein dose prescription and resource utilization can be optimized based upon the volume of disease and OAR doses at BT, and allocating the restricted available facilities to those requiring dose optimization using MRI-based IGABT.

Our results are in line with previously published studies including those from our institute in support of the safety and efficacy of delivering a dose of 9 Gy HDR with good local control, survival rates, and manageable toxicity while improving compliance with overall treatment time.[22,30] This fractionation schedule has also been recommended by the ABS as a feasible option in resource-poor countries.[31]

This study has limitations owing to its single-institutional and retrospective nature, which could have led to selection bias during response assessment as well as under-reporting of toxicities. Our results represent a selected subgroup of patients with LACC with well-responding limited volume residual disease that can be considered suitable for point-based ICBT, thereby sparing the limited available IGABT facilities for patients requiring dose escalation. Utilization of MRI in cases such as those with intrauterine extension could have entailed the scope of further improvement in the rates of local control. It is also pertinent to mention that the outcomes with point-based utilization for patients with advanced stages (IIB-IVA) described in this study represent only a carefully selected cohort and hence should not be considered as standard for all patients with LACC. Hence, it is important to identify through clinical trials the patient cohorts that can be treated with point-based ICBT without compromising disease control and toxicity outcomes.

Through this analysis, we were able to demonstrate the utility of point-based BT with CT planning in a large homogeneous patient cohort with long-term follow-up. CT

scans were performed at each BT fraction, and individual plans were made for each session. Standard protocols were followed for planning and treatment. This study represents the real-world scenario in LMICs, which contribute to a majority of the cervical cancer burden and continue to face disparities in the availability of technology and basic radiotherapy facilities. We suggest a rational implementation of point-based BT in this era of MRI-guided adaptive BT to optimize the utilization of available resources and achieve the best possible clinical outcome.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

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