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Early outcomes of abbreviated multi-fractionated brachytherapy schedule for cervix cancer during COVID-19 pandemic

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ABSTRACT

PURPOSE: Brachytherapy (BT) for cervix cancer was listed as a level I priority and reduced number of implants and multiple fractions were recommended during COVID-19 pandemic. We present early clinical outcome of this approach.

METHODS AND MATERIALS: Patients treated with (chemo)radiotherapy and BT with single implant and multiple fractions BT were included. Treatment protocol included 3−5 fractions of 5−8.5 Gy with an aim to achieve point A dose of 70 Gy $EQD2_{10Gy}$ (or HRCTV dose of >80 Gy $EQD2_{10Gy}$) in those undergoing intracavitary (IC) and HRCTV dose >85 Gy EQD2 10Gy in patients undergoing Intracavitary-Interstitial (IC/IS) whereas maintaining bladder (B2cc), rectum (R2cc), sigmoid (S 2cc) doses of 90, 75, and 75 Gy $EQD2_{3Gy}$. Time to event analysis was used to report oncological endpoints. Toxicity was reported using crude proportions.

RESULTS: From April 2020 to March, 2021, 64 patients with stage IB2-IV received single implant and multi-fraction BT after external radiation of 45 Gy/25 fractions/5 weeks. Only 76.7% ($n=49$) received concurrent chemotherapy. Median overall treatment time (OTT) was 56 days (38−131 days). Overall, 62.5% ($n=40$) patients received IC and 37.5% ($n=24$) received IC+IS. The median HRCTV was 34.7 cc (IQR 25−41). Median (IQR) point A dose, HRCTV D90, B2cc, R2cc, and S2cc for those undergoing IC was 74 Gy (71−78), 80 Gy (73−84), 86 Gy (82−89), 70 Gy (65−74), 65 Gy (59−73) respectively. For the IC+IS cohort, HRCTV D90, B2cc, R2cc, and S2cc was 84 Gy (78−89 Gy), 89 Gy (86−92), 70 Gy (67−74), 68 Gy (59−76). At a median follow-up of 16 months (5−27) the 2-year local control, pelvic control, cause specific and overall survival was 88%, 85.3%, 92.2%, and 81.3% respectively. Late gastrointestinal and genitourinary grade ≥III toxicities were 14% and 1.5% each.

CONCLUSIONS: Abbreviated BT outcomes are encouraging for oncological outcomes despite delays in overall treatment time and omission of chemotherapy. Further mature follow up is needed.

Keywords: Intra-cavitary brachytherapy; Image guided brachytherapy; Interstitial brachytherapy, Single application multifractionated brachytherapy

Background

Brachytherapy is an integral component for curative treatment of locally advanced cervical cancer (LACC), and its omission is related to worse survival outcomes (1,2). Exceeding the overall treatment time to more than 8 weeks is known to have detrimental effect on survival in patients with cervical cancer (3,4). During the first phase of Covid-19 pandemic, a complete nationwide lockdown was implemented from March 2020 in India that reopened

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in various phases. The treatment policy for those undergoing active treatment were reorganized (5). In the first few months of the pandemic, beginning April 2020, the institutional guidelines suggested temporary suspension of concurrent chemotherapy in patients with cervical cancer. However, BT for cervical cancer was listed as level 1 priority, and consensus guidelines suggested using reduced applicator insertions with multiple fractions treatment, with minimum number of repeat anesthesia procedures (5–8). This would facilitate completion of treatment within stipulated time considering the anticipated unexpected delay. This was also expected to reduce the need for multiple patient visits and anesthesia and to help to balance available workforce and patient care needs. A phase II study from our institute (that was as yet unpublished at the beginning of pandemic) demonstrated feasibility of single application multi fraction BT in patients with LACC (9). Due to the unforeseen pandemic situation and evolving international consensus guidelines, an abbreviated BT schema where entire treatment was delivered in 24−48 hours (rather than 2−4 weeks) was adopted. We present the clinical treatment data and early clinical follow up with this abbreviated multi fractionated BT schedule delivered during the first 12 months of COVID-19 pandemic.

Methods and materials

Institutional review board approval was obtained to review and report outcomes of treatment schedules adopted for gynecological cancers during the COVID-19 pandemic. The present report is an audit of patients with LACC treated with radical (chemo)radiation and single application multi fraction BT during the COVID 19 pandemic. Between April 2020 to March 2021, patients who received single insertion and multiple fractions (3−5) BT over a 24−48 hours (instead of standard delivery schedule of 2−4 insertions and treatment over 2−4 weeks) were identified from the gynecological unit database. All patients received external beam radiotherapy to the pelvis (with/without para-aortic nodal irradiation when indicated) to a dose of 45–50 Gy at 1.8−2Gy per fraction, with 3DCRT or IMRT technique. Use of concurrent chemotherapy was at the discretion of medical oncologist and based on institutional treatment guidelines during COVID 19 pandemic. After completion of (chemo)radiation patients were considered for BT. The use of abbreviated schedule was adopted by the clinical team during phases of lockdown when patients expressed inability to come for weekly fractionated treatment. Other indications included already a prolongation of overall treatment time either due to COVID-19 infection related break or delay in reporting to the facility due to lockdown or fear of contracting COVID-19. Patients underwent reverse transcriptase polymerase chain reaction (RT-PCR) test for COVID-19 before the BT procedure. Patients were admitted a day before the procedure (after a negative RT-PCR report). Patients who tested positive for Covid-19 on RT-PCR were isolated for a period of 14 days, after which repeat testing was done and BT was performed once patients tested negative. All patients underwent bowel preparation with enema a night prior and in the morning of the procedure.

On the day of procedure, patients underwent general or spinal anesthesia after which examination under anesthesia was performed for assessment of residual disease at BT. Patients with central or medial parametrial disease received intracavitary (IC) BT and those with residual lateral parametrium disease received intracavitary and interstitial (IC+IS) BT. Select patients with unacceptable organ at risk dose during the first intracavitary application subsequently received IC+IS implant and all treatment was delivered in one subsequent IC+IS implant and multiple fractions. All patients had on table transabdominal ultrasound to guide placement of intrauterine tandem and in a vast majority of patients the treatment planning was performed using CT. During transabdominal ultrasound, anteroposterior thickness and width of the disease was determined to guide target delineation. During this period transrectal probe for ultrasound measurements was not available in operation theatre hence could not be used. Due to restrictions in the available infrastructure and resources, MR planning was not feasible for many patients. Whereas IC+IS patients had a volume-based prescription to high-risk clinical target volume (HRCTV) those undergoing IC had treatment prescribed to point A. The target delineation in IC+IS patients was performed using examination under anesthesia findings supplemented by on table transabdominal ultrasound findings along with CT visualization of the disease in the anteroposterior and mediolateral direction. In all cases, two-thirds of uterine height was considered as part of HRCTV unless there was clear indication of disease extending to fundus at diagnosis (10). A vast majority of target delineations in this case was done by an advanced clinical practitioner (SC) with experience in MR based image guided BT within and outside the context of clinical trials. Treatment protocol included 3−5 BT fractions of 5−8.5 Gy with an aim to achieve point A dose of ≥70 Gy $EQD2_{10Gy}$ in those undergoing IC and HRCTV dose ≥85 Gy $EQD2_{10Gy}$ in patients undergoing IC/IS whereas maintaining bladder (B2cc), rectum (R2cc), sigmoid (S 2cc) doses of ≤90, ≤75, and ≤75 Gy $EQD2_{3Gy}$ respectively.

IBS-GEC-ESTRO-ABS guidelines were referenced (10) and HRCTV delineation was retrospectively performed for patients who received point A based prescription for IC BT for the purpose of uniform dose reporting to HRCTV in both the cohorts. The clinical notes that listed examination findings at diagnosis, index MRI images, examination under anesthesia findings at BT were referenced for retrospective HRCTV delineations by one clinician (JM-observer 1). Another clinician (SC-observer 2) with experience in target delineation within the context of MR based BT repeated retrospectively the HRCTV delineations in patients receiving intracavitary alone whereas remaining

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blinded to contours delineated by observer 1. JM (Observer 1) and SC (Observer 2) thereafter jointly reviewed and examined both HRCTV contours. For dosimetric reporting and summary, for the IC-IS cohort we used the HRCTV contours that were used to deliver BT whereas for the IC cohort we retained HRCTV contours by both observers as they were retrospectively delineated (10).

Electronic medical records of patients were reviewed to obtain information on disease control (local, nodal, and distant) and adverse effects. Time to event analysis was used to report oncological endpoints like local control, loco-regional control, disease free survival and overall survival. All outcomes were calculated from date of diagnosis to date of relapse or last follow up as applicable. Death due to any cause was considered as an event for disease free survival analysis. Local control was defined as absence of any residual or recurrent disease in cervix, uterus, parametrium, or vagina. Pelvic control was defined as absence of any residual or recurrent disease locally or in pelvic nodes. Loco-regional control was defined as absence of any residual or recurrent disease in the pelvis or in the para-aortic nodal region. Whereas disease free were estimated to include relapse or death due to any cause was reported, it was understood that during COVID-19 such a parameter may not be a reflection of true outcome. Similar limitation could occur with overall survival. Hence, cause specific survival was also reported. Death due to disease progression or treatment or adverse effect related mortality was considered for estimating cause specific survival.

Early and short-term toxicity was reported using crude proportions. Univariate analysis using log rank test was performed for local control and survival endpoints and to estimate impact of known prognostic and predictive factors on outcomes. Cox regression was used for Multivariate Analysis.

Results

Three hundred and sixteen patients with cervical cancer received radical(chemo)radiation between April 2020 and March 2021. Of these, 64 patients received single application multiple fraction treatment and were included in the study. The clinical situations for considering such a treatment are already enumerated in the methodology.

The median age of the study cohort patients was 55 years (range 34−75 years). Patient and disease characteristics are enlisted in Table 1. FIGO 2018 was stage IB1-IIA in 3 (4.6%) patients and stage IIB in 16 (25%, stage III B in 9 (14.1%), stage III C1 in 19 (29.7%), IIIC2 in 10 (15.6%), and IVA in 5 (7.8%) patients. Two patients (3.1%) had stage IVB disease. Among patients with stage IVB, one patient had local disease extent upto lateral pelvic wall with histopathologically proven solitary liver metastasis. The second patient with stage IVB disease had local disease extent upto medial parametrium along with para-aortic nodes and solitary ischial tuberosity metastasis. Four patients received neo-adjuvant chemotherapy (for bladder infiltration ($n=2$) or before referral to our institute $n=2$). Fifty-three patients received pelvic EBRT to a dose of 45–50.4 Gy in 1.8−2 Gy per fraction, whereas 11 patient's received extended field EBRT to a dose of 45Gy in 25 fractions. (10 patients with stage IIIC2 and one with stage IVB disease). Nodal boost was given in node positive patients (n = 20) and both simultaneous integrated boost ($n=18$) or sequential boost ($n=2$) were considered. As per institutional protocol during COVID-19 pandemic, concurrent chemotherapy was temporarily suspended and not adminis-

Table 1
Depicting patient and treatment characteristics.

Demographic ($n=64$)	*N*
Stage	
IB1-IIA2	3 (4.8%)
IIB/IIIB	16/9 (25%/14.1%)
III C1/C2	19/10(29.7%/15.6%)
IV A/IV B	5/2 (7.8%/3.1%)
Histopathology	
Squamous cell carcinoma	55 (85.9%)
Adenocarcinoma	9 (14.1%)
Concurrent chemotherapy	
Yes	49 (76.6%)
No	15 (23.4%)
Chemotherapy cycles	
1-4 cycles	23 (35.9%)
≥4	41 (64.1%)
Overall treatment time	
≤60 d	38 (59.4%)
>60	26 (40.6%)
Application	
Intracavitory	37 (57.8%)
Interstitial	27 (42.2%)
HRCTV vol (All application)	
<30cc	21 (32.8%)
≥30cc	43 (67.2%)
Intracavitary	
Pt A EQD2 dose (Gy)	74 (Range 70−84, IQR 72−78)
HRCTV vol (cc)	35 (Range 18−89, IQR 25−41)
HRCTV D90 (Gy)	80 (Range 58−95, IQR 75−84)
Bladder 2cc dose EQD2 (Gy)	86 (Range 70−95, IQR 83−89)
Rectum 2cc dose EQD2 (Gy)	70 (Range 53−78, IQR 66−74)
Sigmoid 2cc dose EQD2 (Gy)	66 (Range 51−82, IQR 60−74)
Intracavitary+Interstitial	
HRCTV vol (cc)	34 (Range 16−62, IQR 25−44)
HRCTV D90 (Gy)	84 (Range 71−106, IQR 78−89)
Bladder 2cc dose EQD2 (Gy)	89 (Range 69−97, IQR 86−92)
Rectum 2cc dose EQD2 (Gy)	71 (Range 59−81, IQR 67−74)
Sigmoid 2cc dose EQD2 (Gy)	67 (Range 47−81, IQR 59−76)

Table 2
Table depicting 1 and 2-year oncological outcomes.

	1-year	2-year
Overall survival	92.2%	81.3%
Disease free survival	85.9%	65.5%
Cause specific survival	96.9%	92.4%
Local control	96.8%	88%
Pelvic control	96.8%	85.3%
Locoregional control	93.7%	82.5%

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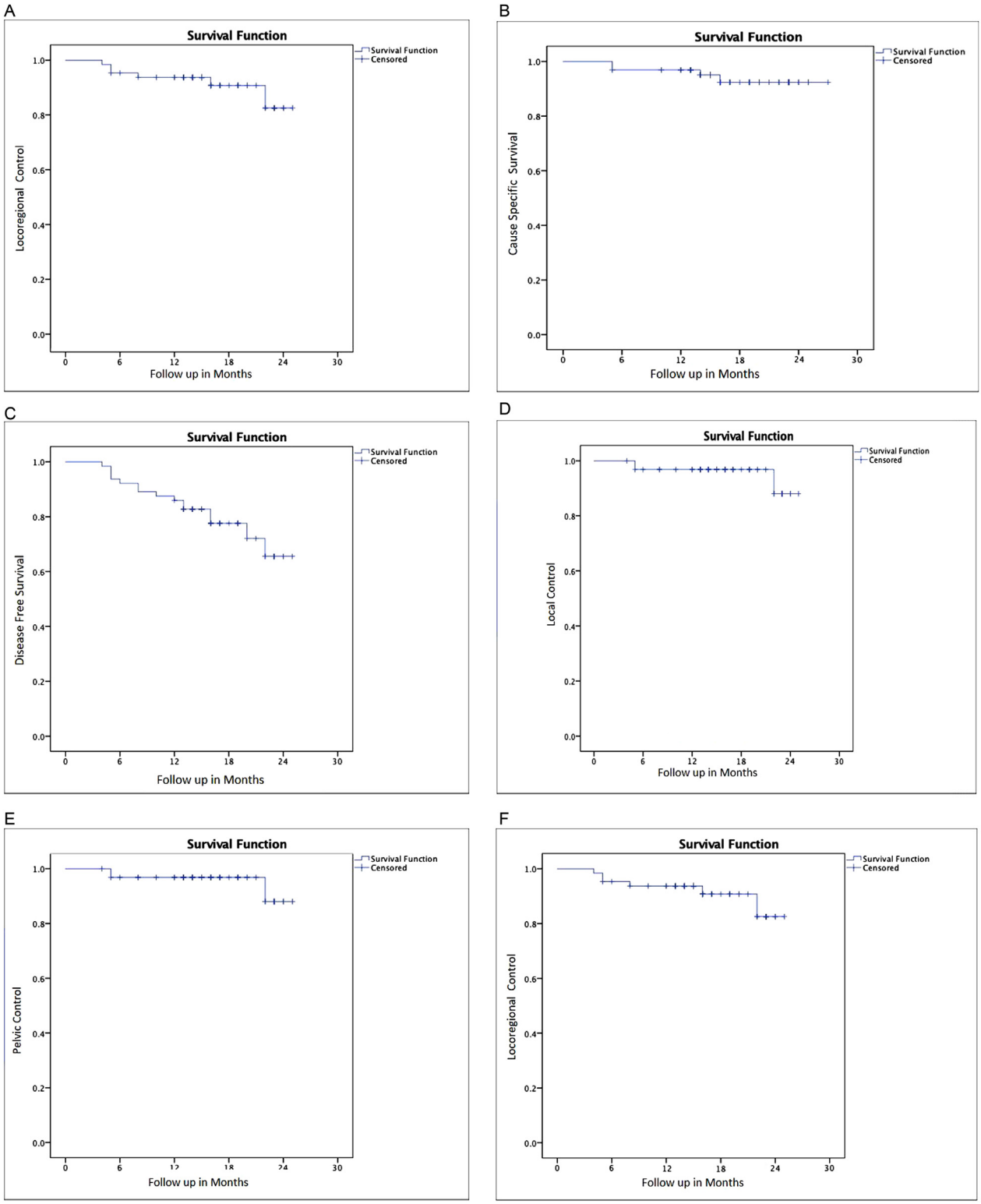

Fig. 1. (a–f): Figure depicting overall survival (a), cause specific survival (b), disease specific survival (c), local control (d), pelvic control (e), locoregional control (f). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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Table 3
Impact of incremental increase of overall treatment time on outcomes.

	1-year local control	2-year local control	1-year cause specific survival	2-year cause specific survival
Entire cohort (n)	96.8%	88%	100%	91.6%
≤ 8 weeks (32)	100%	100%	100%	91.6%
>8 weeks - <12 weeks (21)	95.2%	95.2%	95.2%	95.2%
≥12weeks (11)	91%	0%	91%	91%

tered between the period of April 2020 till July 2020. Thus, only 76.6% ($n=49$) patients received concurrent cisplatin-based chemotherapy. Forty-one (of 49) patient's received ≥ four cycles of concurrent cisplatin.

Within this cohort of 64 patients who received single implant and multiple fractions, 37 (57.8%) received IC BT and 27 patients (42.2%) received intracavitary and interstitial BT. The median volume for HRCTV was 34.7 cc (range 16−89 cc IQR 25−41 cc). Median point A dose, HRCTV D90, B2cc, R2cc, and S2cc for those with IC application was 74 Gy (Range 70−84, IQR 72−78), 80 Gy (Range 58−95 Gy IQR 75−84), 86 Gy (Range 70−95, IQR 83−89), 70 Gy (Range 53−78, IQR 66−74), 66 Gy (Range 51−82, IQR 60−74). For IC+IS patients, the HRCTV D90, B2cc, R2cc, and S2cc was 84 Gy (Range 71−106, IQR 78−89 Gy), 89 Gy (Range 69−97, IQR 86−92), 71 Gy (Range 59−81, IQR 67−74), 67 Gy (Range 47−81, IQR 59−76).

As we essentially worked in CT at diagnosis and CT at BT environment (10), we also attempted evaluation of impact of inter-observer variability in target delineation of HRCTV. The mean absolute difference in HRCTV volume between two observers (JM and SC) was 5.2 cc (Range 0−16 cc) which translated to mean percentage volume difference of 14% (Range 0−35 %). This led to a median change in dose of 5 Gy with an upper limit of 13 Gy.

The median overall treatment time (OTT) for patients completing treatment was 56 days (Range 38−131 days) Prolonged OTT of >60 days was seen in 26 (40.6%) patients, and was either due to COVID- 19 infection during the course of cancer directed treatment ($n=7$, 11%) or delay in referral for BT ($n=16$, 25%) or due to medical co-morbidities that led to time lapse to obtain fitness for general or spinal anesthesia ($n=3$, 4.7%).

At a median follow-up of 16 months (range 5−27), 4 patient (6.2%) had pelvic relapses (three local and one pelvic nodal), 3 patients had para-aortic nodal relapses and 4 patients had distant relapses. The 1-year local control, pelvic control, loco regional control, disease free survival, overall survival, was 96.9%, 96.9%, 93.7%, 85.9%, 92.2%, respectively. The 2-year local control, loco-regional control, pelvic control, disease free and overall survival was 88%, 82.5%, 85.3%, 65.5%, and 81.3% respectively. The 1 and 2-year cause specific survival was 96.9% and 92.4% respectively. (Fig. 1 and Table 1). Nine patients died of which three were due to disease progression and one due to grade V bowel toxicity. Remaining deaths are noncancer related (two due to COVID complications, one due to cardiac related mortality, one due to acute respiratory event (pneumonia), one due to diabetic keto-acidosis.

Table 3 demonstrates the impact of overall treatment time on 2-year local control and cause specific survival. For patients receiving treatment within 8 weeks, the 2-year local control was 100% regardless of other factors (like treatment response or use of optimal concurrent chemotherapy). For patients completing treatment within 8−12 weeks a 5% detriment in local control was observed and in patients completing treatment >12 weeks the local control was 0% ($n=11$) highlighting the importance of OTT. On univariate analysis, local control was significantly impacted by omission of concurrent chemotherapy and prolongation of OTT. On multivariate analysis no factor was significant for local control. However, for DFS OTT (HR 2.4, $p=0.005$) and HRCTV at BT (HR = 8.2, $p=0.04$) were statistically significant.

At a median follow up of 16 months, any late grade ≥II toxicity was 15.6% and grade ≥III toxicity was 12.5%. Late gastrointestinal grade ≥II and ≥III toxicities were 14% and 11% respectively. Late genitourinary grade ≥II and grade ≥III toxicities were 1.5% each. Four patients had grade III proctitis for which argon plasma coagulation procedure was done, 1 patient had grade IV recto-vaginal fistula for which stoma was done, 1 patient had grade IV bowel toxicity (perforation) for which stoma was done. None of the patients with rectal or bladder toxicity exceeded acceptable dose constraints for standard BT.

Discussion

Our hospital is a tertiary cancer care high volume center for treating gynecological cancers. Before COVID-19 pandemic, our center treated 700−800 patients annually with gynecological cancers. At any given time, majority of our patients were from outside the city. In response to the initial stages of pandemic, a nationwide lockdown was implemented in March 2020, and the restrictions were eased in multiple phases over next 12 months. During the initial period, there was no interstate travel or public transport access. Also due to the fear of COVID-19, some patients abandoned treatment mid-way during this period. A study conducted in the member institutions of National Cancer Grid of India showed a 67% proportional reduction in new cancer patients' registration and a 45% proportional reduction in patients accessing radiation treatments during the months of April and May 2020, when compared to April−May 2019 (11). Projection from multiple studies

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Table 4
Univariate analysis of factors impacting local control.

		Local control	*p* value
Stage (FIGO 2018)	IB3 (1)	100%	0.57
	II (29)	96.6% (28)	
	III (27)	96.3% (26)	
	IV (6)	83% (1)	
Concurrent chemotherapy	Yes (49)	100% (49)	0.001
	No (15)	80% (12)	
Chemotherapy cycles	≥ 4 cycles (41)	100% (41)	0.018
	< 4 cycles (23)	87% (20)	
OTT	≤8 weeks (32)	100% (32)	0.048
	8-12 weeks (21)	95.2% (20)	
	>12 weeks (11)	81.8% (9)	
Type of application	Intracavitory (37)	94.6% (35)	0.750
	Intracavitory and insterstitial (27)	96.3% (26)	
HRCTV volume (post EBRT)	<30cc (21)	100% (21)	0.215
	≥30cc (43)	93% (40)	

in this period have shown a possible increase in cancer mortality, more than that from the COVID-19 infection (12–15). A study conducted on cervical cancer patients in India studied the impact of COVID -19 and delay in treatment. The study projected a 2.5−3.8% lifetime increase in deaths caused by cervical cancer with treatment delays ranging from 9 weeks to 6 months compared to no delay in treatment (15).

The goal of cancer care during the pandemic was to complete treatment in the shortest number of visits and least hospital admissions. Thus, we switched to treating patients with hitherto investigational but preferred and recommended approach of single implant and multiple fractions of treatment from March 2020. Though in the initial phase chemotherapy was omitted, we did not use hypofractionated external radiation course. This was done for two reasons. Firstly, we wanted to give time for adequate tumor regression before BT. Secondly, the effect of additional toxicities with abbreviated external radiation as well as BT was unknown. This fractionation regimen was offered to patients who either received treatment during complete lockdown or later who had challenges accessing health care system. This was also considered for those who had treatment interruptions or delays due to COVID-19 infection. A phase II prospective study conducted at our institute had tested single application multi fractionated image guided high-dose-rate BT for cervical cancer in research setting (SIMBRACE). The study included 41 patients with LACC who underwent external beam radiation to pelvis to a dose of 50 Gy/25 fractions with concurrent chemotherapy (9). Brachytherapy was performed with MR compatible intra-cavitary and interstitial applicators. MR based planning was done, and patients were treated to a dose of 9 Gy on day 1, and two fractions of 7 Gy each on day 2, with at least a 6-hour gap between fractions. The planning aim of the study was to deliver >84 Gy EQD2 to HRCTV D90. The study also demonstrated that 85% patients did not require re-planning for BT. At a 22 month follow up, the 2-year local control was 90.1% and 2-year overall survival was 94.5%. One patient developed late grade II rectal toxicity and 2 patients developed grade III rectal toxicity. In the EMBRACE cohort of patients, 5-year local control and overall survival was 92% and 74% (16). Grade ≥3 gastrointestinal, genito-urinary, and vaginal toxicity was observed in 14.6% of patients. For our cohort of patients, the 2-year local control, overall survival and cause specific survival was 88%, 81.3%, and 92.4%. Though broadly the results look almost similar to our previously published outcomes with abbreviated approach (SIMBRACE) there are certain key differences. We observed 5% loss in local control in this cohort in patients completing treatment between 8 and 12 weeks and no patient with 2-year local control (i.e., 0%) if treatment time exceeded 12 weeks. These results in modern times bring back attention to the basics of radiation treatment delivery where adherence to overall treatment time remains the most crucial component of treatment. The excellent results of 100% local control in 32 patients who completed treatment within 8 weeks is noteworthy. This included 7 patients who acquired COVID infection and had chemotherapy omissions. The results also highlight that CT-ultrasound guided BT when used with principles of either point A or image guided adaptive prescription approach may lead to local control which is quite comparable to MR based BT. Unlike our previous phase I study that used MR based BT and advanced interstitial BT, in this cohort we had a vast majority of patients (60%) receiving standard intra-cavitary BT with 40% advanced BT. Although the local control is comparable, we need to further follow up this cohort for understanding evolution of late adverse events which seem to be marginally higher than the cohort treated with IC-IS and MR based BT. Comparison with further mature data from SIMBRACE study (10) would further help to understand if these differences were a function of imaging or technique, as CT based BT often leads to greater uncertainties in target estimation and over-

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estimation of target volume which translates to possibility of delivering higher normal tissue doses.

Conclusions

The 24-month oncological outcomes with abbreviated BT seem comparable to previously published outcomes for cervix cancer despite unique challenges posed for completion of planned treatment during first phase of COVID-19 pandemic. However, careful evolution of adverse events needs to be observed before recommending this fractionation approach as an alternative in clinical practice.

Data availability statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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