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Twice-daily HDR brachytherapy: a one-week apart protocol for treating cervix uteri in a resource-limited setting

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Original Article

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Abstract

Background: High dose rate (HDR) intracavitary brachytherapy (ICBT) plays a crucial role in cervix cancer treatment, with variations in fractionation schedules across different radiation societies. This study aims to assess the effectiveness and tolerability of a 7 Gy per fraction twice daily schedule over two successive weeks versus an 8 Gy per fraction once weekly schedule over three successive weeks.

Patients and Methods: From 2020 to 2022, 87 patients with uterine cervix cancer (Stages II and III) underwent concomitant external beam radiotherapy (EBRT) and chemotherapy, followed by HDR-ICBT. Patients were randomised into two arms: Arm A (8 Gy per fraction once weekly for 3 fractions) and Arm B (7 Gy per fraction twice daily once a week for 4 fractions). Local control is defined as any patient free from local progression (CR + PR + SD) in the first year after ending brachytherapy (BTH).

Results: The median follow-up was 16·5 months. Local control at 1 year was 78·7% in Arm A and 89·2% in Arm B ($p = 0{\cdot}24$). No clinically significant differences in rectal and bladder toxicities were observed between the two arms ($p = 0{\cdot}40$).

Conclusion: There were limited treatment machines and other BTH challenges in Egypt, and the HDR BTH schedule of 7 Gy per fraction twice daily over 2 successive weeks presents an acceptable alternative to the current national standard of 8 Gy per fraction once weekly over 3 weeks. Both schedules demonstrate comparable local control, late toxicity and progression-free survival. Notably, the 7 Gy per fraction twice daily per week for 4 fractions offers the advantage of a reduced total treatment time.

Introduction

Combined chemoradiation is the standard treatment for locally advanced cervical cancers, a common diagnosis in developing countries like Egypt due to limited preventive and early detection programmes.[1,2] The radiotherapy treatment protocol typically encompasses both external beam radiation (EBRT) and intracavitary brachytherapy (ICBT), with or without interstitial needles.[3]

The critical role of ICBT in the definitive treatment of cervical cancer is somewhat limited in our country. This is due, in part, to certain constraints associated with brachytherapy (BTH) machines, such as challenges in replacing radioactive sources and the limited availability of anaesthesia services in radiation departments. In such scenario we face a persistent challenge exists to maintain a standard overall treatment time. According to the literature, the optimal duration for therapy typically falls within seven weeks or 56 days. The duration of therapy is influenced by the limitations imposed by the availability of treatment machines.[4]

The national practice in our setting was 8 Gy in three fractions over three weeks, an acceptable protocol in Indian recommendations, yet with a prolonged overall treatment time of more than 64 days.[5] As most of our study coincided with the COVID-19 outbreak, maintaining this schedule was challenging. Furthermore, our BTH service was the sole provider in Cairo, a city with more than 30 million populations. Reducing the number of insertions was a target because of the shortage of anaesthetists during the epidemic. Exacerbating this challenge was the redirection of resources during the COVID-19 epidemic in our already resource-constrained setting.

In accordance with the guidelines set by EMBRACE and ICRU 89, our approach involves calculating doses to ensure that the treatment plan meets the requirements for target volumes and organs at risk (OAR). In this process, we employ the linear quadratic model and the equivalent dose in the 2 Gy fractions (EQD2) concept.[6] In response to the continuous challenge of long wait times in Egypt, we investigated a novel treatment schedule involving a single

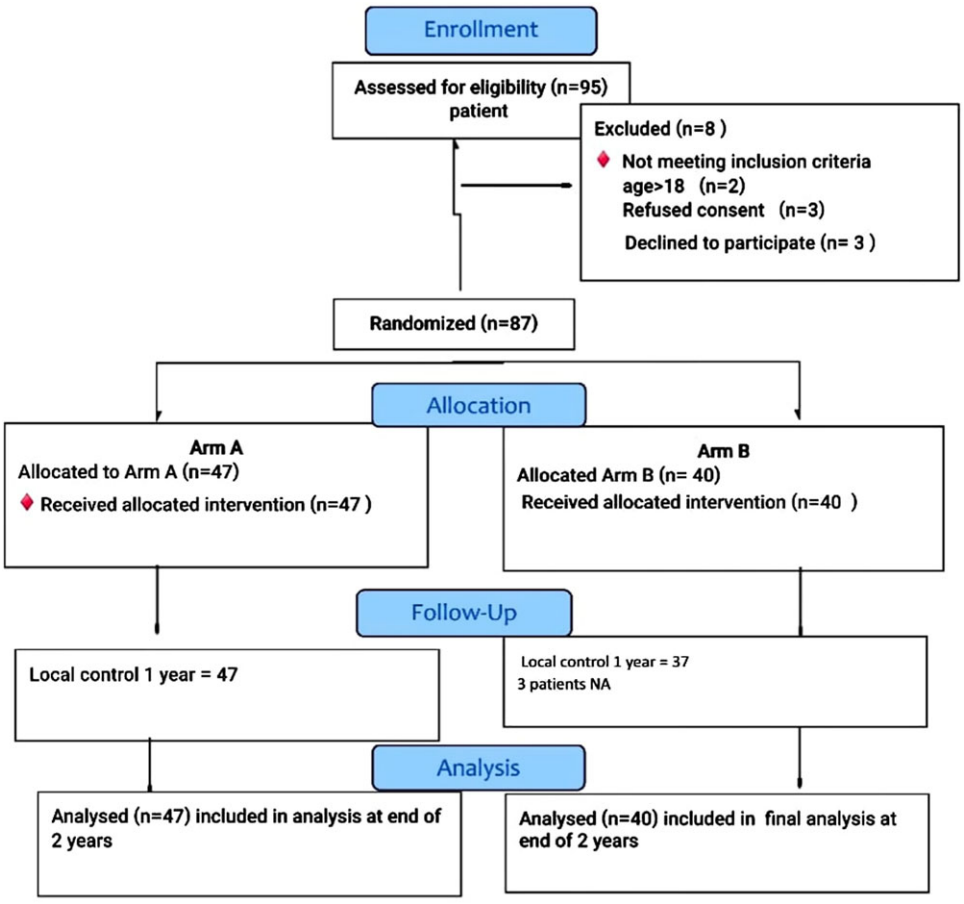

Figure 1. CONSORT flow diagram.

insertion with two daily fractions 6 h apart, delivered over two consecutive weeks. This approach has the potential to significantly reduce waiting lists and shorten the overall treatment duration.[7]

This study evaluates two distinct BTH options. One is high dose rate (HDR) BTH with a schedule of 7 Gy per fraction, administered twice daily over 2 successive weeks, resulting in a total cumulative dose of 28 Gy. The other is 8 Gy per fraction, given once weekly over 3 weeks, totalling a cumulative dose of 24 Gy.

Patients and Methods

This prospective randomised controlled trial was conducted at the Department of Clinical Oncology (NEMROCK), Cairo University, from November 2020 to August 2022. The study aims to compare the current local practice of 8 Gy (ARM A), once weekly fraction for 3 weeks vs 7 Gy/fraction two fractions (Arm B) with more than 6 h gap in between on the same day on two consecutive weeks Figure 1. Patients were followed up for 17 months, with treatment-related responses assessed using Response Evaluation Criteria in Solid Tumour (RECIST) criteria and toxicity evaluated using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.[8]

Ethical Approval

Ethical approval was obtained from Cairo University's faculty of medicine and the ethical committee prior to commencement, and written informed consents were secured from all participants.

Endpoints

- Primary Objectives:
  - Locoregional control.
- Secondary Objectives:
  - Progression-free survival (PFS) at 2 years.
  - Toxicity rates in both treatment arms, e.g., rectal and urinary toxicities.

Participants

Patients who met the inclusion criteria were enrolled subsequent to the completion of EBRT at a prescribed dose of 45 Gy-50·4 Gy over 5 days a week for 5 weeks, with concurrent weekly injections of cisplatin (40 mg/m^2).

Inclusion Criteria

Patients over 18 years old with histologically confirmed squamous cell carcinoma and stages II-III cervical cancer as per the revised FIGO staging for carcinoma of the cervix uteri are considered. They must have essential laboratory characteristics within normal haematological parameters and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less. Additionally, a life expectancy of more than 12 months is required. All patients are required to sign a written informed consent form.

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Exclusion Criteria

The study excludes patients who cannot provide informed consent due to any mental or psychological condition that impairs their decision-making ability, as well as patients who do not comply with the study protocols. Those with an ECOG performance status ≥ 3, Stages I&IV or under the age of 18 years old will also be excluded.

Brachytherapy Procedure

Patient Assessment: Fitness for anaesthesia was assessed using chest X-rays, ECG, CBC, INR and virology tests. Anaesthesia was administered using spinal or low saddle anaesthesia. In clinical examination, all patients underwent vaginal and speculum examinations; assessment also includes per rectal examination to assess parametrial involvement.

A baseline drawing using GEC ESTRO diagrams is performed as a routine, especially before BTH. Imaging: Pre-BTH pelvic MRI was conducted for disease evaluation after EBRT. Tumour size and orientation, uterine position and uterine height are identified to assess the optimum tandem angle, applicator size and need for needles. Intrauterine-sounding cervical dilatation and applicator insertion, using uterine sound, the uterine length and angulation were assessed, and cervical canal dilatation was performed up to Hegar dilator 10. CT scans (3 mm thickness) were taken from the L4-5 junction to the lesser trochanter, with bladder and rectal contrast protocols repeated in each fraction. Contouring high-risk clinical target volume (CTV-THR) included the entire cervix and extra-cervical extensions. Visual fusion using post-EBRT MRI to include parametrial and vaginal extension is performed, and contouring of OARs, including the rectum, bladder and sigmoid, is performed as well. (18) In both treatment arms based on the EQD2 equation, all doses for target volumes and organs at risk will be reported as equivalent to 2 Gy per fraction. Plan acceptance and adherence to EMBRACE guidelines were ensured for dose parameters (D90, D2cc for bladder, rectum and sigmoid).[2] D90 > 85 GY EQD2, D2cc bladder < 80–90 GY EQD2, D2cc rectum< 70–75 GY EQD2, D2cc sigmoid < 60–65 GY EQD2. Local control is defined as any patient free from local progression (CR + PR + SD) in the first year after ending BTH.[8]

Outcome Measures

This included response to treatment 8 weeks post-BTH, overall local control at 1 Year (Any patient free from local progression (CR + PR + SD) in the first year after ending BTH), treatment complications, common adverse effects and toxicity assessment, secondary endpoints PFS.

Follow-up

After 8 weeks of radiation treatment, the patients' tumour responses were evaluated. We used the RECIST criteria to guide the response evaluation process.[9]

Patients underwent monthly examinations for the first quarter of the year, followed by quarterly examinations for the rest of the year, and then examinations every four months for the second year. Throughout the follow-up, patients were assessed for rectal and bladder toxicity, distant failures and local recurrence. Each patient underwent comprehensive clinical examinations, and any necessary investigations were conducted per recommendations. The late stages of bladder and rectal morbidity were graded using the CTCA criteria, and the findings were recorded during the follow-up period.[10]

Table 1. Patient basic demographics and characteristics

Item	ARM A (N) = 47	ARM B (N) = 40
Mean age	51·28 years	52·7 years
Hb level<10	27·6% (13)	27·5% (11)
Hb level >10	70·2% (33)	72·5% (29)
Other medical comorbidities	17% (8)	35% (14)
Stage II	48·9% (23)	47·5% (19)
Stage III	51·1% (24)	52·5% (21)
Tumour size more than 4 cm	80·8% (38)	85% (34)
Tumour size more or less than 4 cm	14·9% (7)	10% (4)
Tumour size NA	4·3 % (2)	5% (2)
Positive LN	40·4% (19)	50% (20)

Statistical Analysis

Chi-square tests and t-tests were employed, with significance set at $p < 0{\cdot}05$ in two-tailed tests. Survival analysis was performed using the Kaplan-Meier method, and the log-rank test was used to compare survival curves. The median follow-up period was calculated using the reverse Kaplan-Meier method. Data were analysed using MedCalc® Statistical Software version 22·021 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2024).

Results

The study involves a cohort with a mean follow-up duration of 17·1 months with a median follow-up of 16·5 months (range: 14·69–18·36 months), shown in Table 1.

The median total treatment time was 74 days in Arm A and 59 days in Arm B ($p < 0{\cdot}0001$), demonstrating a statistically significant shortening of total treatment time in Arm B. On the other hand, there was no statistical significance regarding dosimetric parameters between both groups (Table 2).

Toxicities were evaluated using the National Cancer Institute CTCAE version 4. Gastrointestinal, genitourinary and vaginal toxicities were specifically assessed and presented in Table 3.

There was no statistical significance in response to treatment after 8 weeks post-BTH between both groups with p-value > 0·05. In addition, Arm B lost the follow-up of three patients. All data are presented in Table 4 and Figure 2. Additionally, Figures 3 and 4 report and display the toxicity with time.

HR Hazard ratio

Multivariate Analysis:

Tumour dose was identified as the only significant factor affecting local control ($p = 0{\cdot}023$) (Table 5).

Progression-Free Survival:

The median follow-up duration for all patients was 17·1 months (95% CI: 15·1–19·4). The median PFS for the whole group of patients was not reached, and the one-year and two-year PFS rates were 91·5% and 69·4%, respectively.

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Table 2. Treatment time and dosimetric parameters brachytherapy initiation

Item	Arm A (47)	Arm B (40)	P-value
Total Treatment Time			
Median Time (days)	**74**	**59**	<0·0001*
Dosimetric Parameters (median values)			
Tumour dose (D90)	72·5 Gy	72·7 Gy	0·96
Tumour volume (CTV-CT)	52 cm^3	54 cm^3	0·59
OAR: D2cc (median values)			
Bladder dose	84 Gy	86 Gy	<0·0001*
Rectal dose	72 Gy	74·7 Gy	0·087
Sigmoid dose	63 Gy	65 Gy	0·47

*Significance at p-value<0.05.

Table 3. Patients' common adverse effects and toxicity assessment

Toxicity Category G1 and G2	Arm A (47)	Arm B (40)	*p*-value
Rectal Toxicities			
Proctitis	4 (8·5%)	0	0·036*
G2 rectal ulcer	3 (6·5%)	1 (2·8%)	0·62
G2 diarrhoea	1 (2·2%)	0	1
G2 stool incontinence	3 (6·5%)	1 (2·8%)	0·62
Urinary Toxicities			
G2 Dysuria	21 (44·7%)	17 (42·5%)	0·61
G2 Urinary incontinence	2 (4·3%)	1 (2·5%)	0·37
G1 Urinary frequency	2 (4·3%)	1 (2·5%)	1
Vaginal Toxicities			
G2 vaginitis	1 (2·1%)	1 (2·5%)	1
G2 vaginal discharge	4 (8·5%)	9 (22·5%)	0·18
G2 vaginismus	4 (8·5%)	2 (5%)	0·72

*Significance at *p*-value<0.05.

Table 4. Response to treatment 8 weeks post-brachytherapy

	Arm		
Respons_8w	A N = 47	B N = 37	*P*-value
CR	31(66·0%)	25(67·6%)	0·06
DP	3(6·4%)	3(8·1%)	0·06
PR	6(12·8%)	9 (24·3%)	0·06
SD	7(14·9%)	0(0·0%)	0·06
CBR	42(93·6)	34(91·9)	0·06

CR, complete response, DP disease progression, PR partial response, SD stable disease, CBR clinical benefit rate = CR + PR + SD.

The median PFS for arm A was 28·5 months (95%CI: 19–28·5) and for arm B was 23·3 (95%CI: not reached), and the HR was 0·667 (95%CI: 0·234–1·89] ($p = 0·446$). The 1-year PFS survival rate was 91·1% for arm A and 92·1% for arm B (Figure 5).

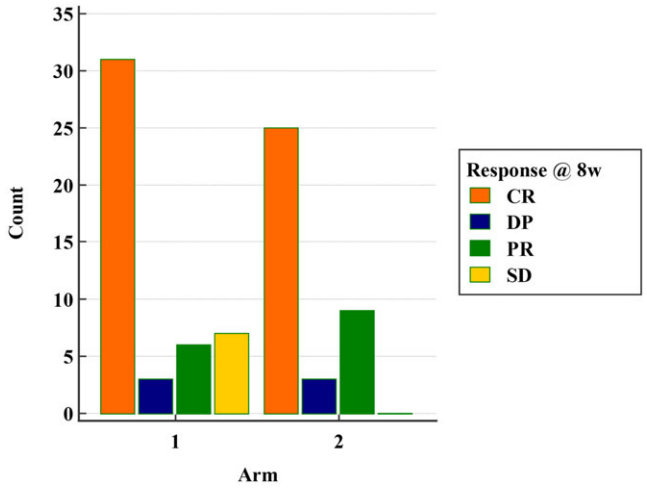

Figure 2. Percentage of response 8 weeks after the end of the brachytherapy in both groups.

The median PFS of stage 2 patients in arm A was 19·3 months (95%CI: 18·5–19·3) and in arm B was not reached, and the HR was 1·5 (95%CI: 0·29–7·7) ($p = 0·627$). The 1-year PFS survival rate was 95·2% for stage 2 patients in arm A and 88·9% in arm B (Figure 6).

The median PFS of stage 3 patients in arm A was 28·5 months (95%CI: 17·4–28·5) and in arm B was 23·3 (95%CI: not reached), and the HR was 0·4 (95%CI: 0·11–1·6) ($p = 0·203$). The 1-year PFS survival rate was 87·5% for stage 3 patients in arm A and 95% in arm B (Figure 7).

For those with a total treatment time ≤ 55 days, the 1-year PFS rate was 87·8%, and for those with a time >55 days was 92·5%, and the HR was 0·6 (95%CI: 0·16–2·19) ($p = 0·44$).

Discussion

The trial compares two BTH arms for cervical cancer: Arm A was the standard treatment, receiving 8 Gy per fraction per week for 3 weeks with overall treatment time exceeding 8 weeks, while Arm B, the experimental and shorter arm, received 7 Gy per fraction twice a day for 2 weeks. The main aim was to study the efficacy and safety of the accelerated Arm B schedule. Most patients in both arms presented with locally advanced disease (Stage III), reflecting a common scenario in developing countries. Notably, despite worse prognostic factors in Arm B (higher incidence of positive pelvic lymph nodes and larger tumour size), the 1-year local control was superior compared to Arm A (89·2% vs. 78·7%). According to the available literature on HDR-BCT, a number of 3–5 fractions of 6–7·5 Gy to point A each twice weekly and preferably to limit the dose per fraction to less than 7 Gy are advised for the treatment of cervical carcinoma according to the Indian Council of Medical Research Consensus paper.[11]

Different researchers also observed that the HDR fraction size had an expected impact on toxicity, as witnessed by a reduction of morbidity rates when the dose to point A decreased to ≤7 Gy compared to >7 Gy for both moderate and severe injuries, with $P < 0·001$.[12] These suggestions are widely acknowledged and incorporated into fractionation protocols by various radiotherapy societies.[13,14]

In our study, the bladder dose was higher in Arm B, yet the incidence of G2 urinary toxicity, such as G2 dysuria, was lower in Arm B. This discrepancy might suggest that factors beyond the

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Table 5. Local control and impact of different factors

Analysis	Arm A n = (47)	Arm B n = (37)	*p*-value
Overall local control at 1 Year	78·7% (37)	89·2% (33)	0·24
Local treatment failure at 1 Year	8·9% (HR 0·666)	7·9% (HR 1·5003)	–
Local control	Arm A (37)	Arm B (33)	–
Stage II	56·7 % (21)	42·4% (14)	0·633
Stage III	43·2% (16)	57·6%* (19)	0·027*
Haemoglobin (HB) Level >10	67·5% (25)	75·5% (25)	0·200
Tumour size >= 4cm	78·3% (29)	84·8 % (28)	0·35
Tumour size <4cm	16·2% (6)	9 % (3)	1
Mean tumour volume (CTV-CT) local control	<= 51·3 cm^3	<= 53·3 cm^3	0·02*
BT initiation >2 weeks:	82·8%	89·5%	0·68
BT initiation 1 week:	60·0%	100·0%	0·95
BT initiation 1–2 weeks:	75·0%	71·4%	1
Mean tumour volume (CTV-CT)	<= 51·3 cm^3	<= 53·3 cm^3	0·020

*Present study.

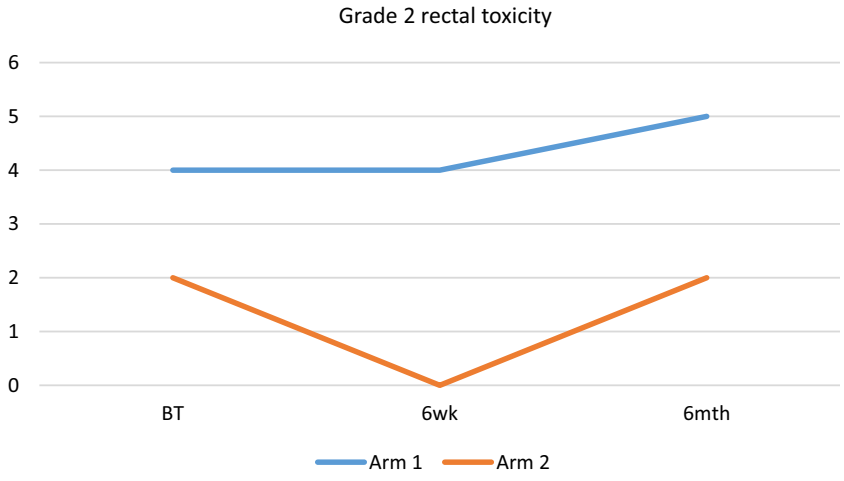

Figure 3. G2 rectum toxicity BT, 6 wk and 6 mth.

Figure 4. G2 bladder toxicity BT, 6 wk & 6 mth.

D2cc bladder dose may influence urinary toxicity, as demonstrated in previous studies.[15] D2cc rectal dose was slightly higher in Arm B, leading to a statistically significant difference in the incidence of G2 proctitis ($p = 0·036$).

The median total treatment time was significantly shorter in Arm B (59 days) compared to Arm A (74 days). This reduction in treatment time in Arm B could explain the improved local control, especially for stage III patients (95% vs. 66·7%, $p = 0·027$). This

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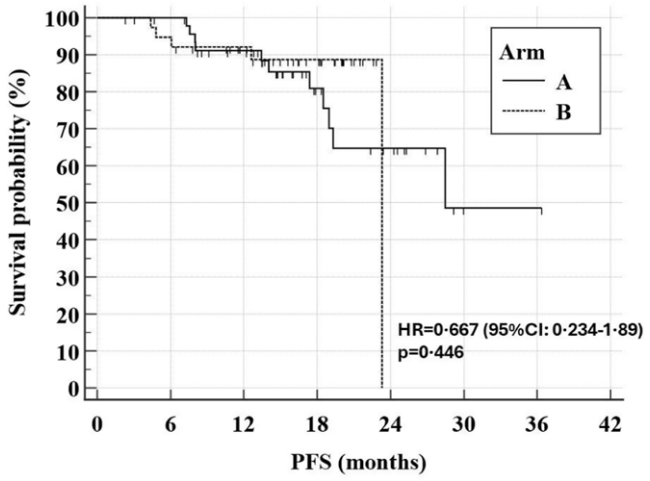

Figure 5. Kaplan–Meier progression-free survival (PFS) curves according to the treatment arm.

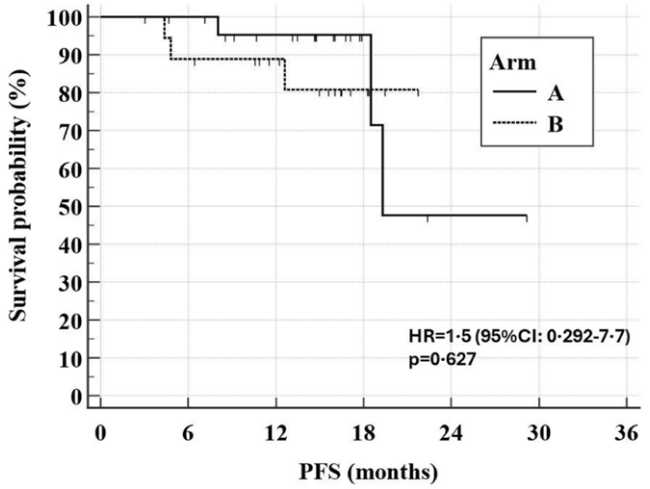

Figure 6. Kaplan–Meier progression-free survival (PFS) curves of stage 2 patients according to the treatment arm.

finding aligns with previous studies showing a positive correlation between shorter treatment times and enhanced tumour control.[5,16]

Both arms demonstrated high rates of radiological complete response at 8 weeks. Arm B showed a slightly higher partial response in comparison with Arm A, indicating comparable efficacy in tumour response. The actuarial 1-year PFS was equal in both arms (91% for Arm A and 93% for Arm B). Mean PFS did not show a statistically significant difference between the arms (27·5 months for Arm A, 21·5 months for Arm B, $p = 0{\cdot}445$).

Patients in Arm B who completed treatment in less than 55 days exhibited better mean survival compared to Arm A (21·2 months vs. 7·5 months, $p = 0{\cdot}045$). Prolonged total treatment time beyond 55 days was correlated with reduced survival, consistent with previous findings emphasising the importance of treatment duration. Our results were in line with research findings from other studies. On the other hand, the data behind the current 8 Gy BTH schedule exceed the recommended timeframe of 56 days, and it is limited to an average treatment duration of around 64 days for

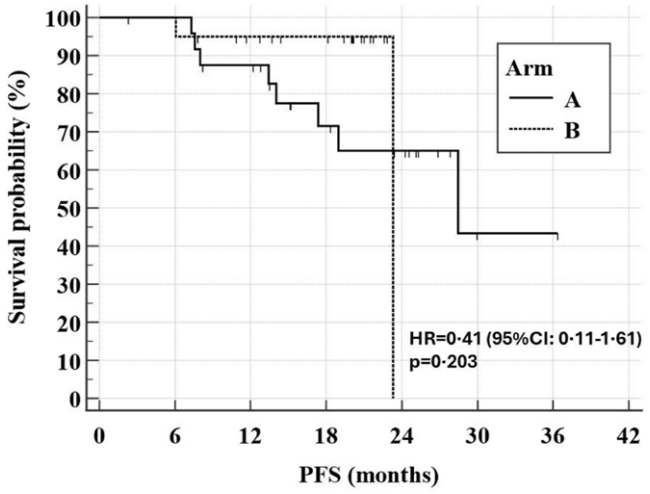

Figure 7. Kaplan–Meier progression-free survival (PFS) curves of stage 3 patients according to the treatment arm.

7,355 cervical cancer patients. Interestingly, their findings also showed an association between shorter treatment duration and improved overall survival.[5,16]

The idea of using single insertion with multiple fractions has been considered by different investigators, mostly within retrospective or Phase II; most of these studies demonstrated non-inferiority in treatment control without significant impact on toxicity profile. However, longer follow-up is essential to evaluate normal tissue tolerance, particularly with such an accelerated schedule.[17,18] For patients with locally advanced cervical cancer, HDR-BT with a single insertion approach and four therapy sessions appear to be appropriate, effective and safe in terms of toxicity.

Most of the studies that addressed the idea of single insertion with multiple fractions were trying to overcome complex workload barriers, limitations of anaesthesia or institutional capacity. In recently published data, the idea was also adopted during the COVID epidemic; while most treatment outcomes are considered acceptable, concerns regarding the gap between fractions and uncertainties of applicator position need further investigations.[19,20]

Conclusion

In a resource-limited environment, our accelerated protocol of 7 Gy in four fractions demonstrated equivalent local control and survival rates compared to the standard treatment. It also offered the added benefits of shorter overall treatment time, reduced hospital costs and fewer anaesthesia procedures, with acceptable toxicities. There was a trend towards a better local control arm in stage III; longer follow-up is recommended to assess therapeutic outcomes and late effects. For patients with delayed treatment, accelerated protocol could be a good alternative to address the prolongation of the overall treatment time.

Data availability statement. Data released upon reasonable request from the corresponding author

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Competing interests. The authors have no potential conflicts of interest to declare.

Institutional Review Board Statement. The study is conducted per the Declaration of Helsinki and approved by the Institutional Review Board. Ethical approval was obtained from the research and ethical committee at Cairo University Hospital.

Informed Consent Statement. Informed consent was obtained from all subjects involved in the study.

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