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*Original Research*

# Radiotherapy Management of Locally Advanced Cervical Cancer during the COVID-19 Era: A Single Centre Report on Treatment Approach, Brachytherapy Fractionation and Timing

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**Abstract**

**Background**: The COVID-19 pandemic had a catastrophic impact on healthcare. Keeping an optimal cancer care routine has been challenging. For cervical cancer (CC) patients external beam radiotherapy (EBRT) and brachytherapy (BT) are key elements for radical treatment. Oncological treatment delays have represented a major issue during the pandemic. Overall treatment time (OTT) is a well-known prognostic factor for CC. Thus, we decided to evaluate radiotherapy timing and modalities, and OTT trends for locally advanced cervical cancer (LACC) patients treated at our center during the Pandemic. **Methods**: We retrospectively collected and analyzed data of patients treated for LACC at our Center, (Department of Oncology, Radiation Oncology, S.Anna Hospital, Turin, Italy), during the COVID-19 pandemic. **Results**: Between March 2020 and March 2022, 36 patients were treated. All patients underwent EBRT (median pelvic dose 48 Gray (Gy)). Concurrent chemotherapy (ChT) was administered in 31/36 patients. High Dose Rate (HDR) BT boost was delivered to 32/36 patients. BT schedules adopted were: 28 Gy in 4 fractions (18 cases, 56.2%), 26 Gy in 4 fractions (5 cases, 15.6%), 21 Gy in 3 fractions (4 cases, 12.5%), 18 Gy in 3 fractions (3 cases, 9.3%), 24 Gy in 4 fractions (one case, 3.2%), 12 Gy in 2 fractions plus 11 Gy in 2 fractions (one case, 3.2%). Most of the patients (25/32, 78.1%) received one fraction per week; 6 patients (18.1%) 2 fractions per week and one patient 3 fractions per week. Median OTT was 74 days (57–99). The median interval from EBRT to HDR-BT was 14 days (6–54). Four patients tested positive for COVID-19 between EBRT and BT. At a median follow-up of 10.7 months (range 1.8–20.3), a complete response was obtained in 25 patients (69.5%), a partial response in 8 cases (22.2%), and a disease progression in two patients (5.5%). **Conclusions**: in terms of radiotherapy management of LACC, brachytherapy resulted as the most affected by the restrictions due to the pandemic. We adopted different schedules and fractionations to optimize the resources available and to keep providing an optimal care. A be-weekly fractionation emerged as a promising option for LACC during the pandemic, with a good toxicity profile.

**Keywords:** cervical cancer; brachytherapy; COVID-19

## 1. Introduction

COVID-19 outbreak was declared a worldwide pandemic on 11 March 2020 by the World Health Organization, and it has resulted in a dramatic global impact on healthcare, society, and economy. In order to minimize the viral spread, strategies such as physical distancing and lockdowns have been adopted. The Italian government declared a lockdown on 9 March 2020.

Healthcare experienced a continuous evolution to face and adapt to this challenge. Medical resources have been reorganized and reallocated towards the frontline of pandemic control in responding to the waves of infections and hospitalization, resulting in a sudden temporary suspension of non-urgent activities, including cancer screening services worldwide [1].

The Epic Health Research Network compared cervical cancer screening data between January and June 2020 to 2017–2019. Cervical cancer screening decreased by 94% during the first restrictions and remained decreased by 35% even after restrictions started to be released. It's been estimated that around 40,000 cervical cancer screenings were missed between March and June 2020 [2]. In Italy, screening tests for cervical cancer decreased by 43.4% in 2020 compared with 2019 [3].

Cancer care has been declared an essential service, which could not be compromised during the pandemic [4,5]. Nonetheless, the European Society for Radiotherapy and Oncology (ESTRO) reported a 57% of reduction among Radiation Oncologist personnel due to family care (29%), staff illness (26%) and, as mentioned before, staff being transferred to other areas (13%); only 11% of clinical activities decreased due to a reduction in patients' numbers [6].

Considering all these aspects, a delay in treatment or diagnosis could potentially lead to a negative impact on the only curative chance for the patient. On the other hand, on-

cologic treatments can affect patients' immune system with a greater risk of severe infection [7]. Therefore, finding a balance between optimal cancer care and the infection risk has been widely debated.

Cervical cancer (CC) is the fourth most common malignancy in women worldwide, the fourth leading cause of cancer death in women, and the first cause of cancer-related death in developing countries [8]. In Italy, it represents the 12th most common malignancy in women, with 12,800 women expected to be diagnosed in 2020. The median age at diagnosis is 48 years [9]. Radiotherapy (external beam radiotherapy - EBRT and brachytherapy - BT), along with concurrent chemotherapy (ChT), represents the cornerstone in locally advanced CC's radical treatment.

Cervical cancer is considered a category 1 disease (a rapidly growing tumor with a short volume doubling time) in which prolongation of treatment should be avoided [10] and delaying treatment delivery more than 4 months after diagnosis leads to a significant decrease in 1- and 5- years survival [11]. Furthermore, overall treatment time (OTT), which includes EBRT + BT, has an essential role in CC, influencing survival outcomes. A prolonged Radiotherapy (RT) duration has a negative impact on local control due to tumor repopulation [12].

A retrospective review on the effect of OTT in CC Stage I to IV showed a 1% decrease in local control and overall survival for every 1-day delay beyond the median treatment time [13]. Other studies showed poor outcomes with OTT longer than 8 weeks (56 days) [13–16]. From a series of 488 CC patients treated with definitive chemoradiation (EBRT + BT) emerged that an OTT $<$7 weeks could improve 3-year OS [17].

Thus, herein, we report our experience in treating with radiotherapy women with locally advanced CC (LACC) during the COVID-19 pandemic, aiming to evaluate treatment timing (focusing on OTT) and modalities.

## 2. Materials and Methods

We retrospectively collected diagnostic and treatment data of women treated at our Institution, Department of Oncology, Radiation Oncology, the Health and Science Academic Hospital, S.Anna Hospital, Turin, Italy, for LACC during the COVID-19 pandemic.

Radiotherapy treatment standards for LACC at our Institution include Intensity Modulated Radiotherapy/Volumetric Modulated Arc Therapy (IMRT/VMAT) delivery for pelvic irradiation. Target definition and organs at risk contouring for EBRT is based on image registration between the planning CT-scan and diagnostic imaging available (contrast enhanced whole abdomen CT-scan, pelvic Magnetic Resonance Imaging - MRI and Positron Emission Tomography and Computed Tomography - PET-CT). The elective target for nodal disease is treated with 45–50 Gy EBRT only (low risk clinical target volume, LR-CTV). Macroscopic disease such as pelvic side wall disease or pelvic and para-ortic nodes, where the contribution from intracavitary BT would be non significant, is treated with EBRT boost (up to 55–66 Gy) or with interstitial BT. EBRT is followed by High Dose-Rate (HDR) BT boost delivered to the whole cervix and the remaining residual tumour tissue at the time of BT. BT is performed using applicators (intracavitary tandem and ovoid or cylinder, intersitial) inserted after spinal anesthesia in the operating room. After applicator insertion, a CT-scan is acquired for BT planning for every fraction, and target volume and organs at risk (OaRs) are defined according to the Indian Brachytherapy Society (IBS) Groupe Européen de Curiethérapie (GEC) and European SocieTy for Radiotherapy and Oncology (ESTRO) American Brachytherapy Society (ABS) (IBS-GEC ESTRO-ABS) recommendations [18]. We routinely employ a mixed point-volume approach with a prescription of 100% dose to Point A (Manchester plan) and evaluation of the OaRs where the hot spot dose is reported in 2 $cm^3$ (D2cc), according to the GEC-ESTRO recommendation [19]. The standard BT schedule at our institution is 28 Gy delivered in 4 fractions, 1 fraction per week.

EBRT + BT Total Dose is calculated with the biologically equivalent dose in 2 Gy per fraction (EQD2) using the linear-quadratic model with a/b 10 Gy for tumor effects and a/b 3 Gy for late normal tissue damage, according to EMBRACE protocols [20] and International Commission on Radiation Units and Measurements (ICRU) Report 89 [21]. The total recommended EQD2 to target is 80–90 Gy combined dose from both EBRT and BT. The recommended limits of D2cc for the rectum, bladder and sigmoid colon are 75 Gy, 90 Gy, and 75 Gy, respectively.

Since different BT approaches have been used during the pandemic, we decided to retrospectively report on the different fractionations adopted, focusing on treatment-toxicity and OTT.

Acute and late toxicity are routinely assessed at our Institution according to the Common Terminology Criteria for Adverse Events (CTCAE v.4). Acute toxicity is defined as treatment-related adverse events occurring within 90 days from the end of radiation therapy, late effects are seen $>$3 months after treatment completion. We recorded vaginal, genitourinary (GU), and gastrointestinal (GI) toxicity data. Once collected, toxicity data were stratified according to the BT fractionation received.

As for the disease control, due to the short observation period (follow-up), we decided to report the response rates observed, distinguished in complete or partial response and disease progression. Response to treatment is assessed with clinical evaluation and MRI performed 3 months after treatment completion, and PET-CT performed 6 months after end of treatment.

Our Internal Review Board authorized the study.

## 3. Results

Between early March 2020 and 31st March 2022, 36 patients were treated for LACC at our Institution. At diagnosis, the median age was 51 years old (range 28–91). Characteristics of patients are shown in Table 1.

**Table 1. Characteristics of patients.**

| | Number (n = 36) | Percentage (%) |
|---|---|---|
| Histology | | |
| SCC | 29 | 80.6% |
| AC | 5 | 13.9% |
| Other | 2 | 5.5% |
| Grade | | |
| Gx | 11 | 30.5% |
| G1 | 8 | 22.2% |
| G2 | 7 | 19.5% |
| G3 | 10 | 27.8% |
| FIGO stage | | |
| IIA2 | 2 | 5.5% |
| IIB | 14 | 39% |
| IIIB | 2 | 5.5% |
| IIIC1 | 12 | 33.4% |
| IIIC2 | 4 | 11% |
| IVA | 1 | 2.8% |
| IVB | 1 | 2.8% |

SCC, squamous cell carcinoma; AC, adenocarcinoma.

The majority of patients, 34/36 (94.4%), were staged with MRI, while PET-CT was used in 23/36 (63.9%). The median diameter of the cervix was 48.5 mm (range 25–154).

Fourteen out of 36 patients underwent neoadjuvant ChT (NAChT - 38.9%) with weekly carboplatin and taxol.

All patients underwent EBRT (Table 2). The median total dose was 48 Gy (34.2 Gy–50.4 Gy), in 19–30 fractions, 1.8 Gy per fraction, to the whole pelvic volume. One patient died during EBRT at a total dose of 34.2 Gy/19 fractions, from a sudden rupture of a cerebral atero-venous malformation (AVM); one patient decided to stop the treatment at a total dose of 37.8 Gy/21 fractions for acute GI toxicity G2 and low compliance, but underwent subsequent HDR-BT. Lomboaortic nodal volume was included in the treatment volume in 7 cases (19.4%).

EBRT was delivered with VMAT technique to 100% of the patients. An EBRT simultaneous integrated boost (SIB) to the pathologic nodes was delivered in 9 cases (25%), with a total dose ranging between 52 and 66 Gy (median 54 Gy) in 2–2.25 Gy daily fractions. Two patients received a parametrial boost with EBRT, up to a total dose of 63 Gy.

ChT schedules and delivery were not affected by the pandemic, since, as well as at our institution, staff was not shifted toward COVID-19 departments. Concurrent ChT was administered in 31/36 cases (86.1%) for 3–7 cycles according to the eventual toxicity, using weekly cisplatin (CDDP, 40 mg/m$^2$). Five patients did not receive concurrent ChT for different reasons: one refused it, one for age (92 years old), another one decided for exclusive RT due to economic issues (patient from an extra-EU Country without healthcare expenses coverage), one had stage IV kidney failure, and another one had immuno-deficiency after a liver transplant.

**Table 2. Treatment characteristics and results.**

| | |
|---|---|
| EBRT | |
| Total Dose | Median 48 Gy (34.2–50.4) |
| Fractions | Median 27 (19–30) |
| LA Nodes treated | 7 (19.4%) |
| Nodal Boost (n = 9) | Median 54 Gy (44.1–66) |
| Parametrial Boost (n = 2) | 63 Gy |
| Chemotherapy | |
| Concurrent (weekly CDDP) | 31 (86.1%) |
| N° of cycles | Median 5 (3–7) |
| Neoadjuvant ChT | |
| Yes | 14 (39%) |
| No | 22 (61%) |
| HDR-BT (n = 32) | |
| 6 Gy × 3 fractions | 3 (9.3%) |
| 6 Gy × 4 fractions | 1 (3.2%) |
| 7 Gy × 4 fractions | 18 (56.2%) |
| 7 Gy × 3 fractions | 4 (12.5%) |
| 6.5 Gy × 4 fractions | 5 (15.6%) |
| 6 Gy × 2 fr + 5.5 Gy × 2 fractions | 1 (3.2%) |
| Fractionation | |
| 1 fraction × week | 25 (78.1%) |
| 2 fractions × week | 6 (18.1%) |
| 3 fractions × week | 1 (3.2%) |
| Interval from EBRT to BT | Median 14 days (6–54) |
| OTT (EBRT + BT) (n = 32) | Median 74 days (57–99) |
| Response | |
| Complete response | 25 (69.5%) |
| Partial response | 8 (22.2%) |
| Disease progression | 2 (5.5%) |
| NA | 1 (2.8%) |
| Follow up | Median 10.7 mos (1.8–20.3) |

The leading cause of concurrent ChT interruption (patients who received only 3–4 cycles of ChT) was haematologic toxicity, scored as follows: G3 Anemia (one patient); G2 thrombocytopenia (one patient); leukopenia (one case); neutropenia (one case); G2 anemia plus G3 diarrhea (one patient); G2 anemia + G1 neutropenia (one patient).

G1 anemia was recorded in 6 patients, not leading to ChT interruption.

After EBRT, 32/36 patients (88.9%) underwent HDR-BT. One patient refused HDR-BT treatment, one died during EBRT for a ruptured AVM and two patients had a progressive disease (PD) after EBRT completion.

Overall, during the pandemic, operating rooms for all the Gynaecology Department decreased from five to two; for brachytherapy applicators insertion, only 2–3 sessions

per week were available.

Due to the pandemic situation, we used different fractionation schemes for BT-HDR. In the beginning, we continued with our standard weekly fractionation (one fraction per week). Later on, when resources were consistently reduced (as described above), we adopted a biweekly fractionation: after the applicator insertion, a first planning CT-scan was acquired before the first fraction, and a second planning CT-scan was acquired before the second fraction. Patient was hospitalized for one night keeping the applicator in place, and the second fraction was delivered 24 hours after the first one. A rigid image registration between the 2 CT-scans was performed to evaluate any eventual variations.

Another schedule adopted was a tri-weekly fractionation: only one application in operating room was performed, patient was hospitalized for one night keeping the applicator in place. Three fractions were delivered with the same applicator, each one 6 hours apart from the previous one. A total of 3 planning CT-scans was acquired. A rigid registration between the planning CT-scans was performed also in this case.

Before the treatment schedule decision, we allowed patients to decide between the options, after a careful patient selection according to age and performance status.

HDR-BT schedules adopted are shown in Table 2. The majority of patients received 28 Gy in 4 fractions (56.2%).

Most patients received one fraction per week (25/32, 78.1%), in 6 cases (18.1%) a biweekly fractionation was adopted and only in 1 case a tri-weekly fractionation was used.

EQD2 and Biologically Effective Dose (BED) for target ($\alpha/\beta$ = 10 Gy) were calculated for 31 patients who received EBRT + HDR-BT, excluding one patient who did not complete EBRT. The median EQD2 delivered to the tumor (cervix) was 87.5 Gy (range 71.8–89.2), and the median tumor BED was 104.9 Gy (range 86.1–107.1).

Median OTT was 74 days (range 57–99). The median interval from EBRT end to HDR-BT start was 14 days (range 6–54). Four patients tested positive for COVID-19 between EBRT end and BT start, with the need to postpone the start of BT until they fully recovered.

At a median follow-up of 10.7 months (1.8–20.3), a complete response (CR) was obtained in 25 patients (69.5%), a partial response (PR) was seen in 8 cases (22.2%), and two patients (5.5%) experienced a progression (pelvic and extrapelvic nodal in one case, lung and hepatic metastasis in the other one). Overall, only one patient was lost in follow-up straight after the completion of treatment.

Among the 14 patients who received NAChT: a CR was obtained in 9 patients (64.3%), a PR was seen in 4 patients (28.6%) and one patient (7.1%) had a PD. Considering the 22 patients who did not receive NAChT: a CR was seen in 16 patients (72.8%), a PR in 4 patients (18.2%), one patient (4.5%) had a PD, and one patient (4.5%) was lost in follow-up. Due to the limited population, no statistical analysis was performed.

Data regarding vaginal, GU, and GI, both acute and late, are shown in Table 3.

**Table 3. Acute and late toxicity after EBRT + BT (GU = Genito-urinary, GI = gastro-intestinal) according to CTCAE vol. 4.**

| | Acute (n - %) | Late (n - %) |
|---|---|---|
| Vaginal toxicity | | |
| G0 | 12 (33.3%) | 14 (38.9%) |
| G1 | 5 (13.9%) | 15 (41.6%) |
| G2 | 19 (52.8%) | 5 (13.9%) |
| G3 | - | 1 (2.8%) |
| NA | - | 1 (2.8%) |
| GU toxicity | | |
| G0 | 18 (50%) | 34 (94.4%) |
| G1 | 8 (22.2%) | 1 (2.8%) |
| G2 | 10 (27.8%) | - |
| G3 | - | - |
| G4 | - | 1 (2.8%) |
| GI toxicity | | |
| G0 | 21 (58.3%) | 35 (97.2%) |
| G1 | 8 (22.2%) | 1 (2.8%) |
| G2 | 7 (19.5%) | - |
| G3 | - | - |

Overall, limited G3–G4 toxicity was recorded: in one case a G3 late vaginal stenosis and one patients experienced a G4 late GU toxicity (ureteral stenosis with obstruction requiring urgent intervention).

Table 4 shows acute and late vaginal, GU, and GI toxicity after EBRT + BT according to the regimens used: one fraction per week (25 patients) and 2 or 3 fractions per week (with one applicator - 7 patients). No statistical analysis was carried out, due to the limited number of patients. Looking at crude numbers, a slight higher acute G1 vaginal toxicity (dryness and inflammation) acute G2 GU toxicity (non-infective cystitis, urinary frequency, urinary urgency) and late G1 vaginal toxicity (dryness, stricture) was observed among patients receiving 2–3 fractions per week compared to those receiving one fraction per week (Table 4).

## 4. Discussion

During the COVID-19 pandemic, the management of LACC has certainly been more challenging, due to the need to reorganize hospital protocols leading to an overall reduced availability of healthcare resources and facilities, being shifted toward frontline pandemic control. At our Radiotherapy Department, we didn't experience a reduction of staff (physicians, RTT, medical phyhisics, nurses). Therefore, regarding EBRT, we could keep adopting conventional fractionation schedules, as reported before. Nev-

**Table 4. Toxicity after EBRT + BT: BT with one fraction per week compared to BT with 2–3 fractions per week.**

| | 2–3 fractions per week (n = 7) | One fraction per week (n = 25) |
|---|---|---|
| Acute vaginal toxicity | | |
| G0 | 4 (57.2%) | 6 (24%) |
| G1 | 2 (28.5%) | 2 (8%) |
| G2 | 1 (14.3%) | 17 (68%) |
| G3 | - | - |
| Acute GU toxicity | | |
| G0 | 4 (42.8%) | 11 (44%) |
| G1 | - | 8 (32%) |
| G2 | 3 (57.2%) | 6 (24%) |
| G3 | - | - |
| G4 | - | - |
| Acute GI toxicity | | |
| G0 | 6 (85.7%) | 14 (56%) |
| G1 | - | 7 (28%) |
| G2 | 1 (14.3%) | 4 (16%) |
| Late vaginal toxicity | | |
| G0 | 3 (42.8%) | 9 (36%) |
| G1 | 4 (57.2%) | 10 (40%) |
| G2 | - | 5 (20%) |
| G3 | - | 1 (4%) |
| Late GU toxicity | | |
| G0 | - | 23 (92%) |
| G1 | - | 1 (4%) |
| G2 | - | - |
| G3 | - | - |
| G4 | - | 1 (4%) |
| Late GI toxicity | | |
| G0 | - | 24 (96%) |
| G1 | - | 1 (4%) |
| G2 | - | - |

ertheless, hypofractionated schedules could be an option when staff and resources are limited, and have been widely recommended for several solid tumor due to the possibility of safely reducing the patients' exposure to hospital environments [22,23]. At present, although some prospective trials showed some potential role and interesting trials are ongoing, data on EBRT hypofractionation in CC patients remain scarce [24,25]. In a phase I–II trial from Brazil, 34 patients with stage IIIB CC were treated with hypofractionated RT (40 Gy to the whole pelvis with bis in die - BID fractions of 2.5 Gy on days 1, 3, 15, 17, 45, 47, 59 and 61) followed by LDR-BT with 35 Gy to point A delivered on day 29 and concurrent FU-cisplatin ChT. Treatment was well tolerated, with no G3–4 acute toxicity. A complete response was seen in 85% of patients and 5-years Overall Survival (OS) rate was 59% [26].

A retrospective report from Tata Memorial included 62 patients with stage IIIB CC treated with hypofractionated RT with 39 Gy in 13 daily fractions + subsequent BT, with or without ChT. The 5-years disease-free survival (DFS) was 59%. Five patients experienced late G3 rectal toxicity [27].

Another retrospective study from South Africa included 104 patients with stage IIIB CC, treated with EBRT 40 Gy in 16 fractions + BT boost of 9 Gy × 2 fractions, without concurrent ChT. Treatment was well tolerated, with a CR in 70% of patients. The 20-months DFS was 59% [28].

Currently, the ongoing phase II Canadian HEROICC Trial (Hypofractionated Externalbeam RadiOtherapy for Intact Cervical Cancer) is recruiting CC patients to randomize between a hypofractionated RT regimen of 40 Gy in 15 fractions to the whole pelvis (BED = 45 Gy/25 fr) with simultaneous integrated boost (SIB) to positive nodes up to 48 Gy/15 fr (BED = 57.5 Gy/25 fr) followed by HDR-BT, versus EBRT + HDR-BT standard regimen (45 Gy in 25 fraction). Both arms include weekly concurrent cisplatin 40 mg/m$^2$ for max 5 cycles. Authors assume that a downsizing of larger primary tumors may not be optimal after hypofractionated EBRT. Therefore, to ensure an optimal CTV coverage at the time of BT, patients included have to present with small primary disease and a low burden of nodal spread [29].

Another ongoing phase II trial from Mexico is randomizing patients with locally advanced cervical cancer between EBRT with 45 Gy/25 fractions or 37.5 Gy/15 fractions followed by a BT boost of 28 Gy in 4 fractions to point A. Both arms include weekly concurrent cisplatin [30].

Brachytherapy is an essential component of the CC management, and every effort should be made not be delayed due to the detrimental effect this may have on outcomes [31,32].

Due to the applicators insertion procedure requiring availability of different facilities and specialists (such as operating rooms, anaestesiologists, nurses), brachytherapy treatment delivery reflected a major impact from the pandemic. At our Institution, operating rooms available in the Gynecology Department were reduced from 5 to 2, with only 2–3 sessions per week to insert applicators. In order to optimize the resources and provide optimal care, the strategy adopted was to modify the fractionation, trying to deliver more fractions, reducing the number of applications, thus the need for operating room and anaesthesiologists. In 6 cases, we adopted a schedule with 2 fractions per week, 6 or 7 Gy each fraction (up to 4 fractions), delivering 2 fractions per application; in one case, we adopted the option of 3 fractions delivered in one week (6 hours apart from each fraction) with one application. Treatment was well tolerated; a schedule wih 2–3 fractions per week suggest to have similar toxicity rates compared to the standard fractionation of one fraction per week, as listed before. When a bi- or tri-weekly fractionation was used, 2 or 3 planning CT-scan were acquired (one before each fraction) and a rigid registration between the planning CT-scans was performed, thus ensuring a safe plan evaluation.

The limited study population and the short follow-up

time limit the results interpretation of our analysis. However, a schedule with 2 fractions delivered over one week with one application (up to 4 fractions) emerged as a safe option for LACC during the pandemic.

In an attempt to reduce OTT during the pandemic and based on previously published experiences, schedules of 2 to 3 sessions have been recommended by International Societies [33–35]. It has been demonstrated a similar local control and similar toxicity, with better compliance from the patients, using a schedule of 8 Gy × 3 fraction compared to 6 Gy × 4 fraction [35].

International multicenter studies reported excellent local control and toxicity outcomes with a schedule of 7 Gy × 4 fractions, delivered in 2 applications over one week, with 2 fractions per application in most cases [18,36]. This is an appealing regimen considering the possibility of limiting the application to 2 without decreasing the number of fractions. Another option explored during the pandemic, is to deliver 2–3 fractions every 6 hours, with one single application [23,37]. BT could also be interdigitated with EBRT. In this case, ABS recommends a schedule of 5–6 Gy × 5–6 fractions [33], even if considering the high number of necessary applications compared to other regimens; this makes this schedule of limited use. An attractive option could be to deliver a higher dose per fraction, limiting the application to 2 (i.e., 9 Gy in 2 applications); retrospective and prospective studies reported comparable OS rates with this regimen but decreased local control [33,38,39]. Therefore, these schedules should be cautiously adopted and after a proper patient selection (small volume of disease after EBRT or older patients). As for treatment-related toxicity, Kirchheiner *et al*. [38] reported, among the 630 patients included (with a median follow-up 24 months), a 2-year actuarial estimate for vaginal stenosis G $\geq$2 of 21%. Recto-vaginal reference point dose (HR (hazard ratio) = 1.025, $p$ = 0.029), EBRT dose >45 Gy/25 fractions (HR = 1.770, $p$ = 0.056) and tumor extension in the vagina (HR = 2.259, $p$ = 0.001) were risk factors for vaginal stenosis, adjusted for center reporting effects. Based on the model curve, the risk was 20% at 65 Gy, 27% at 75 Gy and 34% at 85 Gy (recto-vaginal reference point dose). No statistically significant difference in adverse events was found in the study by Hendry J. *et al.* [39].

Unfortunately, OTT was prolonged (median 74 days, range 57–99). Few patients got tested positive for COVID-19 so treatment start was delayed. The effect of the prolonged OTT needs further evaluation on disease control and late toxicity, with longer follow-up time. In the present report, the wait-time interval from diagnosis to chemoradiation start was not assessed, considering that 14/36 patients received NACHT, which could be a confounding factor. Nevertheless, a study conducted in the same period showed that a short wait-time interval (6.1–9.8 weeks) from diagnosis to start of chemoradiation for locally advanced cervical cancer might not be associated with increased mortality risk for patients not showing aggressive tumor factors [40].

## 5. Conclusions

During COVID-19 pandemic, a delay in diagnosis or treatment, and a prolonged radiation therapy overall treatment time for cervical cancer patients was likely to happen worldwide. Brachytherapy was the hardest challenge for us, due to the background situation. Thus, we adopted different schedules and fractionations to tailor the treatment case by case and to optimize the resources available and we were able to keep providing an optimal care.

A be-weekly fractionation (2 fractions delivered over one week with one application, up to 4 fractions) emerged as a safe and convenient option for LACC during the pandemic. Our results are in line with the literature, treatment was well tolerated and this schedule is promising.

## Author Contributions

All authors significantly contributed to the present manuscript. JDM, CG, FO and AM collected the clinical data. VC, JDM and UR wrote the manuscript. VC, JDM, AM and UR revised the manuscript. AP and EM performed the descriptive analysis and the dosimetric calculations. All authors read and approved the final manuscript.

## Ethics Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later amendments or comparable ethical standards. The present study has been reviewed and approved by the Internal Review Board of the Department of Oncology of the University of Turin at AOU Citta' della Salute e della Scienza, Turin, Italy. The policy of our Hospital and IRB is not to require formal approval for academic retrospective studies.

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## Conflict of Interest

The authors declare no conflict of interest.

## References

[1] Hamilton W. Cancer diagnostic delay in the COVID-19 era: what happens next? The Lancet Oncology. 2020; 21: 1000–1002.

[2] Mast C, Munoz del Rio A. Delayed cancer screenings—a second look. 2020. Available at: https://ehrn.org/articles/delayed-cancer-screenings-a-second-look/ (Accessed: 12 January 2021).

[3] Battisti F, Falini P, Gorini G, Sassoli de Bianchi P, Armaroli P, Giubilato P, *et al*. Cancer screening programmes in Italy dur-

ing the COVID-19 pandemic: an update of a nationwide survey on activity volumes and delayed diagnoses. Annali dell'Istituto Superiore di Sanità. 2022; 58: 16–24.

[4] World Health Organization. Maintaining essential health services: operational guidance for the COVID-19 context, interim guidance, 1 June 2020. 2020. Available at: https://www.who.int/publications-detail/covid-19-operational-guidance-for-maintaining-essential-health-services-during-an-outbreak (Accessed: 4 May 2022).

[5] Enabling Delivery of Essential Health Services during the COVID 19 Outbreak: Guidance note. Available at: https://www.mohfw.gov.in/pdf/EssentialservicesduringCOVID19updated0411201.pdf (Accessed: 4 May 2022).

[6] Slotman BJ, Lievens Y, Poortmans P, Cremades V, Eichler T, Wakefield DV, *et al.* Effect of COVID-19 pandemic on practice on European radiation oncology center. Radiother Oncology. 2020; 150: 40–42.

[7] Iorio GC, Ricardi U, Dal Pra A. Radiation-Induced Lymphopenia Beyond the COVID-19 Pandemic. Frontiers in Oncology. 2020; 10: 617302.

[8] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a Cancer Journal for Clinicians. 2021; 71: 209–249.

[9] AIOM-Airtum. I Numeri del Cancro in Italia 2021. Available at: https://www.aiom.it/wp-content/uploads/2021/10/2021_NumeriCancro_web.pdf (Accessed: 4 May 2022).

[10] Mehta S, Ramey SJ, Kwon D, Rich BJ, Ahmed AA, Wolfson A, *et al*. Impact of radiotherapy duration on overall survival in squamous cell carcinoma of the anus. Journal of Gastrointestinal Oncology. 2020; 11: 277–290.

[11] Shen S, Hung Y, Kung P, Yang W, Wang Y, Tsai W. Factors involved in the delay of treatment initiation for cervical cancer patients. Medicine. 2016; 95: e4568.

[12] Allam A, Perez LA, Huang P, Taghian A, Azinovic I, Freeman J, *et al*. The effect of the overall treatment time of fractionated irradiation on the tumor control probability of a human soft tissue sarcoma xenograft in nude mice. International Journal of Radiation Oncology, Biology, Physics. 1995; 32: 105–111.

[13] Fyles A, Keane TJ, Barton M, Simm J. The effect of treatment duration in the local control of cervix cancer. Radiotherapy and Oncology. 1992; 25: 273–279.

[14] Girinsky T, Rey A, Roche B, Haie C, Gerbaulet A, Randrianarivello H, *et al*. Overall treatment time in advanced cervical carcinomas: a critical parameter in treatment outcome. International Journal of Radiation Oncology, Biology, Physics. 1993; 27: 1051–1056.

[15] Lanciano RM, Pajak TF, Martz K, Hanks GE. The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: a patterns-of-care study. International Journal of Radiation Oncology, Biology, Physics. 1993; 25: 391–397.

[16] Song S, Rudra S, Hasselle MD, Dorn PL, Mell LK, Mundt AJ, *et al*. The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy. Cancer. 2013; 119: 325–331.

[17] Tanderup K, Fokdal LU, Sturdza 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. Radiotherapy and Oncology. 2016; 120: 441–446.

[18] Mahantshetty U, Poetter R, Beriwal S, Grover S, Lavanya G, Rai B, *et al*. IBS-GEC ESTRO-ABS recommendations for CT based contouring in image guided adaptive brachytherapy for cervical cancer. Radiotherapy and Oncology. 2021; 160: 273–284.

[19] Pötter R, Haie-Meder C, Limbergen EV, Barillot I, Brabandere MD, Dimopoulos J, *et al*. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): 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. Radiotherapy and Oncology. 2006; 78: 67–77.

[20] EMBRACE Studies and EMBRACE Research. 2015. Available at: https://www.embracestudy.dk (Accessed: 4 May 2022).

[21] ICRU-report89, Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix. J ICRU. 2013.

[22] Simcock R, Thomas TV, Estes C, Filippi AR, Katz MS, Pereira IJ, *et al*. COVID-19: Global radiation oncology's targeted response for pandemic preparedness. Clinical and Translational Radiation Oncology. 2020; 22: 55–68.

[23] Dewan A, Mitra S, Aggarwal S, Barik S, Kaur I, Umesh P, *et al*. Management of cervical cancer during the corona virus disease-19 (COVID-19) era. The British Journal of Radiology. 2021; 94: 20200686.

[24] Miriyala R, Mahantshetty U. Brachytherapy in cervical cancer radiotherapy during COVID-19 pandemic crisis: problems and prospects. Journal of Contemporary Brachytherapy. 2020; 12: 290–293.

[25] Mendez LC, Raziee H, Davidson M, Velker V, D'Souza D, Barnes E, *et al*. Should we embrace hypofractionated radiotherapy for cervical cancer? A technical note on management during the COVID-19 pandemic. Radiotherapy and Oncology. 2020; 148: 270–273.

[26] Viegas CM, Araujo CMM, Dantas MA, Froimtchuk M, Oliveira JAF, Marchiori E, *et al*. Concurrent chemotherapy and hypofractionated twice-daily radiotherapy in cervical cancer patients with stage IIIB disease and bilateral parametrial involvement: a phase i-II study. International Journal of Radiation Oncology, Biology, Physics. 2004; 60: 1154–1159.

[27] Muckaden M. Hypofractionated radiotherapy in carcinoma cervix IIIB: Tata Memorial Hospital experience. Indian Journal of Cancer 2002: 9: 127–134.

[28] Komen A. A retrospective study of advanced carcinoma of the cervix treated with a hypofractionated radiation therapy protocol at the department of radiation oncology. University of the Witwatersrand: Johannesburg, South Africa. 2014.

[29] NCT04583254. Hypofractionated External-beam RadiOtherapy for Intact Cervical Cancer (HEROICC-Trial): A Feasibility Study. Available at: https://clinicaltrials.gov/ct2/show/NCT04583254 (Accessed: 4 May 2022).

[30] NCT04070976. Chemotherapy and Pelvic Hypofractionated Radiation Followed by Brachytherapy for Cervical Cancer. Available at: https://clinicaltrials.gov/ct2/show/NCT04070976 (Accessed: 4 May 2022).

[31] Kumar D, Dey T. Recapitulating intracavitary brachytherapy in cervical cancer patients during the COVID-19 pandemic: a viewpoint. Future Oncology. 2020; 16: 2143–2146.

[32] Williams VM, Kahn JM, Harkenrider MM, Chino J, Chen J, Fang LC, *et al*. COVID-19 impact on timing of brachytherapy treatment and strategies for risk mitigation. Brachytherapy. 2020; 19: 401–411.

[33] Albuquerque K, Hrycushko BA, Harkenrider MM, Mayadev J, Klopp A, Beriwal S, *et al*. Compendium of fractionation choices for gynecologic HDR brachytherapy—an American Brachytherapy Society Task Group Report. Brachytherapy. 2019; 18: 429–436.

[34] Souhami L, Corns R, Duclos M, Portelance L, Bahoric B, Stanimir G. Long-term results of high-dose rate brachytherapy in cervix cancer using a small number of fractions. Gynecologic Oncology. 2005; 97: 508–513.

[35] Rao BS, Das P, Subramanian BV, Jena A, Rashmi P, Konakalla

VLA, *et al*. A comparative analysis of two different dose fractionation regimens of high dose rate intracavitary brachytherapy in treatment of carcinoma of uterine cervix: a prospective randomized study. Journal of Clinical and Diagnostic Research. 2017; 11: XC06–XC10.

[36] Mahantshetty U, Krishnatry R, Hande V, Jamema S, Ghadi Y, Engineer R, *et al*. Magnetic Resonance Image Guided Adaptive Brachytherapy in Locally Advanced Cervical Cancer: an Experience from a Tertiary Cancer Center in a Low and Middle Income Countries Setting. International Journal of Radiation Oncology, Biology, Physics. 2017; 99: 608–617.

[37] Dessai S, Nachankar A, Kataria P, Abyankar A. Management of patients with gynecological cancers during the COVID-19 pandemic. Cancer Research, Statistics, and Treatment. 2020; 3: 40–48.

[38] Kirchheiner K, Nout RA, Lindegaard JC, Haie-Meder C, Mahantshetty U, Segedin B, *et al*. Dose–effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. Radiotherapy and Oncology. 2016; 118: 160–166.

[39] Hendry J, Jones GW, Mahantshetty UM, Sarria G, da Motta NW, Fidarova E, *et al*. Radiobiological Analysis of Outcomes Using External Beam Radiotherapy Plus High Dose-Rate Brachytherapy (4x7 Gy or 2x9 Gy) for Cervical Cancer in a Multi-Institution Trial. International Journal of Radiation Oncology, Biology, Physics. 2017; 99: 1313–1314.

[40] Matsuo K, Huang Y, Matsuzaki S, Ragab OM, Roman LD, Wright JD. Association between definitive chemoradiotherapy wait-time and survival in locally-advanced cervical cancer: Implications during the coronavirus pandemic. Gynecologic Oncology. 2021; 161: 414–421.