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COVID-19 Rapid Letter

Should we embrace hypofractionated radiotherapy for cervical cancer? A technical note on management during the COVID-19 pandemic ☆

Lucas C. Mendez [a,b,*], Hamid Raziee [c], Melanie Davidson [e], Vikram Velker [a,b], David D'Souza [a,b], Elizabeth Barnes [d,e], Eric Leung [d,e]

[a] Division of Radiation Oncology, London Health Sciences Centre; [b] Department of Oncology, Western University, London; [c] Department of Radiation Oncology, BC Cancer, Surrey; [d] University of Toronto, Department of Radiation Oncology; and [e] Sunnybrook Health Sciences Centre, Toronto, Canada

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ABSTRACT

Cervical cancer is a deadly disease and the COVID-19 pandemic has the potential to further impact its lethality. Hypofractionated radiotherapy could mitigate this impact, however robust data in cervical cancer setting still is lacking. Information provided here could help institutions in reducing radiotherapy fractions for cervical cancer patients.

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Dear Editor(s),

Cervical cancer continues to be a frequent source of morbidity and mortality among women worldwide with more than 310,000 deaths per year [1]. Approximately 85% of theses fatalities occur in low- and middle-income countries (LMIC) [2], where multiple factors including insufficient screening programs, referral delays and an unmet gap between treatment need and availability play a role in this serious global health issue.

The current COVID-19 pandemic has the significant potential to further impact cancer treatment delivery globally including within high income countries. Strategies to reduce viral spread such as physical distancing or reducing the frequency of interaction between patient and staff have been advocated in an effort to flatten the transmission curve, potentially affecting the routine delivery of oncological treatments. In addition, funding reallocation to the front line of pandemic control could have a negative impact on resources available to oncological services, especially in LMICs already working under strained healthcare systems [3,4].

Radiotherapy plays an integral role in the curative treatment of locally-advanced cervical cancer, and in light of the foreseeable reduction in surgical procedures amid the current pandemic crisis, may be increasingly used as first-line treatment in early-stage cervical malignancies. Radiation therapy has also experienced a transformational evolution in recent decades driven by technological advances including 3D planning, intensity-modulated radiotherapy and image-guidance. These advances have allowed for a higher degree of treatment precision and facilitated a reduction in the number of radiotherapy fractions in a variety of disease sites. As a result, hypofractionation has not only the capacity to increase convenience and efficiency, but also to mitigate radiotherapy shortages faced especially by cancer treatment services in LMIC. Likewise, hypofractionation may be even more relevant in these current times due to worldwide shortages of resources, including in radiotherapy, related to the COVID-19 pandemic [5].

There is still a need for further large-scale studies on hypofractionated radiotherapy for cervical cancer, however, prospective data has shown some promise in shorter schedules of radiation. In a phase I-II trial from Brazil, 34 patients with stage IIIB cervical cancer were treated with hypofractionated radiotherapy together with concurrent 5-fluorouracil 400 mg/m^2 and cisplatin 15 mg/m^2 given on days 1–3, 15–17, 45–47, and 59–61. The whole pelvis was treated with a four-field box technique to a total dose of 40 Gy with BID fractions of 2.5 Gy on days 1, 3, 15, 17, 45, 47, 59 and 61. Low-dose rate brachytherapy with 35 Gy prescribed to

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* Correspondent author at: Division of Radiation Oncology, London Health Science Centre, Canada.
E-mail address: lucas.mendez@lhsc.on.ca (L.C. Mendez).

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point A was delivered on day 29. All patients concluded treatment and this was considered well tolerated, with no grade 3 or 4 acute toxicity. Four and 1 patients developed late grade 3 or 4 gastrointestinal and urinary toxicity, respectively. Complete response rate was 85% and the 5-year overall survival rate was 59% [6].

In another report coming from South Africa, 104 patients with stage IIIB cervical cancers were treated with external beam radiotherapy (EBRT) 40 Gy in 16 daily fractions (AP/PA fields) plus brachytherapy with 9 Gy × 2 fractions. No concurrent chemotherapy was given and outcomes were reported retrospectively. Complete response was registered in 70% of patients and disease free-survival (DFS) at 20 months was 59%. No late GU toxicities were seen, while 4 late GI toxicity were registered [7]. A retrospective report from Tata Memorial investigated the role of hypofractionated radiotherapy in 62 stage IIIB cervical cancer patients treated with 39 Gy in 13 daily fractions (mostly AP/PA fields) followed by intracavitary brachytherapy. The 5-year DFS rate was 59%, and 5 patients had late G3 rectal toxicity [8].

Altogether, the experience of these three clinical series, with a total of 200 stage IIIB cervical cancer patients treated with hypofractionated radiotherapy with or without chemotherapy, provides some insight into this treatment strategy. Although heterogeneity among series is perceptible, with differences mostly in treatment delivery and chemotherapy use, some conclusions can be formulated. First, hypofractionated radiotherapy with a total dose of 39–40 Gy and fractions ≥2.5 Gy (followed by brachytherapy boost) may lead to a reasonable tumour response considering the patient population included and the brachytherapy technique offered. Second, concurrent chemotherapy with hypofractionated radiotherapy is possible and did not lead to exacerbated levels of late toxicity in the Brazilian experience, despite use of conformal technique only. Lastly, G3-4 late toxicities were seen in approximately 10–15% of patients. This is roughly similar to most modern series [9], withstanding differences in data collection.

Currently, an ongoing Mexican phase II trial is randomizing patients with locally advanced cervical cancer between EBRT with 45 Gy/25 fractions or 37.5 Gy/15 fractions. EBRT is being delivered with a 4-field box and weekly concurrent cisplatin followed by brachytherapy boost to point A with 28 Gy in 4 fractions in both arms [10]. In Canada, funding has been secured for a multicentric Phase 2 randomized trial (Hypofractionated External-beam RadiOtherapy for Intact Cervical Cancer (HEROICC)-Trial) that randomizes cervical cancer patients between two experimental hypofractionated radiotherapy regimens. Different from studies reported above, this trial seeks to only include patients with a small bulk of primary disease and a low burden of nodal spread (Table 1). The rationale behind this inclusion criteria is to ensure optimal high-risk CTV (CTV_{HR}) coverage at the time of brachytherapy, assuming that the downsizing of larger primary tumours might not be optimal at EBRT completion with hypofractionation if compared to longer standard regimens. If this assumption is true, offering hypofractionated radiotherapy to large primary tumours could increase the need for more sophisticated brachytherapy, such as comprehensive interstitial techniques, due to unfavourable geometry at the time of brachytherapy implant. Of note, radiation

Table 1
HEROICC-Trial Arm 1 – EBRT technical summary.

Inclusion criteria	• Cervical cancer with squamous, adenosquamous or adenocarcinoma histology • Stage IA-IIA • Stage IIB with <5 cm in width in MR scan • Stage IIIC1 patients are allowed as long as the following is met: no common iliac node, <3 cm in the largest dimension, <3 pathologic nodes and primary with stage IA-IIB (IIB <5 cm in width)
Radiotherapy	
Simulation	• CT Scan (full and empty bladder) fused with MR scan OR MR Scan (full and empty bladder) fused with CT Scan. If available, fusion with FDG PET-CT is allowed. *Bone fusion between scans* • Preparation: Drinking protocol- empty bladder followed by 400 mL of water before scan. Rectum should be empty with diameter <4 cm in the AP diameter
Contours and Field	• Contour CTV_{LR} as per EMBRACE 2 protocol [11] in different scan sets. Ensure that a 5 mm is provided around the CTV_{HR} towards the bladder and rectum and that contours are expanded inferiorly by 2 cm to cover the uninvolved vagina. • Generate a primary internal target volume, ITVp, by combining contours from the various image-sets (CTV_{LR} contoured on empty- and full-bladder CT and MR scans) • Generate an elective nodal clinical target volume, CTVn by contouring nodes as follows: o IA-IB2 AND no suspicious nodes: CTVn - Obturator, External and Internal illiacs and Presacral o IB3-IIB OR positive pelvic node: Nodes as specified above + common illiacs until aorta bifurcation • $GTV_{HighDose}$ = suspicious or cancerous pelvic lymph nodes • Contour OAR: o Bladder: Whole organ including bladder neck o Rectum: from ano-rectal sphincter to recto-sigmoid junction o Sigmoid: from recto-sigmoid junction to left iliac fossa o Bowel: outer contour of bowel loops including the mesentery in a single contour o Femurs: Right and left femoral heads o Bone Marrow: Pelvic bones as a surrogate
Planning	• VMAT preferably (or IMRT) • $ITV_{LowDose}$ = ITVp + CTVn • $PTV_{LowDose}$ = $ITV_{LowDose}$ + 5 mm isotropic expansion • $PTV_{HighDose}$ = $GTV_{HighDose}$ + 5 mm isotropic expansion • Refer to Table 2 for suggested dose constraints
Dose-prescription	• $PTV_{LowDose}$ = 40 Gy in 15 fractions • $PTV_{HighDose}$ = 48 Gy in 15 fractions (SIB)
Treatment delivery	• Image verification: Perform daily CBCT and align to bone anatomy • Assess necessary shifts: Automatic correction if <1 cm of translation. If translation larger ≥1 cm or 4 degrees of rotation, repeat patient setup and CBCT. • Assess soft tissues: Verify rectal diameter and bladder filling. Inspect bowel position in regards to $PTV_{LowDose}$ and $PTV_{HighDose}$. Verify if cervix and uterus are within $PTV_{LowDose}$ volume. • Troubleshooting: Consider removing patient from bed and waiting longer or offering more fluid if bladder is empty or bowel significantly intruding PTV space. Empty rectum if full (AP diameter >6 cm) or if this is significantly pushing the vagina and cervix anteriorly
Chemotherapy	• Weekly Cisplatin with 40 mg/m^2. Aim for 5 cycles including weeks in which brachytherapy fractions are delivered

will be given using intensity-modulated technique and with concurrent weekly cisplatin.

While it would be ideal to have more robust data before changing fractionation protocols in this curative disease, limitation and depletion of resources due to COVID-19 pandemic may require the consideration of shortening treatment schedules. The practical resource and disease implications of staying with standard fractionation may result in reduced overall access to radiotherapy. It could also potentially lead to suboptimal outcomes, if treatment fractions are interrupted in patients who become suspected or infected with COVID-19. Conscientious of the international effort to mitigate havoc caused by the COVID-19 pandemic and acknowledging a decreased allocation of resources for oncological patients, investigators from the HEROICC-trial have report on planning constraints and rationale related to Arm 1 of this study protocol (Tables 1 and 2).

The authors would like to state that there is no indication that the suggested dose-fractionation is effective for tumour control or safe to the surrounding organs at risk. The intended aims of the HEROICC trial are in fact to investigate these questions. However, the following points provide our rationale for the dosimetric choices made for the HEROICC-trial, for institutions considering a hypofractionated option.

1. The proposed organ-at-risk (OAR) constraints are largely conservative biologically effective dose (BED) transformations of well-recognized clinical trials (α/β = 3 Gy). And alike constraints in other studies [11], they are meant to provide planning goals for dose optimization, as they are not based on clinical evidence.
2. The proposed dose to target volume (40 Gy in 15 fractions) has similar BED to conventionally fractionated strategies (i.e. 45 Gy/25 fractions) if total treatment time and repopulation factors are taken into consideration in the equation (see formula below). As an example, a meta-analysis of two randomized clinical trials looking at the role of radiosensitizing drugs in bladder cancer patients (BC2001 and BCON) has indicated a higher tumour control in the hypofractionated (55 Gy in 20 fractions) group versus the group treated with normally fractionated radiotherapy (64 Gy in 32 fractions), despite a lower BED, calculated with the standard BED formula (76.8 Gy vs 70.1 Gy, α/β = 10 Gy) [12]. As the role of overall treatment time is known to be predictive of cancer control in cervical cancers, it is fair to hypothesize that larger true BEDs can be achieved with faster treatment deliveries.
3. Brachytherapy is an excellent boost therapy that could easily compensate dose and allow further dose-escalation, if necessary, to the CTV_{HR} in early cancers. Dose escalation with brachytherapy (i.e. CTV_{HR} D90% > 700 cGy per fraction) are frequently achieved in a daily basis without significantly incrementing dose to the surrounding organs.
4. Simultaneous integrated boost (SIB) to the node with 48 Gy in 15 fractions has approximately the same BED of 57.5 Gy in 25 fractions ($BED_{10} \approx$ 63–66 Gy) if overall treatment time and repopulation are considered.
5. Chemotherapy is known to improve overall survival when given concurrently to radiotherapy especially in early stage cervical cancer patients. Weekly cisplatin is maintained in this protocol with a maximum total dose of 200 mg/m^2 (5 cycles). Similar approach has been used in the already open Mexican trial [10].

Table 2
HEROICC Trial Arm 1 – Target and OAR constraints.

Volume	No boost	SIB
$PTV_{LowDose}$	V3800cGy > 95%[B] V4200cGy < 2%	V3800cGy > 95% b[B]
$ITV_{LowDose}$	V4000cGy > 95% Dmin > 3800cGy[B]	V4000cGy > 95% Dmin > 3800 cGy [B]
ITVp	V4000cGy > 95%	V4000cGy > 95%
CTVn	V4000cGy > 95%	V4000cGy > 95%
$PTV_{HighDose}$	NA	V4560cGy > 95% Dmax < 5136cGy[B]
$GTV_{HighDose}$	NA	V4800cGy > 98%[B]
PTVopti = PTV -($PTV_{HighDose}$ + 1 cm)	NA	V4200cGy < 5% (optimal, not required)
ITVopti = ITV − ($PTV_{HighDose}$ + 1 cm)	NA	Dmax < 4560 cGy (optimal, not required)
Bowel	Dmax < 4280 cGy (107%) V3450cGy < 100 cc (maximally < 250 cc)[A] Optional: V2667cGy < 500cc[B]	Dmax < 4900cGy[F] V3450cGy < 250cc[A] (maximally V3850cGy < 250cc[C]) Optional: V4275cGy < 20cc[E] V2667cGy < 500cc[B]
Sigmoid	Dmax < 4280 cGy (107%)	Dmax < 4900cGy[F]
Bladder	Dmax < 4280 cGy (107%) V3850cGy < 50%[C] (maximally V4000cGy < 50%[D]) V3450cGy < 75%[A] (maximally V3556cGy < 75%[B]) V2650cGy < 85%[A] (maximally V2667cGy < 85%[B])	Dmax < 4900cGy[F] V3850cGy < 50%[C] (maximally V4000cGy < 50%[D]) V3450cGy < 75%[A] (maximally V3556cGy < 75%[B]) V2650cGy < 85%[A] (maximally V2667cGy < 85%[B])
Rectum	Dmax < 4280 cGy (107%) V3850cGy < 50%[C] (maximally V4000cGy < 50%[D]) V3450cGy < 85%[A] (maximally V3556cGy < 85%[B]) V2650cGy < 95%[A] (maximally V2667cGy < 95%[B])	Dmax < 4900cGy[F] V3850cGy < 50%[C] (maximally V4000cGy < 50%[D]) V3450cGy < 85%[A] (maximally V3556cGy < 85%[B]) V2650cGy < 95%[A] (maximally V2667cGy < 95%[B])
Femurs	Dmax < 4280cGy[A] (107%)	Dmax < 4280cGy[A] (maximally < 4900cGy[F])

Legend:
[A] EMBRACE (BED-scaled, alpha/beta = 3 Gy).
[B] EMBRACE (linearly-scaled by: 40 Gy/45 Gy).
[C] NRG-GY006 (BED-scaled, alpha/beta = 3 Gy).
[D] NRG-GY006 (linearly-scaled by: 40 Gy/45 Gy).
[E] BED-scaled from 50 Gy < 20 cc (alpha/beta = 3 Gy) from Stanic et al. (2013) [16].
[F] BED-equivalent to 58 Gy/25, alpha/beta = 3 Gy.

6. Intensity-modulated radiotherapy (preferably VMAT) is mandatory. This technique has been shown to reduce dose to bowel and bladder and to reduce acute adverse effects like diarrhea. IMRT also improves patient-reported outcomes (PRO), as bowel and urinary domains were less impacted when compared to four-field box radiotherapy [13]. Differences in toxicity and PRO between treatment modalities persisted at 1- and 3-years post treatment [14].

Constraints presented in Table 2 rely in an institutional planning study developed for this trial purpose. In this, fifteen cervical cancer patients were planned with this suggested approach and 60% of these patients have met all optimal constraints in Table 2. Five patients failed to meet the optimal bowel constraint (V3450cGy < 100 cc) but met the alternative constraint (V3450cGy < 250 cc). This alternative value, however, will be difficult to be met in patients with an excess of 250 cc of bowel in the PTV, as was the case with one of our fifteen patients. 80% and 90% of cases met the optimal rectum and bladder values, respectively, with all meeting the alternative constraints provided. While the optimum constraints for bladder and rectum may be difficult to achieve when more than 50% of the organ is encompassed by the PTV, the alternative values should provide reasonable flexibility in these instances (Internal Data– not published). To evaluate the negative dosimetric impact of the additional dose from SIB in planning, five of the most difficult cases were re-planned with two nodes being boosted to the proposed SIB dose. Bowel constraints became increasingly challenging to achieve with the inclusion of SIB volumes. Thus, we have increased the allowance of bowel dose in the SIB setting based on constraints derived from the NRG-GY006 clinical trial [15].

In summary, the information presented here could serve as a practical method for institutions that require to decrease radiation utilization during the COVID-19 pandemic, while attempting to preserve radiation quality using a hypofractionated regimen. Of note, the protocol here presented is a prospective clinical trial and is not intended for use in standard treatment circumstances. However, given the potential impact of the pandemic on individual institutions and regions, the dose targets and rationale are presented here to help guide hypofractionation strategies. They should be considered cautiously and analyzed and recommended at the discretion of the most responsible physician. Authors do not recommend use of this treatment strategy in patients that may need elective radiotherapy to the paraaortic drainage, unless in a clinical trial protocol. This regimen may not allow for a good geometry during brachytherapy implant, especially if significant downstaging is necessary, like commonly seen in patients with FIGO stage IIIA–IVA. The results of the HEROICC trial will not be known for years, however it is possible that this information may help guide institutions and patient population living in extreme conditions, like the one currently affected by the COVID-19 pandemic.

*BED equation with repopulation: BED = $N.d\ (1 + d/\alpha/\beta) - kT$, where N = number of fractions; d = dose per fraction; k = tumour growth rate (assumed to be 0.3 Gy/day); T = time after repopulation is initiated (repopulation assumed to occur after 21 days).

Conflict of interest

None.

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