



# Gynecologic radiation therapy in low and middle income countries during the COVID-19 pandemic

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## ABSTRACT

The COVID-19 pandemic has forever affected healthcare and posed an incredible challenge to our society to care for our sick. Patients with cancer were found early on to have higher rates of complications with COVID-19. Radiation therapy is an integral part of treatment for many types of gynecologic cancer and adaptation on its utilization during the pandemic varied across the globe. In this review, we detail certain guidelines for the use of radiation in gynecologic cancers during the pandemic as well as real world accounts of how different countries adapted to these guidelines or created their own based on individualized resources, staffing, government restrictions, and societal norms. Critically, this review demonstrates the breadth of fractionation schemes and technologies used when resources were limited but highlights the importance of long term follow-up for many of our patients during this time.

## INTRODUCTION

When the novel coronavirus SARS-CoV2 (COVID-19) pandemic was declared a public health emergency by the World Health Organization on March 11, 2020, healthcare access shifted drastically as entire health systems reacted and adapted to the rapidly evolving pandemic. Diagnosis and management of cancer was impacted, and at times delayed. In low and middle income countries, the pandemic put additional burdens on already strained healthcare systems, often without national guidelines that were specific to a region's resources or capabilities. Early studies from China demonstrated that among 1506 patients with acute respiratory symptoms who were hospitalized, 18 patients had a history of cancer.<sup>1</sup> Although a small sample size, this early study suggested that patients with a cancer history had 3.56 times (95% confidence interval (CI) 1.8 to 16.1) higher rates of severe events in comparison with those without cancer.<sup>1</sup> Furthermore, a retrospective study of 28 COVID-19 patients undergoing oncologic treatment within 2 weeks of infection identified cancer as a risk factor for severe events (hazard ratio 4.07, 95% CI 1.08 to 15.3).<sup>2</sup>

In the early months of the pandemic, patients and providers across the globe were challenged with facing both the COVID-19 pandemic and continuing

cancer care treatments in a safe environment. Expert panels convened to help provide guidance on how to appropriately prioritize patients requiring urgent or emergent radiation treatment.<sup>3–5</sup> For example, in India, gynecologic oncologists developed a scale to triage patients if resources were limited and made recommendations for alternative treatments, such as the use of simultaneous integrated boost instead of sequential cone down boost to limit both the number of daily treatments required and patient travel.<sup>5</sup> However, this technique is not always possible with the basic conventional radiotherapy machines in low and middle income countries. In low and middle income countries, caring for and treating cancer patients is further complicated by resource scarcities.<sup>6</sup> In this review, we aim to provide an overview of guidelines issued during the COVID-19 pandemic with regards to delivery of gynecologic oncology treatments and associated real world examples of how different departments across low and middle income countries adapted to provide safe effective treatments during a global pandemic.

## GYNECOLOGIC ONCOLOGY COVID-19 TREATMENT GUIDELINES

Management of all cancer patients during the pandemic is a challenging task, further complicated by the fact that this patient population is often immunocompromised, either due to their underlying malignancy or associated therapies.<sup>7</sup> To date, there exist two multi-institutional international cohort studies (CovidSurg-Cancer and CovidSurg-Cancer Gynecological Oncology) that are investigating the impact of COVID-19 on the care of cancer patients requiring surgery.<sup>8</sup> Societal guidelines were developed to guide management decisions of cancer, specifically gynecological cancers, during the COVID-19 pandemic. Within 3 months of the pandemic onset, at least 16 guidelines were published, providing guidance on caring for gynecologic cancer patients during COVID-19.<sup>4</sup>

In August 2020, Elledge et al published a set of radiation oncology guidelines set forth by a panel of international experts in gynecologic radiation as



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a framework for decision making during this time. Specifically, patient scenarios were triaged into three priority groups:

1. Priority A: patients with curable, rapidly progressive tumors deemed critical and required treatment during a pandemic (even if known to be COVID positive)
2. Priority B: patients who required treatment, but whose situation was non-critical (ie, could be delayed 8–12 weeks without significant harm in the setting of personal protective equipment or resource shortages).
3. Priority C: patients with non-life threatening conditions whose treatment may be delayed without anticipated change in outcome for an indeterminate period of time (ie, patients who may undergo observation and/or alternative therapies).

These scenarios were further broken down by disease site (cervical, vulvar, vaginal, endometrial, and ovarian). Bleeding or severely painful lesions in patients with metastatic disease were routinely considered priority A and were recommended treatment with 10 Gy in one fraction, or 'quad shot' 3.7 Gy twice daily for 2 days (14 Gy in four fractions) to limit transfer in and out of radiation centers.<sup>5</sup>

For gynecologic cancers, brachytherapy is an especially critical consideration given the need for intubation and multiple visits to the hospital, conferring a higher risk of COVID-19 transmission. Williams et al published brachytherapy specific guidelines regarding both timing and fractionation schemes for cervical, uterine, and vaginal cancers.<sup>9</sup> Recommendations included the use of locoregional anesthesia or conscious sedation over general anesthesia to minimize aerosolizing procedures, including intubation due to an increased risk of virus transmission. Additionally, routine testing of patients prior to operative procedures was recommended to allow for appropriate adjustments (ie, additional personal protective equipment) or alternative treatments to be considered (ie, use of non-operative techniques such as stereotactic body radiotherapy treatment instead of brachytherapy to avoid the increased risk of viral transmission in an operative setting). The authors highlight the important factor of timing in completion of both external beam and brachytherapy for cervical cancer. While the pandemic forced delays due to resource limitations, workflow changes, and other factors outside of our control, completing cancer treatment for a potentially curable disease is critical to maintain. Numerous studies have shown that pelvic control of disease and 5 year survival vary between completing treatment <55 days and duration >55 days, and that the time between external beam radiation and initiation of brachytherapy was the most common cause of treatment prolongation.<sup>10</sup> The authors discuss strategies to limit this delay in the era of COVID-19, including prioritization of patients and varying fractionation schedules. An additional benefit of fractionation schedule changes included minimizing the number of fractions when possible to limit number of potential exposures.<sup>5,11</sup>

Beyond specific radiation recommendations, three overarching categories for delivering oncologic care during COVID-19 were addressed: (1) caring for healthcare professionals and workforce; (2) patient care in the outpatient setting; and (3) treatment decisions.<sup>12</sup> First, guidelines proposed that hospitals prioritize safe working conditions for hospital staff and health professional teams via supply of appropriate personal protective equipment and prioritizing virtual teleconferencing (virtual tumor board and departmental meetings) over in-person meetings. In terms of outpatient care,

changes to workflow included minimizing face-to-face appointments and increasing use of telephone and video consultations, and maintaining 'social distancing' in waiting rooms.<sup>4</sup> Treatment decisions were made on a case by case basis, accounting for disease and patient characteristics, and the resources available. Given the potential for curable disease in localized cervical cancer, it was recommended that all patients with stage I–IVA disease were considered a treatment priority. Treatment plans were modified to include postponement of early stage cancer treatment, if possible, or completion of chemotherapy instead of interval debulking surgery for ovarian cancer to avoid prolonged surgical and operative exposures. Additionally, hypofractionated radiation plans were offered in the case of cervical cancer.<sup>13</sup> However, surveys found that departments' responses to the pandemic were heterogenous in terms of the treatment decisions made for patients. An online survey of providers from 49 countries who used radiation treatment for patients with gynecologic malignancies found that 45.7% reported no significant changes to treatment regimens, 42.9% described an increased use of hypofractionation to reduce hospital admissions, and 24.3% noticed an increase in radiation treatment indications.<sup>14</sup>

## REAL WORLD ACCOUNTS

### Asia Pacific

Early in the pandemic, in June 2020, an online survey of the Association of Gynecologic Oncologists of India was distributed to assess the response to changes in gynecologic cancer treatment. At that time, cervical cancer was managed with standard optimal therapy (surgery or definitive chemoradiation, depending on stage) for two-thirds of patients whereas in about a third of patients, neoadjuvant chemotherapy was used to delay surgery, a proven alternative in a limited resource setting.<sup>15</sup>

At Tata Memorial Hospital in Mumbai, Indian, physicians documented their procedural changes for gynecologic cancer during the lockdown period between March 23 and June 30, 2020. These included: suspension of all concurrent chemotherapy for cervical, endometrial, and vulvo–vaginal cancers during radiation, given that most of their patient populations were from geographic locations with high rates of COVID-19; preferential use of hypofractionated external beam treatment for elderly patients (age >75 years) to minimize the need for travel; and preferential use of single application with multiple fractions of intracavitary interstitial brachytherapy or multiple applications with reduced time interval to prevent inpatient admissions and procedures. For patients who tested positive for COVID-19 infection, a policy of restarting treatment with external beam therapy after 10 days of diagnosis was implemented.

Compliance with radiation therapy decreased to 66% (from 85% during non-COVID times) due to patients' fears of contracting COVID-19 and logistical concerns during lockdown, including quarantine or difficulties with interstate or intrastate transportation. Institutionally, most patients were treated with conventional fractionation despite the recommendation to treat with hypofractionation. Given that data supporting hypofractionation are still maturing, conventional treatments were preferred over hypofractionation due to concerns for toxicity in normal tissue.<sup>16</sup> Additionally, Tata Memorial adjusted brachytherapy fractionation and almost

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70% of patients received as a single implant with multiple fractions. Importantly, both fractionation and chemotherapy adjustments will need to be followed long term to look at data regarding side effects, toxicities, and progression free survival.

Tata Memorial also used telemedicine for follow-up visits of gynecologic oncology patients. These visits included telephone calls when video capabilities were unavailable. A structured assessment for vaginal discharge, abdominal pain, nausea/vomiting, and blood in urine/stools was employed. Of note, because of sociocultural reasons and concern for lack of privacy, questions related to sexual functioning were not asked. In the first phase of the pandemic, the gynecology radiation oncology unit treated at one-third of its capacity (similar to the rate of cancer hospitalizations in other countries) as a result of reorganization and limited human resources. If patients reported concerning symptoms, radiation oncology staff followed up with short interval video calls or a referral to the nearest facility.<sup>16</sup>

In Chandigarh, India, Srinivasa et al documented their experience with rationing treatment for gynecological cancer during COVID-19. At the tertiary center of the Institute of Medical Education and Research, Chandigarh, India, they reported 160 cases of gynecologic malignancies in March and April 2020. In addition to the consensus guidelines, which included wearing personal protective equipment and sanitizing equipment between patients, palliative hypofractionated radiotherapy was converted to single fraction treatments. For brachytherapy, minimizing the total length of stay in the hospital was preferred (ie, two fractions of 9 Gy high dose rate brachytherapy instead of four fractions of 7 Gy each). Of note, there are mixed data into the efficacy of 9 Gy  $\times$  two fractions in the literature, with one multi-institutional international study showing inferior 5 year tumor control (88% for 7 Gy  $\times$  four treatments; and 78% for 9 Gy  $\times$  two treatments).<sup>17</sup> Brachytherapy procedures were done under conscious sedation instead of general anesthesia to minimize exposure risks from intubation. A survey of providers across India (61 total respondents, 63.9% gynecologic oncologists, 18% radiation oncologists) noted that 95% of respondents felt that COVID-19 had modified their patterns of care for patients with gynecologic cancer. Additionally, 40.9% of respondents said they provided radiation to cases based on an urgency scale, and 9% reported having implemented hypofractionation in response to the pandemic.<sup>18</sup>

### Middle East and Africa

In Turkey, an online survey of gynecologic oncology specialists found that 57.1% reported a preference for hypofractionated radiotherapy for locally advanced cervical cancer.<sup>19</sup>

In Morocco, ElMajjaoui et al detailed their experience with precautions for COVID-19 and treatment of gynecologic cancers. Cervical cancer is the most common cancer in the country. Given the data supporting brachytherapy and the importance of minimizing delays between external beam radiation therapy and brachytherapy, the authors recommended reduced brachytherapy fractionation schemes (8 Gy  $\times$  three fractions or 7 Gy  $\times$  four fractions). The four fraction regimen consisted of two insertions 1 week apart; for each insertion, patients received two fractions per day separated by a 6 hour interval. For elderly patients, or those with significant comorbidities, a shortened schedule of 9 Gy per fraction in two fractions, 1 week apart, was considered. For patients with early endometrial

cancer, vaginal vault brachytherapy was recommended in intermediate risk patients; however, while the data support differences in vaginal relapse, they do not support differences in disease free survival or overall survival. Thus the authors suggest a delay in vaginal vault brachytherapy for up to 12 weeks for intermediate risk patients in the setting of a regional COVID-19 outbreak. For stage II endometrial cancers, adjuvant vaginal vault brachytherapy was delivered exclusively or after external beam radiation therapy but allowed for postponement up to 24 days if an outbreak occurred. The authors' recommendation for early stage vaginal cancer, for which brachytherapy is exclusively the treatment of choice, was delivery of an equivalent dose in 2 Gy fractions (EQD2) of 60–85 Gy to the tumor with a 2 cm margin (7 Gy  $\times$  five fractions), and for those with significant comorbidities, to postpone brachytherapy by 1–2 months.<sup>20</sup>

Physicians in Lebanon described the use of virtual multidisciplinary teleconferencing platforms to discuss new patient cases. They noted that limitations of this modality included concerns over patient privacy, staff attentiveness, and lack of face-to-face patient interactions that normally allow for nuanced discussion and follow-up questions. Additional difficulties of virtual conferencing stemmed from unreliable internet network connections in Lebanon. Despite these limitations, this physician group felt that it was an encouraging experience that will likely play a more permanent role in healthcare settings moving forward.<sup>21</sup>

In Botswana, the use of a smartphone application was an important tool to communicate with gynecologic oncology patients during a period of lockdown that lasted from April 3 to May 21, 2020 due to the pandemic. The application, Out Patient Care (OPCare) is a smart phone application that was used to communicate with patients regarding the cancellation of appointments and then rescheduling of such appointments. OPCare, previously described,<sup>22</sup> is the only telemedicine system used for oncology care in sub-Saharan Africa, and provided benefit in a country without a widespread integrated electronic medical system. Physicians were able to communicate with patients in real time with text message reminders and tracking missed appointments and cancellations to ensure continuation of gynecologic oncology care.<sup>23</sup>

In Zambia, the most prevalent cancer among women is cervical cancer, and thus Zambia's sole comprehensive cancer center was required during the pandemic to ensure radiotherapy and surgery were continued in a safe environment for both patients and staff. Over 90% of the new cancer cases registering for care at the center present at late stage with severe symptoms. Central to the success of implementation of these measures was a bottom-up approach, where management sought solutions from daily experiences of staff in the hospital. Fractionation regimens for gynecologic cancers changed as follows: cervical external beam radiation therapy stage III (bulky disease) from 50 Gy in 25 daily treatments to 41.25 Gy in 15 daily treatments; for cervical brachytherapy from 7 Gy  $\times$  four daily treatments to 8 Gy  $\times$  three daily treatments or 9 Gy  $\times$  two treatments (1 week apart); and for palliative cervical bleeding or fistula treatment, a previous 15 fraction regimen was proposed to change to 10 Gy  $\times$  two fractions that was 4 weeks apart.<sup>24</sup>

In an online survey conducted among 79 cancer care providers across 18 African countries, Martei et al detailed experiences of cancer centers, patient retention and delay, and treatment modifications. A majority of respondents reported that patient surveillance



visits for their institutions were postponed, and 30% reported that new patients experienced delayed initiation of treatment (most common time period of delay was <2 months). Low income countries were significantly more likely to delay curative radiation treatment compared with lower middle and upper middle income countries. Similar to what was reported in India, more than 75% of respondents reported that their centers had reduction in patient volumes due to fears of exposure to virus, economic, or financial barriers, but also due to national and institutional factors, including restrictions on travel or telemedicine policies in place. This was one of the first surveys to report on the fear of infectivity of the virus, leading to further staff shortages and a decrease in patient volumes in this context.<sup>25</sup>

### Latin America and the Caribbean

A survey by Martinez et al queried 229 radiation–oncology facilities across 15 Latin American and Caribbean countries, noting that treatment for gynecologic primaries or sites of disease were minimally affected compared with other disease sites. Fewer than 10% of centers reported radiation treatment delays for gynecologic disease: cervical 3.5%, uterine 7.8%, and vaginal/vulva 1.7%.<sup>26</sup> This could be related to a preference of surgeons across the region to delay surgical management for about 3 months in an early stage setting, according to a recently published survey, leading patients to seek opportune treatment by other means.<sup>27</sup> Furthermore, the impact on cancer research is yet to be accounted for. A recent publication has revealed that approximately 80% of regional centers have experienced interruptions of trial accrual. This is particularly sensitive in a classically underfunded area, barring risks of trial cancelation or results impairment.<sup>28</sup>

### Brief Note about the USA

Parashar et al published disease site specific guidelines for curative radiation treatment based on their experience of cancer treatment in New York City during the height of the pandemic. These guidelines were based on principles, including limiting surgery and hospital avoidance. For gynecologic cancer, they recommended the utilization of stereotactic body radiation or intensity modulated radiation therapy boost instead of brachytherapy for intact cervix patients, given the limited resource setting of a pandemic that prevents full utilization of operating room space, anesthesia, and surgical equipment.<sup>29</sup> While there are retrospective phase I and II data concerning the use of stereotactic body radiation therapy, the authors comment that stereotactic body radiation therapy does not historically replace brachytherapy, but is an option if brachytherapy cannot be performed.<sup>30 31</sup>

### CONCLUSION

We acknowledge the vast heterogeneity in response to the pandemic based on varying resources, government actions, and societal norms. General principles extracted from published guidelines and real world experiences suggest that several patterns of treatment and organization of care emerged from the challenges of the COVID-19 pandemic. First, there was heterogeneity in the fractionation regimens used during COVID-19 for cervical cancer, depending on the feasibility and comfort level with hypofractionation given the current paucity of data. More common, however,

was the use of limited insertions of brachytherapy applicators and reduced fractionation of brachytherapy. While brachytherapy was recognized as a critical component of gynecologic cancer treatment, efforts were made to include this in the most ethical and safe manner during periods of COVID-19 outbreaks. Brachytherapy use was further limited due to strains in staffing because of its heavy skill based personnel requirement. Because the use of the 9 Gy × two fraction regimen is associated with conflicting long term results, it will be important to follow these patients in the long term. Second, international guidelines may not present treatment options that are feasible for healthcare facilities in low and middle income countries depending on their resource availability. For example, the ability to have a simultaneous integrated boost versus a sequential cone down boost is limited to centers with access to facilities for intensity modulated radiation therapy techniques in order to safely administer such treatment plans. Further, in low and middle income countries, the majority of patients are treated with conventional two-dimensional/three-dimensional conformal radiation therapy and thus some of the recommendations for reduced fractionation schemes with hypofractionation was minimal.

Of note, hypofractionation for cervical cancer is generally less well studied than other disease sites due to the lack of long term data. In a recent international European Society of Therapeutic Radiation Oncology survey, respondents in low and middle income countries were significantly less likely to hypofractionate than their peers in high income countries. A large hesitation in the use of hypofractionation in this context is the lack of long term data and concerns about acute and late toxicity.<sup>32</sup> The Cervix Cancer Research Network, founded by the Gynecologic Cancer Intergroup to increase access to high quality clinical trials, especially among patients in low and middle income countries, have launched two phase II trials to further assess this question. These studies will randomize patients to conventionally fractionated (45–50 Gy in 25 fractions) or hypofractionated treatment (40 Gy in 16 fractions), followed by definitive radical hysterectomy or brachytherapy. Future of hypofractionation to assist in patient access and compliance to radiation in these settings will be further assessed with the results of this trial and will be critical in light of the recent pandemic.<sup>32 33</sup>

Similarly, non-operative treatment alternatives for brachytherapy, such as stereotactic body radiation therapy, are only an option for centers with the resources, technology, and appropriately trained personnel to safely deliver such high dose per fraction treatments. Finally, many centers exemplified the innovative use of existing technologies. Smartphone applications to assist in areas without integrated electronic medicine systems and use of online videoconferencing platforms to assist with multidisciplinary tumor boards or clinics have all been embraced as useful tools during this pandemic.

With the advent of the COVID-19 vaccine, a critical next step for oncologists everywhere will be to work with policy makers to ensure patient and community access to the vaccine. Accounts from oncologists across the globe highlight the resiliency of patients and providers to adapt to current conditions in order to provide safe and effective treatments in the critical times. The many real world accounts shed light on the innovative treatment regimens, workflows, and adaptations made by oncology providers. Many of these accounts stem from accumulation of data during the first year of the pandemic; however, it is critical to continue to follow our patients to evaluate the long term impact on delays to care and

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treatment modifications undertaken. Further, the inequitable distribution and access to COVID-19 vaccination is an imperative point to be addressed for the further care of our patients.

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