ARTICLE

Cervical Cancer in the COVID-19 Era – the Potential Role of Adapting Newer Treatment Protocols

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Abstract: Background: The COVID-19 pandemic has resulted in unprecedented problems in both cancer management and providing a safe organised workflow for oncological health care systems to operate. The treatment of advanced cervical cancer stage IIB - IVA has received higher priority in most international guidelines for risk adaptation in relation to COVID-19 situation. There is an urgent need to revise the established standard treatment protocol of concurrent chemoradiation followed by brachytherapy, usually delivered over 6-7 weeks, which is associated with technical difficulties and would pose risks to both the patient and treating health care personnel.

Aims & Objectives: To propose alternative treatment protocols that are supported by scientific data and may be better suited to meet the needs of the unique situation.

Methods: A systematic literature search was performed using PubMed and other search engines. The studies evaluated were those published from 1990 to April 2020. The focus was on scientific rationale and non-inferiority with standards of care.

Conclusions: The authors propose Simultaneous Integrated Boost for treatment of large volume disease and Stereotactic Body Radiotherapy boost for smaller tumour volumes, where facilities are available. 3DCRT with an integrated or sequential IMRT boost can be considered in institutes with technical limitations.

Keywords: Cervical cancer; SBRT; SIB; EBRT Boost

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1. Introduction

The first appearance of corona virus disease (COVID-19) and the resultant severe acute respiratory distress syndrome (SARS – CoV-2) was reported in December 2019 in China [1]. From that point of time until now, i.e., April 25, the total number of reported cases exceed the confirmed deaths [2-3]. The current pandemic has paralysed healthcare in the management of cancer in more than 150 countries all over the world. The oncology health care systems are facing many hurdles to restart cancer care while optimizing safety to the patients and treating personnel. Cancer patients are mostly immunocompromised, several are in the age group 60 years and above and may also have comorbidities that are associated with an increased mortality.

So, Oncology centres have mostly adopted a policy of risk categorization to stratify patients whose survival is more dependent on immediate cancer treatment over the chance of complications of contracting COVID-19 [4]. Several international guidelines with conceptual framework
from ASTRO, ESTRO, ESMO, UK NHS, Cancer Care Ontario and several more are emerging from regional boards.

In India, gynaecological cancers are the second most common female malignancy. The age standardised incidence and age standardised mortality of carcinoma cervix (Ca. Cx) is 12 to < 15 per 100000 women years in India as per Global Cancer database (GLOBOCAN) 2018 reports [5,6]. India and China together contribute to 35% of the global cervical cancer cases as well as deaths [5]. In most of the conceptual frameworks of risk categorization, locally advanced cervical cancer falls in the first priority level whereas patients who have undergone surgery for Ca. Cx assume the third level of priority [4]. The delivery of concurrent chemo-radiation may be paramount in improving the survival and significantly provide them with a better quality of life. The standard treatment protocols currently may extend to 6-7 weeks, involve daily radiation (5 days/week), concurrent chemotherapy and 3-4 sessions of brachytherapy [7]. This prolonged treatment schedule poses several safety related risks to the patient, treating staff and increases the burden on the limited hospital resources. In several other major cancer sites such as breast, prostate and lung, the international guidelines are strongly advocating hypo-fractionated short course treatments either with shorter high dose regimes or stereotactic treatments where possible.

However, the management of cervical cancers pose several problems that make them unsuitable to such strategies.

Firstly, radiobiology does not support use of hypo fractionated treatment. Majority of cervical cancers are moderately or poorly differentiated, have a high proliferation rate and alpha/beta value in the range of 10 [8].

Brachytherapy is an integral part of treatment of cervical cancer with established survival benefits [9,10] and superiority over other external beam boost techniques [11]. However, in the current COVID scenario, delivery of the same poses several problems such as (i) Delay in treatment in order to restrict the number of brachytherapy procedures per day. (ii) Additional visits to the hospital with additional ward stay and exposure (iii) Burden of the health care system in terms of additional imaging, safety and sterile procedures which would call for exposure of the health care personnel involved. In such a scenario, we have recognized a growing need for evaluating new scientifically sound novel protocols that may help to circumvent some of these problems.

To be noted that these protocols suggested by the authors in this article have been designed to meet the special requirement of the COVID-19 scenario and not to be considered as alternatives to the current standard of care.

Brachytherapy remains the gold standard for focal delivery of a higher boost dose to the primary tumour in the treatment of cervical cancer. The inclusion of brachytherapy has shown advantages in terms of both local control and overall survival compared to teletherapy alone [9,10]. However, in the COVID setup, Brachytherapy may pose additional problems. Cervical dilatation is often challenging after shrinkage of advanced disease and altered anatomy. It often requires anaesthesia, which in turn involves inpatient preparation, OT time and exposure and post-delivery stay. The procedure has to be scheduled and considering the number of safe procedures that can be done per day, this could result in an undesirable prolongation of the overall treatment time.

Over the past few decades, the newer advances in Intensity modulated radiotherapy, the wider availability of image guidance and logistic advantage of adaptive software has rekindled the interest in delivery of External Beam Radiotherapy (EBRT) boost to the primary tumour volumes.

Although most studies have proven inferior, there might be mitigating circumstances that account for this [12,13,14,15]. The treatment cohorts were often heterogeneous, had unfavourable anatomy, non-uniformity of treatment technique and delivery with suboptimal sparing of normal tissues. But under the current circumstances, it is worthwhile to explore EBRT as a potential contingency substitute. We would like to propose two possible models of EBRT that can be considered for adapting to the current COVID-19 set-up.

2. Protocol 1: Simultaneous Integrated Boost (SIB)

2.1. Clinical considerations:

- This might be suitable for large volume primary disease as the dose can be delivered to the distorted anatomy and integrated over a period of time.
- There need not be a different physical treatment setup or additional plan
- Incorporating adaptive re-planning when available can allow for modifications in tumour shrinkage with fast-
er re-planning. Positive nodes can be addressed simultaneously.

• Additional radiobiologic advantages of shortening the overall treatment time addressing accelerated repopulation.

• More homogenous treatment boost in comparison to brachytherapy as the tumour may have relatively hypoxic areas.

2.2 Technical Considerations:

Delivering optimal dose: The total physical dose delivered with SIB technique may be lesser than the 80-90 Gy historically proven to be effective for larger tumours. However, studies have shown that reduction in overall treatment time may partly or completely offset this disadvantage\[16,17\].

The Biological Equivalent dose (BED) formulation\[17,18\]

\[
BED = \frac{nd}{1 + \frac{d}{\alpha/\beta}}
\]

was modified to take the overall treatment time and tumour repopulation into account as follows

\[
BED = \frac{nd}{1 + \frac{d}{\alpha/\beta}} - TF
\]

Where

- \( n \) = number of fractions
- \( d \) = Dose per fraction
- \( TD = \) total time duration (SIB – 35 days vs HDR/SBRT – 56 days)
- \( TK = \) accelerated repopulation time (21-35 days)\[19\]
- \( T_{pot} = \) Potential tumour doubling time (3 – 6 days)\[20\]
- \( \alpha = \) tumour radio sensitivity; ranges from 0.1 Gy\(^{-1}\) (radioresistant) to 0.5 Gy\(^{-1}\) (radiosensitive)

Some interesting observations of this composition was that the tumour control probability favoured simultaneous integrated boost for larger tumour volumes. The sparing of late reacting tissues was also favoured by the SIB concept with a BED of 154.2 Gy with SIB-IMRT vs 162 Gy for WPRT+ HDR (6Gy x 5 fractions)\[17\].

Thus, SIB may theoretically provide a radio biologically feasible alternative for larger volumes when brachytherapy is not a consideration.

Most studies have used the following guidelines for target volume delineation\[16\]: Clinical target volume (CTV) – SIB is delineated based on the findings of clinical examination and the high signal intensities on T2W MRI. The hypermetabolic areas on Positron Emission Tomography (PET) scan have been used in some centres\[21\]. CTV-tumour (CTV-T) includes the CTV-SIB, entire cervix, if not already included within CTV-SIB contour; uterus with bilateral parametrium, ovaries; the entire mesorectum if uterosacral ligament was involved; the upper two-thirds of the vagina; CTV-N includes common, internal, and external iliac, obturator, and presacral nodes. A Planning Target Volume (PTV) expansion of 5mm upon CTV-SIB, 8mm upon CTV-T and 7 mm upon CTV-N is commonly used, which varies according to institutional protocol.

In post-operative cases, the CTV-SIB includes the proximal two-thirds of the vagina and paravaginal soft tissue with a PTV expansion of 5-10mm\[22\].

Dose constraints to OARs are variable but when considering 66Gy to the primary, the following constraints may be considered\[16,22\]:

- \(<50\%\) bladder to receive 50 Gy (V50 < 50%); V64.5 Gy < 20\% for bladder;
- \(<50\%\) rectum to receive 50 Gy, (V50 < 50%); V64.5 Gy < 15\% for rectum;
- \(<30\%\) of small bowel to receive 40 Gy,
- \(<5\%\) of the femoral heads to receive 50 Gy.

Several promising schedules have been evaluated in the past\[17,21\]. Guerrero et al\[17\] suggest treating the larger pelvic PTV at 1.8 Gy per fraction while simultaneously, the cervical PTV boost volume to a higher total dose of 3.1 Gy (total 77.5 Gy). Many other studies have considered SIB in the adjuvant setting after radical surgery\[22\].

Another issue that may be potentially addressed by SIB is the ‘High risk CTV boost’, which indicates area of macroscopic residual disease. In the 2D era, this was done with a midline block and involved extended treatment time. Currently, there is evidence to suggest that such a boost can be dosimetrically achieved with IMRT. Jen-Yu Cheng et al\[23\] have found that both VMAT-SIB and IMRT-SIB as promising techniques for delivering an
additional boost of 5.4 Gy to the parametrium. L.A. Daley et al [24] have evaluated this clinically in 43 patients with locally advanced cervical cancer. The parametrial boost volumes received 53.6-60 Gy in 24-25 Fr. They found the SIB-IMRT to be feasible with no acute grade IV toxicities. The acute grade 3 toxicities were 7% gastrointestinal, 2.3% genitourinary and 16.3% hematologic. However, these patients did receive brachytherapy boost to the residual cervical disease so, it may not be completely representative of the situation when SIB is inclusive of the primary.

A few potential dose regimens that have been evaluated in the past are given in Table 1.

Table 1. Evidences for Protocol 1: SIB

<table>
<thead>
<tr>
<th>Evidence</th>
<th>No. of pts.</th>
<th>Follow up (months)</th>
<th>WPRT Dose/ Dose per fraction (Gy)</th>
<th>Boost Dose/ Dose per fraction (Gy)</th>
<th>SIB technique</th>
<th>Tumour BED (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial EBRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazza et al [16]</td>
<td>30</td>
<td>30</td>
<td>54/1.8</td>
<td>66/2.2</td>
<td>IMRT*</td>
<td>80.5</td>
</tr>
<tr>
<td>Neo-adjuvant/Adjuvant EBRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vande casteele et al [21]</td>
<td>30</td>
<td>24</td>
<td>45/1.8</td>
<td>62/2.4</td>
<td>IMRT*</td>
<td>77</td>
</tr>
<tr>
<td>Wang et al [22]</td>
<td>80</td>
<td>34</td>
<td>50.4/1.8</td>
<td>60.2/2.25</td>
<td>IMRT*</td>
<td>72</td>
</tr>
</tbody>
</table>

*IMRT-Intensity Modulated Radiotherapy


Hypo-fractionated image guided conformal radiotherapy would be closest to mimicking HDR Brachytherapy. It maximizes the therapeutic ratio by allowing for the more circumscribed doses to be delivered. When a sufficient inter-fraction gap is provided, the observed side effects are not inferior to that which may be expected with HDR Brachytherapy [25-29]. From a tumoricidal perspective, a higher BED10 [ achievable with high dose/fraction] should result in better tumour control probability (TCP). However, in the absence of large volume studies or randomized clinical trials, this is difficult to validate.

High dose EBRT Boost can be provided through more than one type of teletherapy technique. With 2-dimensional treatment, it can be delivered as a bicentric arc boost. When 3DCRT is used for delivering Whole pelvic RT, it may be in the form of 3-Dimensional Conformal Radiotherapy (3DCRT) or Intensity Modulated Radiotherapy (IMRT) with Image Guided Radiotherapy (IGRT) boost[30]. Other alternatives include Helical Tomotherapy[31] and proton therapy[32].

3.1 Clinical Considerations

A high dose per fraction EBRT boost might best safely benefit patients with low volume primary disease at presentation. The local response as well as the compromised rectum and bladder mucosa by the CTV-PTV expansions are better served when treating tumour volumes are smaller.

Traditionally, delivery of SBRT boost has been after WPRT. This may not benefit the patient in terms of total duration of treatment. Most centres will be treating a few patients on Saturdays to deliver gap corrections for patients whose treatments were interrupted during the acute phase of lockdown. When primary tumour volumes are small, SBRT could be delivered in a very similar manner as integrated HDR Brachytherapy. The SBRT boost fractions could be scheduled on Saturdays from the second week onwards.

3.2 Technical Considerations

Most studies have used the following guidelines for target volume delineation for SBRT[26,27,31]; Gross tumour volume (GTV) is delineated using the high signal intensities on T2W MRI and findings of clinical examination. The entire cervix and the extra-cervical disease present on the pre-SBRT MRI has been included in CTV-Boost. A modified PTV expansion of 3-5 mm is commonly used, which varies according to institutional protocol.

Although high dose per fraction protocols are the most likely to radio-biologically mimic the standard of care Brachytherapy, they pose several technical uncertainties [33,34].

- There is a higher chance of both tumour miss and unanticipated normal tissue exposure due to movement uncertainties.
- If image guided adaptation is not employed in the weekly boost, there is a risk of creating unwanted toxicity.
- Image guidance and other higher technology may not be accessible to majority of the patients

A number of dosimetric studies have demonstrated an equivalent and occasionally superior target coverage and sparing of normal tissues with SBRT [25-28]. The results of boost treatments with 2D techniques and IMRT are inferior, however, still have acceptable control rates and manageable toxicities.

A few of these studies have been detailed in Table 2. & Table 3.
Table 2. Evidences for Protocol 2: SBRT.

<table>
<thead>
<tr>
<th>Evidence</th>
<th>No. of pts</th>
<th>Follow up (months)</th>
<th>WPRT Dose/ Dose per fraction (Gy)</th>
<th>Boost Dose/ Dose per fraction (Gy)</th>
<th>SBRT Boost setting</th>
<th>Tumour BED (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radical EBRT</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Haas et al[26] (2012)</td>
<td>6</td>
<td>14</td>
<td>50.4-61.2/1.8</td>
<td>19.5-5.6/20/4</td>
<td>CK*</td>
<td>78-85</td>
</tr>
<tr>
<td>Marnitz et al[25] (2013)</td>
<td>11</td>
<td>6</td>
<td>50.4/1.8</td>
<td>30/6</td>
<td>CK*</td>
<td>108</td>
</tr>
<tr>
<td>Mantz et al[28] (2016)</td>
<td>42</td>
<td>62</td>
<td>45/1.8</td>
<td>40/8</td>
<td>NRΨ</td>
<td>125</td>
</tr>
<tr>
<td><strong>Adjuvant EBRT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Molla et al[35] (2005)</td>
<td>7</td>
<td>13</td>
<td>45-50.4/1.8</td>
<td>14-7 - 20/4</td>
<td>LINAC**</td>
<td>84-88</td>
</tr>
<tr>
<td>Jorcano et al[36] (2010)</td>
<td>9</td>
<td>47</td>
<td>45-50.4/1.8</td>
<td>14/7</td>
<td>LINAC**</td>
<td>84</td>
</tr>
</tbody>
</table>

*CK-CyberKnife, **LINAC-Linear Accelerator, ΨNR: Not Reported

Table 3. Evidences for Boost by other techniques

<table>
<thead>
<tr>
<th>Evidence</th>
<th>No. of pts</th>
<th>Follow up (months)</th>
<th>WPRT Dose/ Dose per fraction (Gy)</th>
<th>Boost Dose/ Dose per fraction (Gy)</th>
<th>Boost technique</th>
<th>Tumour BED (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radical EBRT</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Park et al[37] (2004)</td>
<td>10</td>
<td>18</td>
<td>50/2</td>
<td>30/5</td>
<td>3DCRT*</td>
<td>105</td>
</tr>
<tr>
<td>Chan et al[33] (2006)</td>
<td>8</td>
<td>23</td>
<td>45-50/1.8</td>
<td>25.2/1.8</td>
<td>3DCRT*</td>
<td>85-90</td>
</tr>
<tr>
<td>Baraclough et al[34] (2008)</td>
<td>38</td>
<td>27</td>
<td>40-45/2-2.5</td>
<td>15-25/1.8</td>
<td>3DCRT*</td>
<td>66-87</td>
</tr>
<tr>
<td><strong>Adjuvant EBRT</strong></td>
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</tbody>
</table>

*3DCRT - 3-Dimensional Conformal Radiotherapy *IMRT-Intensity Modulated Radiotherapy

4. Discussion

The current COVID-19 Pandemic has inflicted an immense strain and difficult responsibility upon all oncology services. The global pandemic raises three fundamental issues:

1) The optimal treatment of each individual patient

2) The safe delivery of optimal treatment without providing undue risk to the patient or health care personnel

3) The best utilization of the health care systems to serve the maximum number of high priority patients

In this article, the authors have proposed certain adaptations in the standard treatment protocol for advanced cervical cancer that might be temporarily employed to circumvent the crisis.

Although cervical cancer receives high priority for radical radiotherapy in most national and international guidelines, the actual delivery is involved with several hurdles.

The extended 5-7 weeks duration of treatment with separate individual visits for brachytherapy may be deleterious to the patients’ individual risk of exposure to COVID-19. This is especially so as many patients have to travel from distant areas and inpatient facilities will be restricted to emergencies in the COVID-19 set up. The limitations of OT procedures may result in a waiting list that can delay total treatment duration beyond 7 weeks and compromise cancer care.

The authors have proposed revisiting the alternatives of boosting the primary disease with external beam techniques. Even though the scientific data is not robust enough to suggest equivalence, the treatment can be delivered with manageable side effects.

The alternate treatment protocols are

1. Simultaneous Integrated Boost (SIB) with the advantage of reduction in overall treatment time for large volume disease

2. Stereotactic Body Radiotherapy (SBRT) for small volume disease, which can mimic brachytherapy dosimetry to the best advantage. This may have an additional benefit of reduced treatment time if the boost can be delivered on Saturdays.

3. In centres without image guidance, 3DCRT with IMRT boost on weekends or after WPRT.

4. Concentric arc boost in centres with the limitation of 2D facilities

Although these suggested protocols are practical and scientifically feasible, the actual implementation will involve additional problems. Institutes will have to adopt rapid ethical clearance in the interest of COVID-19 emergency. They may have to reframe the cost structure of the treatment to address the new protocols. The Physics department may have to accommodate additional work hours for advanced planning and there may be a strain on the execution of quality assurance protocols.

However, the authors feel that these adaptations if employed have the potential of benefiting the patients with advanced cervical cancer by providing effective radical treatment with a lesser risk of exposure to COVID-19.
It would also have the advantage of helping the radiation oncologists and radiation therapists to deal with the responsibility of safely delivering treatment to the maximum number of deserving patients and reduce the inevitable long waiting lists that exist in the current COVID-19 scenario.

References


