Hypofraction... Revisited: The emerging role of shorter treatment schedules for locally advanced cancers during the COVID-19 pandemic

Authors
Dr Bindhu Joseph¹, Dr Nithin Bhaskar V², Dr Nikhila K R³, Dr Sanjay R⁴, Dr Lokesh V⁵
¹Associate Professor, Department of Radiation Oncology, Kidwai Memorial Institute of Oncology
²,³Assistant Professor, Department of Radiation Oncology, Kidwai Memorial Institute of Oncology
⁴Senior Resident, Department of Radiation Oncology, Kidwai Memorial Institute of Oncology
⁵Head of the Department, Department of Radiation Oncology, Kidwai Memorial Institute of Oncology

Abstract
Introduction: The COVID-19 pandemic is now imposing an immense strain on the oncology health care system, both in terms of optimal cancer care and safe delivery and execution of treatment. The period of lockdown has also created additional concerns over completion of interrupted treatments, progression of disease, the delay and increasing waiting list in the backdrop of limited health care resources and personnel. In Asian countries, a large bulk of patients present with locally advanced cancers of the head and neck, breast and cervix. However other cancers involving esophagus, lung and brain also impose a problem during the pandemic because of the morbidity and mortality associated with postponed treatment.

Purpose and Objectives: In the midst of the COVID-19 pandemic, priority to minimise the risk of exposure of infection to patients and health care personnel is critical in ensuring the sustenance and completeness of treatment. The authors would like to provide optional hypofractionated protocols supported by scientific data that may be used as an interval expedient during this crisis.

Materials and Methods: A systematic literature research was done using Pubmed and other search engines. The focus was on scientific rationale, clinical adaptability, manageable toxicity and with comparable treatment outcomes with the standards of care.

Conclusions: The authors propose shorter, hypofractionated protocols with the option of selective concurrent chemotherapy in the management of head and neck cancer as well as the potential of shorter treatment options for esophageal and lung cancers and high grade gliomas. A few alternatives for an integrated boost to counter the reduced availability of brachytherapy have also been elaborated on.

Keywords: COVID-19, locally advanced cancers, hypofractionation.

Background
The COVID-19 outbreak which started in Wuhan, China, in December 2019 and the subsequent global pandemic has resulted in several difficult challenges in the radiotherapeutic management of cancers. This is especially dramatic for Asian countries where the larger percentage of presentations are locally advanced and mandate early initiation of treatment. Majority of these cancers fall into the high risk group as per the
conceptual frameworks charted out by ASTRO, ESTRO, ESMO, NHS, Cancer care Ontario and several regional boards. We also face a scenario more akin to the late pandemic stage because of the pending backlog of interrupted treatments as a result of stricter curfew restrictions.

In this setting, hypofractionation provides a very attractive and probably a crucial alternative for mitigating the damage done to existing cancer treatments as well as providing a safer alternative for future treatments. In the current article, the authors have attempted to provide evidence for protocols based on hypofractionated schemes that can be safely adopted to suit the COVID situation in a few key sites especially, locally advanced cancers of the head and neck, lung, esophagus and high grade gliomas especially glioblastoma.

Methods
The authors have conducted a detailed literature search covering articles from Pubmed and other search engines. Additional resources included updates from national and international webinars conducted recently addressing the issues faced by the radiation community in dealing with this crisis. The suggestions offered by the authors have been restricted to the management of locally advanced cancer, and the clinical scenario related to the same.

Locally advanced Head and Neck Cancer (LAHNC)
The standard of care for inoperable locally advanced cancers of the head and neck is concurrent chemo-radiation. The most commonly used schedule is 2Gy per fraction to a total dose of 66-70Gy over a period of 7 weeks. For operable cancers a similar need for chemo irradiation is present when high risk factors exist.

The rationale for considering an alternative to the standard of care is the risk to benefit ratio in the pandemic scenario that would favour a shorter treatment duration, thus reducing the chance of exposure and death related to exposure. Even if not associated with serious infection, the positivity alone would result in interrupted treatment till the patient can be safely restarted. In addition to this, the staff who come in contact would need to be quarantined thereby, reducing the manpower. The impact of interruption of treatment and subsequent accelerated re-population will probably adversely impact the anticipated survival. In the past decade the wider availability of advanced technology has rekindled the interest in hypofractionation for counteracting accelerated repopulation. Younger patients with good general condition should still receive the standard of care when feasible.

Scenarios where hypofractionated scenarios can make an acceptable alternative may include:

- Limitation of machine access due to reduction in health care staff being affected/quarantined.
- Unacceptably long delay in initiating treatment because of prioritisation to clear backlog of interrupted treatments.
- Patients older than 65yrs with feeding procedure support and may not require inpatient care.
- As an alternative to boost the therapeutic potential when the facilities to provide concurrent chemotherapy are not available or not safe.

The possible hypofractionated schedules and trial based references are given in Table 1. The authors have only considered schedules that reduce treatment time greater than a week.

Palliative regimens with short weekly regimen (Quad Shot and similar) can be considered for patients with an anticipated survival of > 4 months. This gives an opportunity to consolidate with further cycles of radiotherapy if the patient responds.

Nguyen et al(1) had reported 8 Gy fractionations repeated every week for 3 consecutive weeks to result in good palliation of symptoms. As a high dose per fraction was used, Intensity Modulated Radiation Therapy (IMRT) was required. A continuous regimen with five fraction of 4Gy to a total dose of 20 Gy was tried by Paliwal et al(2) with 2D technique. They reported good symptom palliation with acceptable toxicity (<5%
mucositis). As weekly fractionations may pose an increased risk for acquiring the infection from external contacts, the preferred palliative regimen for the COVID-19 situation would be 20-25 Gy completed over one week. It is advisable when using shorter high dose regimens to anticipate prolonged mucositis and ensure at home supportive care is communicated. Also, it would be wise to stress the importance of proper nutrition to the patients as this can potentially decrease unplanned admissions.

### Table 1

| Radical regimens | Total dose | dose per fraction | OTT | Background | Limitations |
|------------------|------------|-------------------|-----|------------|-------------|
|                  |            |                   |     |            |             |
| **66Gy**         | 2.2 Gy     | 6 weeks           |     | Franzese et al (4) in a randomised cohort of 145 patients observed comparable survival and toxicity | Requires IMRT facilities. |
| **60Gy**         | 2.4 Gy     | 5 Weeks           |     | Tandon et al (5) randomised cohort of 60 patients showed comparable survival and toxicity | Patients in hypo fractionated arm had significantly more fatigue |
| **Palliative Regimens** | **24Gy** | 8Gy (weekly) |     | A critical review by Grewal et al (6) showed 82% symptom palliation with three weekly fractions of 8 Gy | Requires IMRT facilities. |
| **20 Gy**        | 4 Gy       | 5 days            |     | Paliwal et al (2) have reported good symptom palliation with acceptable side effects (mucositis<5%) | |

IMRT = intensity modulated radiotherapy

### Non-Small cell Lung Cancer (NSCLC)

In addition to the possibility of increasing susceptibility of lung cancer patients to COVID-19, the chances of complications once a lung cancer patient gets infected is higher. Minimisation of travel and the risk of exposure would be desirable for safe uninterrupted treatment. The management of stage III and IV lung cancers is of particular concern as the risk benefit ratio is weighed upon by several factors. These include:

1. Possibility of increase susceptibility of the infection to patients during the long 5-6 week course
2. Increases chance of complications from COVID-19 (7)
3. The need for concurrent chemotherapy in advanced disease to allow for optimal survival benefit by standard of care.

These issues were evaluated in detail by the combined ESTRO-ASTRO (8) task group who have issued guidelines as practice recommendations. In the Asian set-up, these may have to be adapted slightly to accommodate the different form of presentation and limitation of advanced technology. As the majority of medical centers are facing a backlog of pending patient treatments, we would directly have to adopt guidelines for the late pandemic stage. There was strong consensus favouring hypofractionated radiotherapy as appropriate when radiotherapy was given alone or when chemotherapy was planned sequentially; and the majority agreed hypofractionation may not be advisable with concomitant radiochemotherapy. This can be supported by emerging evidence favouring a four week treatment regimen for locally advanced NSCLC. Majority of the studies...
have employed modest hypofractionation of 2–3 Gy per fraction. In patients receiving radiation alone, three studies including those by Ngyun et al and Amini et al (9,10), comparing standard fractionation to hypofractionation evidenced comparable toxicity and outcomes. A phase II (11) by Maguire et al has shown that hypofractionated radiotherapy of 55 Gy in 20 fractions delivered over 4 weeks was both feasible and reasonably safe. The survival rates were also promising. The results using the same regimen from four UK centres, involving 609 patients were assessed (12) and the data in terms of survival parameters was promising.

### Table 2

| Evidence         | Dose          | Comparator                 | Response rates, LRC, and OS comparable to those in the cohort treated by a total dose of 60-66 Gy at 2 Gy per fraction over 6 to 6.5 weeks | Retrospective data. KPS 50-70. Only RT | Retrospective data. Only RT |
|------------------|---------------|----------------------------|---------------------------------------------------------------------------------|-------------------------------------|------------------------------|
| Nguyen et al     | 45 Gy/15#     | 60-66Gy/30-33#             | no difference in cumulative incidence of loco/regional or distant failures between the RT groups in the presence of competing factors |                                     |                              |
| Amini et al      | 45Gy/15#      | 60-63Gy over 6 weeks       | Large series of 609 patients. Showed comparable results to those reported for similar schedules |                                     |                              |
| Din et al        | 55Gy/20#      |                            |                                                                                  |                                     |                              |

LRC = Loco-regional control, OS = Overall Survival, RT = radiotherapy, # = fractions

**Locally Advanced Cervical Cancer**

Two thirds of all locally advanced cervical cancers present at Figo stage III/IV (13) in India. Concurrent chemo-radiation (CCRT) followed by Brachytherapy (BT) is the established standard of care for locally advanced cancers of the cervix which may be paramount to improving survival and providing a better quality of life (13). The effect of COVID-19 pandemic in the treatment of cervical cancer is two-fold. The extended concurrent external beam component of treatment requires 5-6 weeks to deliver 45-50 Gy with conventional fractionation. The second problem is the integration of brachytherapy boost to the high risk tumor volume without an unacceptable treatment gap. It is essential to note that locally advanced cervical cancers, with large volume residual disease post EBRT, would benefit only from advanced applications such as hybrid or interstitial brachytherapy, which may not be feasible in the current COVID-19 setting where resources are constrained.

To address the first issue, the authors have reviewed studies considering hypofractionation of the external beam component of treatment. The various schedules used have been listed in Table 3. All these employed 2-D conventional Radiotherapy. Although the local control reported were non inferior, acute grade 2 toxicity of > 20% as well as significantly higher rates of late proctitis and cystitis were observed. The chances of higher acute toxicity would result in treatment interruptions and defeat the purpose of planning a shorter treatment regimen. Radiobiological response pattern and sensitivity of the critical normal structures ie., rectum and bladder would preclude a safe response when larger volumes are treated to higher doses. The authors would recommend employing such regimens with extreme caution, using advanced technology and preferably limited to a severe shortage of resources. The use of concurrent platinum chemotherapy may accentuate the acute toxicity and may preferably be avoided in the current COVID-19 scenario.
Table 3

Hypofractionated Regimen for Radical WPRT

| Evidence | EBRT dose | Dose per fraction | Background | Limitations |
|----------|-----------|-------------------|------------|-------------|
| Mishra et al (14) (2017) | 45Gy/18 Fr | 2.5 Gy | Local control rates comparable to the conventional fractionation, Higher grade 2 toxicity but not statistically significant | Late toxicities not reported, Concurrent cisplatin at similar dose as with conventional fractionation may be responsible for numerically higher grade 2 toxicity |
| Mahobia et al (15) (2015) | 42Gy/15 Fr | 2.8 Gy | Local control and disease free survival at one year was comparable to conventional fractionation, | Statistically significant higher incidence of acute toxicities - vomiting, proctitis & cystitis, probably due to use of concurrent Cisplatin with hypofractionation |
| Komen A.A et al (dissertation) (2014) | 40Gy/16Fr | 2.5 Gy | Local control comparable to conventional fractionation of other studies. Acute Toxicities limited to grade 2. Concurrent chemotherapy not used. | No direct comparison with conventional fractionation |
| Muckaden et al (16) (2002) | 39 Gy/13 Fr | 3Gy | Local control and survival at 5 years comparable to conventional fractionation | Higher grade 2 acute rectum & bladder toxicity |

Patients with advanced disease presenting with severe vaginal bleeding/ bilateral hydroureteronephrosis with deranged renal parameters or severe pelvic pain may be beyond the possibility of cure. Such patients, who are expected to have a survival of less than a year may be considered for palliative radiotherapy. The widely spaced palliative regimen of once a month dose of 10 Gy/Fraction suggested by several studies (17–20) (21) may be revisited in the current covid scenario, to minimize the patient visits as well as achieve the intended palliation. The PMH 0-7-21 schedule of 7 Gy per fraction on day 0, day 7 and day 21 is another useful option for palliation of symptoms (22)

The second issue of delivering the boost treatment, however, does have some promising alternatives that can be considered in the COVID-19 situation with reduced access to brachytherapy facilities or timely treatment.

1. Simultaneous integrated boost (SIB):

Guerrero et al (23) used SIB to simulate equivalent plans for patients with stage III cervical cancer to an total dose of 77.5 Gy with comparable toxicity parameters to the standard regimen. In this study the cervical boost volume received 3.1 Gy/Fraction. A few studies that have clinically employed SIB-IMRT are given in table 4.

Clinical advantages: This might be suitable for large volume primary disease as the dose can be adapted to the distorted anatomy. Incorporating adaptive re-planning when available can allow for faster re-planning and positive nodes can be addressed simultaneously. The major limitation would be the availability of the higher technology required to deliver image guided treatment.
Table 4

| Evidence | DPRT Dose/ Dose per fraction (Gy) | Boost Dose/ Dose per fraction(Gy) | Background | Limitations |
|----------|----------------------------------|---------------------------------|------------|-------------|
| **Radical EBRT** | | | | |
| Mazzola et al (24)(2017) | 54/1.8 | 66/2.2 | SIB in 30 patients > 70 years old, provided comparable LC and 3 year OS with conventional fractionation, Acute toxicities limited to Grade2. | PET-CT based target delineation and VMAT plans, which may not be available in all centres |
| Vandecasteele et al (25)(2013) | 45/1.8 | 62/2.48 | SIB in 30 patients, No grade 3 and above acute toxicity of bladder/recum. | Used as neoadjuvant CRT-RT, pts underwent surgery, so cannot comment on local control |

2. Hypofractionated boost SBRT/IMRT/3DCRT:

   Hypofractionated image guided conformal radiotherapy would be the closest to mimicking HDR Brachytherapy. It maximizes the therapeutic ratio by allowing for a more circumscribed dose to be delivered. The advantage also applies to delivery, which may be more widely feasible. A hypofractionated boost can be delivered using 3 dimensional Conformal Radiotherapy (3 DCRT) or via IMRT/IGRT and also with 2D technique using bicentric arcs. Scheduling the delivery of hypofractionated EBRT boost on Saturdays may be done alike interdigitating Brachytherapy. Clinical examples of protocols that have employed the above are given in table 5

Even though the scientific data is not robust enough to suggest equivalence, the treatment can be delivered with manageable side effects and considerable efficacy in terms of safe completion of treatment within a favourable time frame.

Table 5

| Evidence for SBRT boost | WPRT Dose/ Dose per fraction (Gy) | SBRT Boost (Dose per fraction) | Background | Limitations |
|------------------------|-------------------------------|-------------------------------|------------|-------------|
| Haas et al (26)(2012)  | 50.4-61.2/1.8                 | 19.5/6.5–20/4                | CK boost used, Tumor BED = 78-85 Gy achieved, 100% LC; no >Grade 2 toxicity | Limited no. of patients; 6 months follow up |
| Marnitz et al (27)(2013)| 50.4/1.8                      | 30/6                         | CK boost used, Tumor BED = 108 Gy achieved, 100% LC; no >Grade 2 toxicity | Limited no. of patients, 14 months follow up |
| Kubicek et al (26)(2013)| 45/1.8                        | 25/5                         | Tumor BED=77 Gy; 75% LC | MRI were used for target delineation for boost phase, IGRT with use of organ implanted radio-opaque fiducial markers. 1/11 pts Grade 3 acute proctitis |
| Hsieh et al (29)(2013) | 50.4/1.8                      | 16-27/3-4.5                  | Tumor BED=91.2 Gy; 78% LC at 3 years; | Limited no. of patients 1/9 pts Grade 3 acute proctitis |
| Mantz et al (30)(2016) | 45/1.8                        | 40/8                         | Tumor BED of 125 Gy achieved, 78.6% LC at 5 years; no > Grade 2 toxicity | PET/CT & MRI were used for target delineation for boost phase, IGRT with use of organ implanted radio-opaque fiducial markers. |
Evidence for 3DCRT boost

| Evidence for 3DCRT boost | WPRT Dose/ Dose per fraction (Gy) | 3DCRT Boost Dose/ Dose per fraction (Gy) | Background | Limitations |
|--------------------------|-----------------------------------|------------------------------------------|------------|-------------|
| Park et al (31) | 50/2 | 30/5 | Total tumor BED of 105 Gy | IGRT with use of organ implanted radio-opaque fiducial markers. |
| Chan et al (32) | 45-50/1.8-2 | 25.2/1.8-2 | Total tumor BED of 85-90 Gy | |
| Barraclough et al (33) | 40-45/2-2.5 | 15-25/1.8-2.5 | Total tumor BED of 87 Gy, comparable local control, 3 year overall survival and toxicity profile | |

BED = Biological effective dose; CK=CyberKnife; LC=local control

### High grade Glioma

Even though high grade gliomas carry a poor prognosis, radiotherapy with concurrent chemotherapy has shown to improve survival\(^\text{34}\). Surgery followed by radiotherapy to a total dose of 60 Gy over a period of 6 weeks with concurrent chemotherapy remains the standard of care in good performance patients with Glioblastomas.\(^\text{34}\) In the pandemic scenario, these patients need some special mention.

- The neutropenia and lymphopenia as a result of concurrent temozolomide can be risky in patients with increased susceptibility to COVID 19 [age >65, KPS <50 and uncontrolled comorbidities.]
- The neurologic deficits that accompany the disease make them dependent on health care provider support and might pose a problem in terms of the need for prolonged in-patient admission.
- Benefits of hypofractionation have already been proven in low performance and elderly patients with glioblastoma\(^\text{35–37}\). However during the pandemic it may also be considered for providing a better risk benefit ratio to patients less than 65 years with significant comorbidities. MD Anderson has come out with practice guidelines to address this scenario.

### Table 6

| Evidence | Clinical condition | Dose investigated | Background |
|----------|-------------------|------------------|------------|
| Roa et al\(^\text{38}\) | > 60yrs | 40Gy/15fractions | no survival difference when compared to 60Gy/30# |
| J Perry et al\(^\text{37}\) | Age > 65yrs, good GC | 40Gy/15fractions with conc. TMZ | Survival benefit with adding conc TMZ with 40Gy/15# |
| Mallick et al\(^\text{39}\) | Age <65yrs. KPS >60 | 60Gy/20fractions: SIB with conc. TMZ | Comparable survival outcomes with 60Gy/30# with TMZ |

TMZ = temozolamide, SIB= simultaneous integrated boost, \# = fractions

### Esophageal cancer

The commonest presentation of advanced esophageal cancer in Asian countries is potentially resectable and inoperable. Standard treatment for such scenarios consists of neoadjuvant chemoradiotherapy followed by surgery or definitive chemo irradiation. In addition to the long treatments, the associated dysphagia can lead to increased weight loss and associated need for inpatient care. It is preferred to consider a lower threshold for enteral nutrition to avoid acute admissions and rapid morbidity of early onset dysphagia\(^3\).

Hypofractionation may be considered in the scenario of 1. Patients unfit for surgical management after neoadjuvant chemotherapy.
Pre-operative set up where facilities for radical surgery are still functional. Radical definitive radiotherapy. Even though there are limited studies comparing neoadjuvant to radical chemoradiation in esophageal cancer, there is promising data to suggest they might have comparable outcomes. The option of deferring 5Fu may be considered in the concurrent set up to avoid the need for inpatient care. Weekly platinum based chemotherapy with or without paclitaxel can be considered as an alternative.

If the risks of prolonged treatment are high and chemotherapy facilities are limited hypofractionated radiotherapy maybe a viable option. A recently published retrospective series by Jones et al. has looked into 50Gy in 16 fractions for tumors up to 5cm and 50-52.5 Gy in 20 fractions for tumors up to 10cm in length. They described the regimen to be safe and tolerable with promising survival outcomes. A few options of hypofractionated treatment regimens are given in table 7.

| Table 7 |
|-------------------|-----------------|-----------------|
| Total Dose        | dose per fraction | Background                                      | Limitations |
| Neo-adjuvant      |                  |                                               |             |
| 30 GY/10 Fractions| 3 Gy             | Jiahua Luy et al (2019) in a recent series of 110 patients have found pathological downstaging similar to CRT with no additional morbidity. | IMRT        |
| 40Gy/15 fractions | 2.67 Gy          | Ning Li et al (2018) established this schedule as optimal MTD (maximal tolerated dose in Gastric cancer) | IMRT        |
| Radical           |                  |                                               |             |
| 54-60Gy           | 3Gy              | Maj B et al (2012) in an RCT with 110 patients found equivalent local control |             |
| 50Gy              | 3.12 Gy          | Christopher M Jones et al observed similar survival |             |
| CRT = concurrent chemo-radiotherapy, IMRT = intensity modulated radiotherapy, RCT = randomised controlled trial |

Summary
The COVID-19 Pandemic has and will continue to have a significant impact on cancer treatment and care. The treatment recommendations suggested by the authors are only temporary alternatives that can be considered to mitigate the current burden on the radiotherapy community and are no way to be considered as substitutions for the standard of care.

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