Review Article

Role of Altered Fractionation in Radiation Therapy with or without Chemotherapy in Management of Carcinoma Cervix: Time to Revisit in the Current COVID-19 Pandemic

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Abstract

Severe acute respiratory syndrome coronavirus 2 as COVID-19 virus has affected the entire world and so to the cancer care and health-care facility. Cancer cervix is one of the common malignancies among women in developing and underdeveloped countries. Various challenges are being faced by patients and health-care providers to deliver optimal treatment under prescribed time frame. Faster delivery of whole treatment is desirable in the current pandemic. Overall treatment time in cancer cervix has prognostic value. Adoption of altered fractionation to delivered external beam radiation therapy could be a method for faster delivery of whole treatment. Altered fractionation such as hyperfractionation (HFX), hypofractionation, and accelerated fraction alone or with HFX has already been experimented for the past three decades. The total duration of treatment has been significantly reduced without addition of much toxicity. Few studies had also highlighted the feasibility of addition of chemotherapy to such fractionation schedule. However, prospective studies are still warranted to generate data to further support its use in the future.

Keywords: *Accelerated fractionation in cancer cervix, altered fractionation in cancer cervix, hyperfractionation in cancer cervix, hypofractionation in cancer cervix, severe acute respiratory syndrome coronavirus 2*

Introduction

Severe acute respiratory syndrome coronavirus 2 as COVID-19 virus has hit the entire world, and approximately more than 30 million people worldwide have been affected so far.[1] The infection rate is still not under control and getting worsened each day with increasing number of active cases worldwide. India as a developing country is among the 2nd worst affected with more than 6 million population got infected so far and with still rising trend of incidences of infection.[2]

Cancer incidences in India are about 1.1 million cases per year, and approximately 0.7 million succumb to death annually. Among all sites, incidences of cervical cancer annually amount approximately 96,000 with nearly 60,000 death/year as per a recently published GLOBOCAN 2018 report.[3]

Due to COVID-19 infection and several government advisories for containment of the rate of infection, cancer treatment has also got severely jeopardized.[4]

Various associations and authors worldwide have guided with few novel approaches for timely and prompt delivery of cancer treatment during the current pandemic. A recent advisory from the Association of Radiation Oncologists of India emphasized upon introducing radiation therapy (RT) with altered fractionation, to curtail treatment time for patients, without compromising efficacy of treatment.[5]

Cancer cervix is the third most common cancer in India among both sexes and second most common in female population. After the National Cancer Institute alert in 1999, concurrent chemoradiotherapy is the standard of care for Stage IB2–IVA in carcinoma cervix.[6]

RT for carcinoma cervix includes external beam radiation therapy (EBRT) followed by brachytherapy to attain equivalent dose in 2 Gy/fraction (EQD2) of 85–90 Gy to point A. Radiation treatment by conventional

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fractionation is delivered at 1.8-2 Gy per fraction in 5 days a week and therefore entire treatment duration ranges from 5-6 weeks.

Considering the current pandemic, and daily visit to hospital for this long duration of treatment could be a risk for patient to get infected. Therefore, patient would be skeptical to continue or seek the prescribed treatment. Furthermore, arrangements for this lengthy stay for entire period could be another challenge for patients and caregivers in view of government advisory for lockdown and suspension of services.

Hence, a possible solution to circumvent these problems for both health care providers and patients could be the adoptions of altered fractionation in the EBRT schedule. Guidelines and policies published during the current pandemic have also advocated the adoption of altered fractionation as hypofractionation for treatment in head and neck, brain tumors, and sarcomas.[7-9]

Altered fractionation with or without chemotherapy in cancer cervix had already been experimented for the past three decades through various Phase I/II clinical trials. Results of most studies except few have shown it to be equivalent to conventional treatment with no added increase in acute and late normal tissue toxicities.

Material and Methods

We did a literature search from PubMed Central and Google Scholar with keywords "hypofractionation in Cancer Cervix," "hyper-fractionation in cancer cervix," "accelerated fractionation in cancer cervix," "altered fractionation in cancer cervix," "chemoradiotherapy with hypofractionation in cancer cervix," "six fraction radiation in cancer cervix," "accelerated fractionation with chemotherapy in carcinoma cervix," and "hyper fractionation with chemotherapy in cancer cervix." We selected a total 22 studies including both retrospective and prospective, which have described EBRT delivered with adopting altered fractionation schedule with or without chemotherapy for the management of carcinoma cervix.

Studies which included altered fractionation as boost therapy after definite treatment were excluded.

The aim is to determine the feasibility and safety of altered fractionation with or without chemotherapy, so that it could be embraced in management of carcinoma cervix in the current pandemic situation.

Hyperfractionation schedule in external beam radiation therapy in cancer cervix

Altered fractionation as hyperfractionation (HFX) is defined as treatment delivered in small dose per fraction schedule (<1.8 Gy) as twice daily with a gap of usually 6 h between two treatment. Treatment time in HFX is usually equivalent or less than that of conventional fractionation duration.

Studies on RT for cancer cervix about 2–3 decades back had mainly focused on such schedule to augment the clinical outcome till concurrent chemoradiation became as standard of care. Different studies which had adopted this fractionation schedule are summarized in Table 1.

Faria *et al*. implemented RT with HFX alone to a total dose of 72 Gy without brachytherapy. The study reported as high as 74% rate of acute Grade II bowel toxicity, which could be attributed due to high delivered pelvic dose of radiation.[10] Similarly, a prospective study by Varghese *et al*. reported to be the first experiment on HFX in cancer cervix. Patients with Stage IIB–IIIB were treated to 60 Gy with 1.2 Gy twice-daily fractionation followed by intracavitary brachytherapy of 30 Gy to point A using low-dose-rate (LDR) brachytherapy.[11] These two experiments were Phase I/II study which tested the dose escalation in order to enhance tumor control probability. Compared to conventional treatment, the study arm reported higher bowel toxicity both at acute and late stages.

However, studies reported by Komaki *et al*. and Gynecologic Oncology Group (GOG) 8801 and 8901 did not have a higher rate of acute or late toxicities because their prescribed pelvic dose was limited to 24–57 Gy and delivered with HFX schedule.[12,13] GOG 8801 and 8901 also tested the addition of chemotherapy to HFX regimen along with dose escalation of radiation dose. Their results suggested that 57.5 Gy of EBRT with chemotherapy is the maximum tolerable limit for pelvic radiation followed by single session of intracavitary brachytherapy of 35 Gy to point A. A study also aimed to assess the feasibility of reducing the treatment duration by adopting such fractionation schedule. The average treatment time among all dose levels ranges between 35 and 49 days.

HFX has also been experimented by Grigsby *et al*. among patients with positive para-aortic lymph node (LN) at presentation. Total 29 patients were treated with both pelvis and para-aortic LN field to dose 48 Gy and 54 Gy, respectively, followed by 1–2 session of brachytherapy to achieve dose of 85 Gy to point A. Concurrent cisplatin and 5-fluorouracil were also allowed. Total 69% of patients could complete prescribed treatment with 28% reported to be had Grade IV toxicity among all systems. Result did not suggest an advantage of HFX over standard fractionation.[14]

Apart from these, a Korean study by Jun-Sang Kim *et al*. investigated concurrent HFX in patients with recurrent LN at para-aortic region who were treated previously either by definite or postoperative radiotherapy. Para-aortic radiation portal includes upper border of T12 to lower border at L5-S1 junction and boost by lateral field in view to spare spinal cord. Posttreatment 3-year overall survival (OS) was 19% and median survival 21 months. The study did not reported a higher rate of bowel toxicity even though a considerable volume of bowel would also have got simulataneously irradiated. Interestingly, there was a

Table 1: Studies including hyperfractionation radiation with or without chemotherapy in cancer cervix

Authors and year of study	Study arm	Number of patients	Dose, fractionation, and treatment time	OS	Acute toxicities	Late toxicity
Faria and Ferrigno 1997[10]	Hyperfractionation alone	23	72 Gy/60 fractions/1.2 Gy BID/30 days Field reduction at 50.4 Gy	40 months OS-43%	Grade III-IV - 0%	Grade III-IV - 9%
Varghese *et al*. 1992[11]	Hyperfractionation alone versus conventional fractionation	15 each arm	60 Gy/50 fractions/1.2 Gy BID/5 weeks versus 50 Gy/25 fractions/5 weeks	NR	Grade II GI - 94% versus 20% Grade III-IV - no difference	5.4 times more bowel complication with hyperfractionation $P<0.0006$
Komaki *et al*. (RTOG 8805) 1994[12]	Hyperfractionation alone	81	24-48 Gy/1.2 Gy BID	3 years OS-61%	Grade III-IV - 15%	Grade III-IV - 4%
GOG 8801[13]	Hyperfractionation alone with hydroxyurea	38	48 Gy/40 fractions, 52.8 Gy/44 fractions, 57.6 Gy/48 fractions, each 1.2 Gy BID dose	2 years-60%	NS	Grade III-IV - 16%
GOG 8901[13]	Hyperfractionation with cisplatin and 5 FU	30	48 Gy/40 fractions, 52.8 Gy/44 fractions, 57.6 Gy/48 fractions, each 1.2 Gy BID dose	2 years-80%	NS	Grade III-IV - 6%
Grigsby *et al*. 1998[14]	Hyperfractionation + cisplatin 75 mg/m^2 + 5 FU 1000 mg/m^2	29	Pelvis 24-48 Gy/1.2 Gy BD Parametrium 12-36 Gy/1.2 Gy BD Para aortic 48 Gy boost till 54-56 Gy	2 years OS-47%	Grade IV - 28%	NR
Kim *et al*. 2003[15]	Hyperfractionation + paclitaxel 30 mg/m^2	12 (PALN recurrent)	60 Gy/1.2 Gy BID/5 weeks (boost after 50.4 Gy)	3 years-19%	Grade III-IV - 16% (2 pts)	Grade III-IV nil

NR: Not reported; PALN: Para-aortic lymph node; NS: Not significant

survival benefit in patients who had recurrent disease after 24 months compared to <24 months with a median survival of 45 months and 13 months, respectively ($P = 0.026$).[15]

Conventional treatment of carcinoma cervix is concurrent chemoradiation with chemotherapy as weekly cisplatin 40 mg/m^2. The usual total duration of EBRT is 5–6 weeks depending on dose and fractionation selected. Duration in HFX regimen is either equivalent or couple of days less than conventional regimen. Studies described in Table 1 have a treatment time range between 4 and 5 weeks. However, a logistic issue attached is twice-daily treatment.

Hypofractionation in cancer cervix

Hypofractionation by definition is delivering RT with dose/fraction >2.2 Gy, with total delivered dose and total treatment time which is less than conventional regimen. Hypofractionation in carcinoma cervix has gained a recent attention. Few multicentric trials are still recruiting patients under Phase II studies to explore the benefits of hypofractionation over conventional fractionation. Various studies which has tested hypofractionation in treatmnet of cancer cervix are summarised in [Table 2].

Earlier studies such as by Komen *et al*. used hypofractionation alone as curative intent among 104 patients, with 2 years of OS 94%, without much added adverse toxicities.[16] Similarly, a study by Tata Memorial Hospital concluded that hypofractionation has a similar 5-year clinical outcome to conventional RT alone with no added toxicities.[17]

This fractionation regimen has also been used as palliative intent as by Ming Yin *et al*. and Kim *et al*. whose results interpreted that hypofractionation is safe and doable without having high rate of acute or late toxicities.[18,19]

It is known that a combination of chemotherapy with RT increases the effectiveness of RT. A prospective Phase I–II study by Viegas *et al*. investigated twice-daily hypofractionation with doublet chemotherapy in treatment of Stage IIIB carcinoma cervix. The total EBRT dose delivered was 40 Gy and brachytherapy was interdigitated between with LDR to dose of 35 Gy to point A. Treatment was well tolerated without acute severe toxicity with 3-year and 5-year OS 76% and 59%, respectively.[20]

Two currently ongoing trials, NCT 04070976 and Hypofractionated External-Beam Radiotherapy for Intact Cervical Cancer (HEROICC) Trial, are exploring

Table 2: Studies including hypofractionation radiation with or without chemotherapy in cancer cervix

Authors and year of study	Study arm	Number of patients	Dose, fractionation, and treatment time	Survival	Acute toxicities	Late toxicity
Komen 2014[16]	Hypofractionation RT	104	40 Gy/16 fractions/3 weeks	2-year OS - 94%	1/104	7/104
Muckaden *et al*. 2002[17]	Hypofractionation RT	62	39 Gy/13 fractions/2.5 weeks	5-year OS - 50%	Grade III-IV-10%	Grade III - 5%
Lin *et al*. 2016[18]	Hypofractionation RT	35	28 Gy/8 fractions/2 weeks Quad shot (14 Gy)	5-year OS - 14%	NR	Grade III-IV: 6%
Kim *et al*. 2013[19]	Hypofractionation RT	17	25 Gy/5 fractions/1 week	Median - 7.8 mos	Grade III-5%	Grade III-IV - 0%
Viegas *et al*. 2004[20]	Hypofractionation RT + Cisplatin 15 mg/m^2 + 5 FU 400 mg/m^2	34	40 Gy/16 fractions/2.5 Gy BID/61 days	5-year OS - 59%	Grade III-IV-0%	Grade III-IV GI - 10%
NCT 04070976 July 2019-December 2022)[21]	Hypofractionation with CDDP 40 mg/m^2	82	37.5 Gy/15 fractions/3 weeks	NR	NR	NR
HEROICC trial[22]	Hypofractionation RT + weekly CDDP 40 mg/m^2 × 5 cycles	Ongoing	48 Gy/15 fractions/3 weeks (SIB)	NR	NR	NR
Mahobia and Rewadkar 2015[33]	Hypofractionation RT + Cisplatin 35 mg/m^2	30	42 Gy/15 fractions/3 weeks	1-year DFS-50%	NR	NR

NR: Not reported, RT: Radiation therapy, CDDP: Cisplatin plus radiotherapy, OS: Overall survival, DFS: disease free survival, SIB: simultaneous integrated boost

Table 3: Studies including accelerated radiation with or without chemotherapy in cancer cervix

Authors and year of study	Study arm	Number of patients	Dose, fractionation, and treatment time	Survival	Acute toxicities	Late toxicities
kavangah *et al*., 2001[23]	Accelerated fractionation only	20	59.4 Gy/34 fractions/5 weeks	7-year LC and OS - 81% and 36%	Grade III - 10%	Grade III-IV - 40%
Macleod *et al*., 1999[24]	Accelerated hyperfractionation (AHFX) RT	61	57.5 Gy/46 fractions/1.25 BID/5 weeks	3-year OS-38%	65%	15%
Ohno *et al*., 2008[25]	Accelerated hyperfractionation only	120	50 Gy/30 fractions/4 weeks, midline shielding at 30 Gy	5 years - 70%	Grade III-IV 3%	Grade III-IV 5%
Yoon *et al*., 2006[26]	Accelerated fractionation only (6 fractions/week)	43	50.4 Gy/28 fractions/4.5 weeks	3-year OS - 74.7%	4%	2.2%
Chhaya *et al*., 2012[27]	Accelerated fractionation only (6 fractions/week)	28	50 Gy/25 fractions/4.1 weeks	NR	17 events	NR
Sharma *et al*., 2016[28]	Accelerated fractionation only (6 fractions/week)	33	50 Gy/25 fractions/4.1 weeks	3-year OS - 61%	21 events	NR
Kumar *et al*., 2019[29]	Accelerated fractionation (6 fractions/week) + cisplatin 40 mg/m^2	17	46 Gy/23 fractions/4 weeks	3-year OS - 63%	17%	0%

NR: Not reported, RT: Radiation therapy, OS: Overall survival

feasibility and benefits of combined concurrent chemotherapy with hypofractionation regimen. However, these two studies differ in their inclusion criteria as former study included mainly locally advance cases of cancer cervix while later seeks to include patient with small bulk of disease with low burden of nodal presenation.[21,22]

One major benefit which is evident forms all these studies that hypofractionation decreases treatment time from 5 weeks to 3 weeks or less without added toxicity.

Accelerated fractionation in carcinoma cervix

Another attractive approach in order to reduce treatment time and augment the efficacy of radiation is adoption of

accelerated fractionation by delivering extra fraction on weekends or adding on a particular day of treatment. This regimen had been explored either as radiation alone or with addition of chemotherapy. This regimen had been explored either as radiation lone or with addition of chemotherapy has been summarised in [Table 3].

A pilot study tested concomitant boost accelerated superfractionated radiotherapy in Stage III–IVA patients with total 59.4 Gy in 34 fractions through EBRT followed by brachytherapy for total dose 85–90 Gy to point A. The local control and survival were higher than matched standard radiotherapy regimen (P = 0.1 local control, 0.09 survival).[23] Similarly, Craig *et al*. and a multi-institutional study had adopted acceleration along with HFX to augment the delivered dose along with reducing treatment time. A later study included total 120 patients with Stage IIB–IIIB, and the delivered dose to the whole pelvis was 50 Gy/30 fractions/1.5 Gy twice daily for the first 2 weeks using four-field box technique and central shielding at 30 Gy.[24,25]

Radiation with accelerated fractionation alone has also been experimented to compare the efficacy against conventional chemoradiation. Results of Sang Min *et al*., Roy *et al*., and Sharma *et al*. inferred that delivering 6 fractions per week of radiation alone is nontoxic for patients with added advantage of a week earlier treatment completion.[26-28] Yet, another Phase II study by Kumar *et al*. concluded that accelerated radiation with chemotherapy is comparable to conventional chemoradiation both in terms of survival and toxicities. Benefit derived from such regimen is a week reduction in treatment time and also escape from an extra cycle of chemotherapy.[29]

Which fractionation to choose and why: An opinion

Clinical outcome in carcinoma cervix also depends on overall treatment time (OTT). Petereit *et al*. suggested an optimal duration of OTT of <55 days, and extension beyond this results in detrimental clinical outcome.[30] Accelerated repopulation in carcinoma cervix has been predicted to start as early as after 19 days and so delaying the treatment or treatment break could compromise the desired clinical outcome.[31]

Adoption of altered fractionation in cancer cervix has two major benefits. First, it completes treatment before conventional schedule. Second, the delivered effective dose could be higher than standard schedule considering time factor for calculating biologically effective dose (BED). BED equation with repopulation: BED = N. d (1+ d/a/b) kT, where N = number of fractions; d = dose per fraction; k = tumor growth rate (assumed to be 0.3 Gy/day); T = time after repopulation is initiated (repopulation assumed to occur after 19–21 days).

The current COVID-19 pandemic situation has brought a huge challenge for physician, patients, and caregiver to adhere to recommended treatment time. Visit to treatment facility, nationwide suspension of transport facility, and department shutdown due to COVID-19 infection are few such challenges are getting faced by both health care facility and patient care givers during current pandemic.

Nevertheless, choosing altered fractionation for early completion of external beam radiation could be a possible solution.

Comparing above, hypofractionation regimen decreases absolute treatment time significantly by 2 weeks. This decrease in treatment time shall prevent accelerated repopulation and hence higher BED as described above. Evidence in support of this fact is presented by meta-analysis of two randomized clinical trials BC2001 and BCON looking into role of radiosensitizing drug in muscle-invasive bladder cancer. Total 782 patients were randomized to receive 64 Gy in 32 fractions over 6.5 weeks to 55 Gy in 20 fractions over 4 weeks. The hypofractionation arm has a better local control rate by 29% compared to the conventional arm though BEDs were 70.1 Gy and 76.8 Gy (a/b = 10 Gy), respectively.[32] This example shows that larger actual BED could be achieved which could translate into better clinical outcome by faster delivery of whole treatment.

Another fractionation regimen which could be promising to use is accelerated fractionation with or without chemotherapy. Benefit of such regimen is completion of treatment 1 week before conventional treatment. Furthermore, dose and fraction size of RT are equivalent to conventional and so fear of adding severe toxicity during treatment is minimal even though treating by conventional four-field box technique. Few studies described above have also compared delivering six fractions of RT alone in patients with comorbidities found unsuitable for addition of chemotherapy to EBRT. The results have shown to be equivalent in terms of survival and toxicity. Addition of chemotherapy to accelerated fractionation can be feasible for patients which are suitable for chemotherapy. The results of a study by Kumar *et al*. suggest that it does not add toxicities over conventional treatment. However, the OTT is reduced significantly by 6 days (P = 0.004).[33]

HFX regimen in general is not much preferred by majority of the treatment centers. Although results in cancer cervix are encouraging, it has various logistics issues. Patients have to come or wait to complete twice-daily treatment. Furthermore, such fractionation adds acute toxicity and patients may need admission for management which could add the risk of infection in the current situation.

Since evidences for the use of concurrent chemotherapy with altered frcationation is still not robust to consider this regimen as standard treatment. Therefore, its addition to radiation could depend on suitability of patients and physician discretion. However, even if concurrent chemotherapy is warranted with radiation, a number of cycles required shall also be less due to early completion

of treatment. Results of two ongoing prospective trials, NCT 04070976 and HEROICC trial, shall guide us to use chemotherapy with altered fractionation in the future.

Most of the above-illustrated studies were carried in period when advance techniques of radiation delivery were lacking or were not used. Hence, incorporation of modern precise techniques such as intensity-modulated radiation therapy or image-guided radiation therapy in treatment delivery could further enhance clinical outcome with limited treatment toxicities.

Conclusions

Delivering EBRT through altered fractionation seems a feasible and promising option in carcinoma cervix. Considering the current COVID-19 pandemic, where completion of early and safe treatment is most desirable, adoption of such regimen could be followed. This shall provide partial relief for patients and also to health-care providers. Hitherto, evidences are not strong to consider it as standard practice. Nevertheless, ongoing few trials and evidences which could be generated from its use, to explore its feasibility and outcome, shall be a guidance for the future.

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Conflicts of interest

There are no conflicts of interest.

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