Research Article

Clinical Outcomes and Toxicity Profile with HDR Intracavitary Brachytherapy in Carcinoma Cervix using various Fractionation Schedules – A Single Institution Feasibility Study

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Abstract

Purpose: *To compare feasibility of single day two fractions and consecutive two days two fractions with standard weekly fractionation using Intracavitary Brachytherapy Application in patients with Carcinoma Cervix*

Patients and Methodology: *Fifteen adult patients with locally advanced carcinoma cervix treated with definitive chemoradiation followed by Intracavitary Application (ICA) brachytherapy at Onco-Life Cancer Centre, Satara, Maharashtra, India, between August 2018 to December 2019 were included in the study. All patients were divided into three groups for the purpose of analysis. Group A included patients who at some point in time received single application two fractions in a single day with a gap of minimum 6 hours, Group B included patients who received single application two fractions wherein the second fraction was given on Day 2 and Group C included patients treated with standard once a week fractionation throughout their treatment. Altered fractionation schedules were chosen out of no choice by virtue of either high risk status for anaesthesia, difficult uterine anatomy or logistics and socio-financial issues. Standard CT based contouring and planning protocol were used for brachytherapy planning. Overall Treatment Time (OTT) and toxicity profiles were evaluated retrospectively. All statistical calculations were performed using SPSS statistical software for windows IBM SPSS version 25 and RStudio version 1.2.1335.*

Results: *A total of 15 adult patients with locally advanced carcinoma cervix were evaluated. Mean age was 56 years (51-68). 8 out of 15 patients (53%) were stage II while rest (47%) were stage III. 9 out of 15 (60%) patients had received 3 fractions of HDR ICA brachytherapy while rest had received 4 fractions. 7 out of 15 (47%) of the study population had some of other comorbidity like HTN or DM with 4 of them having multiple comorbidities.10 out of 15 patients included in group A and B had received altered fractionation brachytherapy of which 4 were high risk for anesthesia, and 3 each had either difficult anatomy or logistics and socio-financial reasons behind the same. Group A patients had the shortest OTT of 49.2 days with the mean 2cc OAR doses to bladder, rectum and sigmoid as 4.8 Gy, 4 Gy and 4 Gy respectively per application while Group B patients had the OTT of 53.4 days with the mean 2cc OAR doses to bladder, rectum and sigmoid as 5.6 Gy, 5.3 Gy and 4.4 Gy respectively per application. On the other hand, standard fractionation Group C patients had the longest OTT of 64.2 days with the mean 2cc OAR doses to bladder, rectum and sigmoid as 5.6 Gy, 4.6 Gy and 4.7 Gy respectively per application. 2 year OS and PFS was 100 % and maximum acute and late RTOG toxicity was grade I and II across all three groups. None of the patients had failed locally and one patient had distant relapse in lungs till the date of analysis.*

CONCLUSION: *Better clinical outcomes with reduced OTT and equivalent toxicity profiles are feasible with altered fractionation schedules for ICA brachytherapy if adequate inter-fraction immobilization is maintained and may be advisable for patients with high risk for anaesthesia especially in the third world resource limited settings with remotely located centres wherein logistics and socio-financial constraints still play a critical role in the treatment compliance.*

Keywords: *Cervical cancer, concurrent CTRT, ICA brachytherapy, altered fractionation, immobilization, OTT, clinical outcome, toxicity profile, logistics, high risk for anaesthesia, difficult anatomy, compliance*

Abbrevations

HDR – High Dose Rate,

ICA - Intracavitary Application,

OTT – Overall Treatment Time,

HTN – Hypertension,

DM– Diabetes Mellitus,

Gy – Gray,

RTOG – Radiation Therapy Oncology Group,

EBRT – External Beam Radiation Therapy,

BT – Brachytherapy,

- fraction,

FIGO – International Federation of Gynaecology and Obstetrics,

EQD2– Equivalent dose in 2 Gy fraction,

OS – Overall Survival,

PFS – Progression Free Survival

Introduction

Cervical cancer is the third most common malignancy in women worldwide, and it remains the leading cause of cancer-related deaths in women in developing countries. About 86 % of the cases occur in developing countries, with 13 % of them accounting for the female cancers. Worldwide mortality rates of cervical cancers are substantially lower than the incidence. The cervical cancer risk is 1 % during the life of a woman living in a developed country, whereas the corresponding value for a woman living in a country without preventive programs is 5 %, and around 20 % of the global burden of cervical cancer risk falls within India. Latest estimates indicate that every year 1,23,907 women are diagnosed with cervical cancer, and 77,348 die from the disease. Cervical cancer ranks to be second to top frequently occurring cancer among women in India and the top most frequently occurring cancer among women between 15 and 44 years of age. **[**1**]**

At our peripherally located tier II city centre, about 30–50 % of female out-patients comprise of carcinoma cervix. Treatment of cervical cancer comprises of definitive chemoradiation including EBRT with concurrent cisplatin followed by ICA brachytherapy for 3-4 fractions depending upon the EBRT dose used. A retrospective analysis of women treated with weekly cisplatin and pelvic RT according to

the GOG 165 protocol found that treatment delay (> 8 weeks) was associated with worse PFS and OS [2,3,4] Peripheral centres like ours mainly cater to village-based population with limited awareness, compliance, socio-financial and logistic issues. These patients are more likely to remain non-compliant or in certain cases totally default brachytherapy due to the aforementioned reasons leading to longer OTT eventually reflecting upon poor disease control and disease recurrence. Prolongation of overall treatment time (OTT) beyond 50 days, merits total dose increment of 0.6 Gy for each day of prolongation. This is to control the accelerative repopulation of the cells. Increasing dose to control accelerated repopulation is usually not feasible owing to dose-limiting structures around the primary. High risk status for general anaesthesia and difficult anatomy scenarios like retro or anteverted uterus with perforations and postponements of the treatment, further lead to undue extension of OTT. All these factors, make scheduling of HDR brachytherapy of prime importance specially in this set of population wherein completion of the entire treatment within stipulated time period itself becomes a challenging task. As on date, there is still a dearth of real-world data as far as various does fractionation schemes related to ICA brachytherapy is concerned.

In the absence of convincing outcomes data, most fractionation schemes are influenced by practicalities and resource constraints. Fewer insertions are associated with less anesthesia, less chance for operative complications, less demand for operating room time, shorter overall treatment time, with the potential for less repeat imaging and lower use of treatment planning resources. The potential disadvantages include requirements for inpatient care, prolonged patient immobility and its attendant risks, and uncertainty associated with applying a single treatment plan for multiple fractions. Hence, we propose to retrospectively analyse impact of various altered fractionation schedules of HDR ICA brachytherapy on clinical outcomes and toxicity profiles and to assess the feasibility of the same in routine practice.

Methodology

Fifteen adult patients with locally advanced carcinoma cervix treated with definitive chemoradiation followed by Intracavitary Application (ICA) brachytherapy at Onco-Life Cancer Centre, Satara, Maharashtra, India, between August 2018 to December 2019 were included in the study. All patients after being adequately staged using FIGO staging criteria and a confirmed histopathological biopsy report, were treated with definitive concurrent chemoradiation to either 46 Gy or 50 Gy to whole pelvis based on the nodal status using 3DCRT technique and concurrent weekly cisplatin to a dose of 40 mg/m2. This was followed by HDR ICA brachytherapy for either 3 or 4 # depending upon the whole pelvic EBRT dose of 50 Gy or 46 Gy respectively. Brachytherapy was planned sequentially to a dose of 7 Gy to point A within a week of completion of EBRT, after acquiring anaesthesia fitness and settling down of acute reactions if any. Standard operating procedures and ultrasound confirmation for tandem

position for avoidance of perforation were undertaken in the all of the patients. Patients were divided into three groups for the sake of analysis. Group A included patients who at some point in time received single application two fractions in a single day with a gap of minimum 6 hours, Group B included patients who received single application two fractions wherein the second fraction was given on Day 2 and Group C included patients treated with standard once a week fractionation throughout their treatment. Altered fractionation schedules were chosen out of pressing reasons by virtue of either high risk status for anaesthesia, difficult uterine anatomy or socio-financial and logistic issues. Standard CT based contouring and planning protocol were used for brachytherapy planning **[**Figure 1-3**]**.

Non standard altered fractionation group A and B patients were kept on clear liquids and advised strict interfraction immobilization along with use of flatus tube to avoid unwarranted recto-sigmoid gaseous distension. They had undergone repeat planning CT for every consecutive fraction. Standard plans were generated and quantitative parameters like 2cc doses and EQD2 of bladder, rectum and sigmoid were acquired from cumulative dose volume histogram. Overall Treatment Time (OTT), OS, PFS and toxicity profiles were evaluated retrospectively for each of the groups. All statistical calculations were performed using SPSS statistical software for windows IBM SPSS version 25 and RStudio version 1.2.1335.

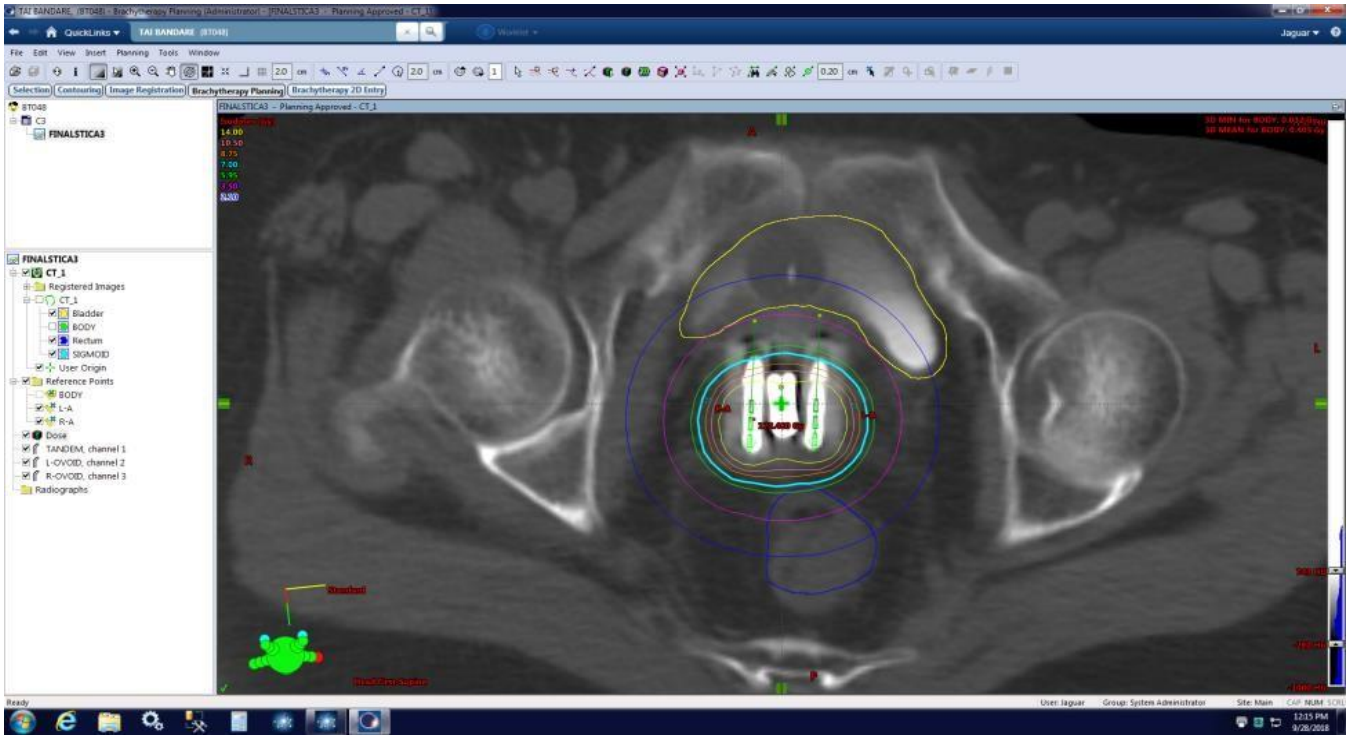

Figure 1 – Depicting cross-sectional planning CT view with applicator in situ showing isodose curves and OARs

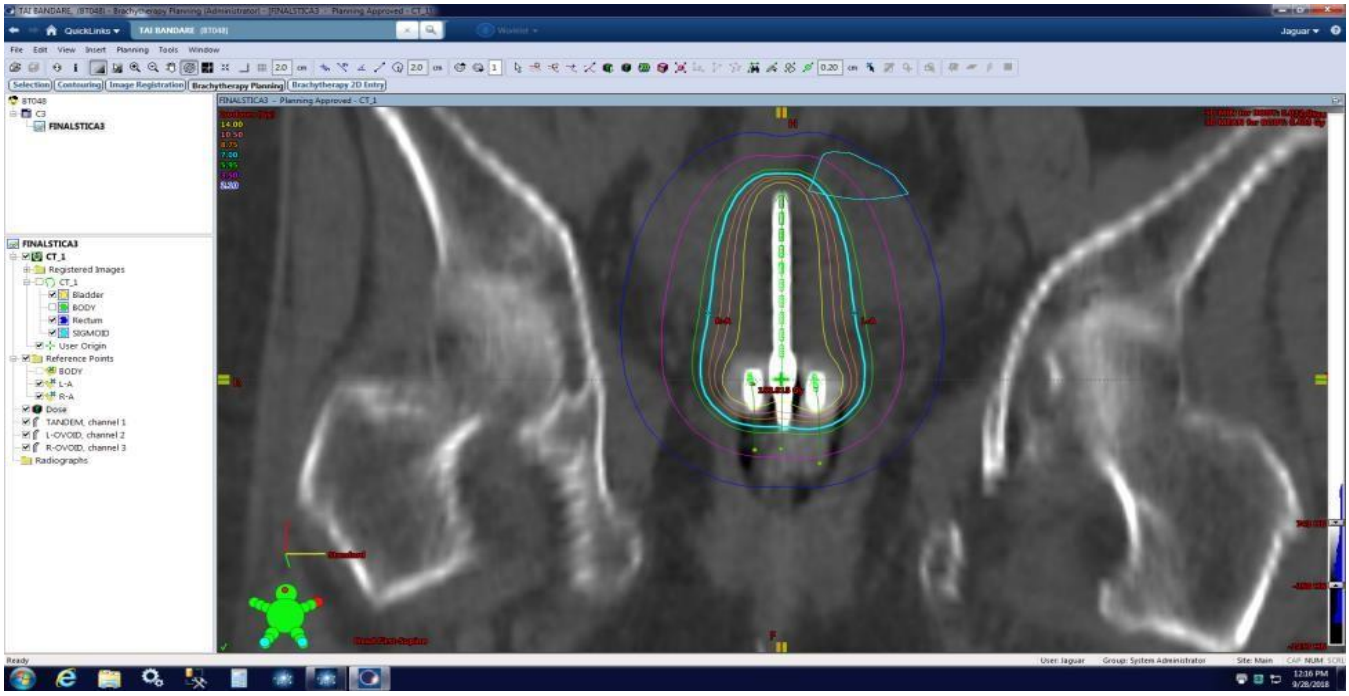

Figure 2 – Depicting coronal planning CT view with applicator in situ showing isodose curves and OARs

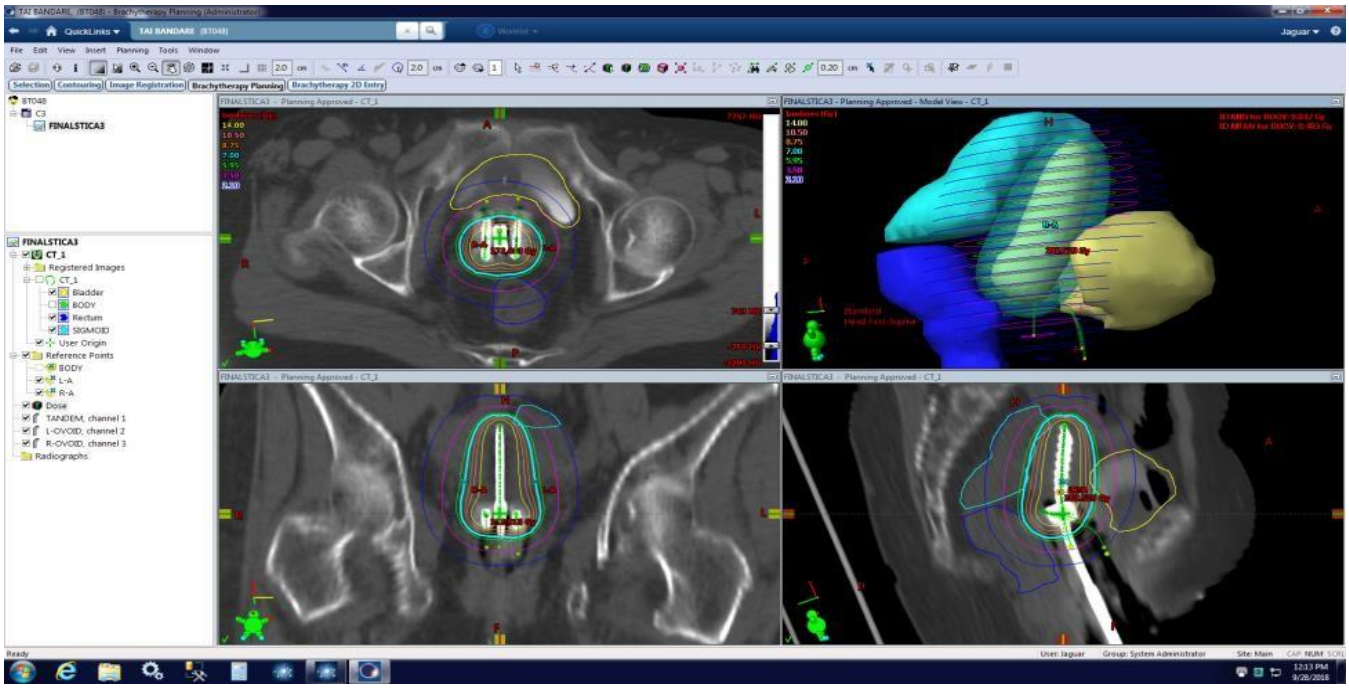

Figure 3 – Depicting 3-dimensional planning CT view with applicator in situ showing isodose curves and OARs

Results

A total of 15 adult patients with locally advanced carcinoma cervix were evaluated. Mean age was 56 years (51-68). 8 out of 15 patients (53%) were stage II while rest (47%) were stage III. 9 out of 15 (60%) patients had received 3 fractions of HDR ICA brachytherapy while rest had received 4 fractions. 7 out of 15 (47%) of the study population had some of other comorbidity like HTN or DM with 4 of them having multiple comorbidities. Patient characteristics have been depicted as below **[**Table 1**]**. 10 out of 15 patients included in group A and B had received altered fractionation brachytherapy of which 4 were high risk for anesthesia, and 3 each had either difficult anatomy or logistics and socio-financial reasons behind the same **[**Table 2**]**.

Group A patients had the shortest OTT of 49.2 days with the mean 2cc OAR doses to bladder, rectum and sigmoid as 4.8 Gy, 4 Gy and 4 Gy respectively per application **[**Table 3.1**]** while Group B patients had the OTT of 53.4 days with the mean 2cc OAR doses to bladder, rectum and sigmoid as 5.6 Gy, 5.3 Gy and 4.4 Gy respectively per application **[**Table 3.2**]**. On the other hand, standard fractionation Group C patients had the longest OTT of 64.2 days with the mean 2cc OAR doses to bladder, rectum and sigmoid as 5.6 Gy, 4.6 Gy and 4.7 Gy respectively per application **[**Table 3.3**]**. 24 month OS and PFS was 100 % (Graph not shown as all of the patients are alive) and maximum acute and late RTOG toxicity was grade I and II across all three groups **[**Table 4**]**. None of the patients had failed locally and one patient had distant relapse in lungs till the date of analysis.

Table 1 – Patient Characteristics

FRACTIONATION GROUP	AGE	STAGE	COMORBIDITIES
A	52	IIB	Multiple
A	58	IV	Multiple
A	47	IIIB	Nil
A	61	IIIB	Multiple
A	64	IIB	Nil
B	65	IIB	Single
B	55	I	Nil
B	57	IIB1	Multiple
B	48	IIB2	Nil
B	52	IIIB	Nil
C	55	II	Single
C	62	IIA	Nil
C	55	IIIB	Nil
C	68	IIIB	Single
C	51	IIB	Nil

Table 2 – Various pressing reasons for altered fractionation schedules

Fractionation Group	High Risk for Anaesthesia	Difficult Anatomy	Logistics and Socio-Financial issue
A	Yes	Nil	Nil
A	Yes	Nil	Nil
A	Nil	Yes	Nil
A	Yes	Nil	Nil
A	Nil	Nil	Yes
B	Nil	Nil	Yes
B	Nil	Nil	Yes
B	Yes	Nil	Nil
B	Nil	Yes	Nil
B	Nil	Yes	Nil
C	Nil	Nil	Nil
C	Nil	Nil	Nil
C	Nil	Nil	Nil
C	Nil	Nil	Nil
C	Nil	Nil	Nil

Table 3.1 – Group A parameters

# No.	DOSE/ # (Gy)	DATE	2CC DOSE TO OAR (Gy)			EQD2			TOTAL DOSE		OTT
			BLADDER	RECTUM	SIGMOID	BLADDER	RECTUM	SIGMOID	EBRT	BT+EBRT	
1	7	11/10/2019	5.3	3.6	4.2	76.4	66.5	77.4	46	85.7	46
2	7	18/10/2019	4.2	4	6.4						
3	7	25/10/2019	4.5	4.5	4.2						
4	7	25/10/2019	5.3	2.9	4.7						
1	7	4/12/2019	6.2	3.3	4	76.6	65.7	70.8	46	85.7	52
2	7	4/12/2019	4.9	3.8	3.6						
3	7	11/12/2019	3.7	3.7	4.5						
4	7	12/12/2019	4.4	3.9	4.9						
1	7	6/3/2019	5.2	5.1	2.3	78.9	69.5	65.7	50	79.8	54
2	7	13/3/2019	5.9	4.3	4.5						
3	7	13/3/2019	5.7	3.7	4.4						
1	7	20/9/2019	3.6	3.2	3.6	67.3	62.9	58.6	50	69.8	45
2	7	27/9/2019	4.2	3.4	2						
3	7	27/9/2019	4.4	3.5	1.9						
1	7	10/6/2019	4.6	5.6	5.3	73.7	75.4	70.4	50	79.8	49
2	7	10/6/2019	4.5	6	5.5						
3	7	19/6/2019	5.7	3.7	2.2						
		Mean	**4.8**	**4.0**	**4.0**	**74.58**	**68**	**68.5**			**49.2**

Table 3.2 – Group B parameters

# No.	DOSE/ #	DATE	2CC DOSE TO OAR (Gy)			EQD 2			TOTAL DOSE		OTT
	(Gy)		BLADDER	RECTUM	SIGMOID	BLADDER	RECTUM	SIGMOID	EBRT	BT+EBRT	
1	7	29/11/2018	3.8	6.4	6.1	83.6	89.3	82.5	46	85.7	55
2	7	30/11/2018	6	6.2	6.2						
3	7	5/12/2018	6	5.7	4.6						
4	7	6/12/2018	6	5.7	4.6						
1	7	5/12/2018	5.3	5.6	3.8	94.5	81.3	66.8	46	85.7	52
2	7	6/12/2018	6.3	5.7	3.6						
3	7	12/12/2018	7	5	3.4						
4	7	13/12/2018	7	4.9	4.4						
1	7	1/2/2019	5.2	6.7	3.1	72.5	80.6	59.9	50	79.8	55
2	7	8/2/2019	4.6	5.3	2.7						
3	7	9/2/2019	4.6	5.3	2.7						
1	7	12/7/2019	6.8	5.1	4.7	78.8	69.8	76.7	50	79.8	53
2	7	19/7/2019	5.2	3.6	4.9						
3	7	20/7/2019	4.6	4.5	6.3						
1	7	9/8/2019	6.2	3.7	4.7	77.4	72	69.9	50	79.8	52
2	7	16/8/2019	4.9	5	4.7						
3	7	17/8/2019	5.1	5.4	3.9						
		Mean	**5.6**	**5.3**	**4.4**	**81.36**	**78.6**	**71.16**			**53.4**

Table 3.3 – Group C parameters

# No.	DOSE/ #	DATE	2CC DOSE TO OAR (Gy)			EQ D2			TOTAL DOSE		OTT
	(Gy)		BLADDER	RECTUM	SIGMOID	BLADDER	RECTUM	SIGMOID	EBRT	BT+EBRT	
1	7	27/7/2019	5.2	4	4	77.5	66.8	46	46	74	70
2	7	2/8/2019	5.4	4.7	4.7						
3	7	8/8/2019	4	2.5	4.8						
4	7	16/8/2019	5.1	3.8	3.8						
1	7	3/9/2018	7.2	3.9	3.9	83.8	73.5	58.9	45	73	71
2	7	10/9/2018	4.3	5.4	3.1						
3	7	17/9/2018	4	5.7	3.8						
4	7	26/9/2018	7	4	4.5						
1	7	23/8/2019	5.2	4.8	4.8	78.2	75.4	50	50	71	64
2	7	29/8/2019	6.1	8.7	8.7						
3	7	5/9/2019	5.2	5	4.5						
1	7	22/03/2019	4.7	3.8	4.2	81.6	66.7	71.7	50	71	56
2	7	29/03/2019	6.2	3.5	4.3						
3	7	5/4/2019	6.7	4.6	5.5						
1	7	17/5/2019	6.8	5	5.5	81.3	67.8	75	50.4	71.4	60
2	7	24/5/2019	5.6	4	4.4						
3	7	31/5/2019	5.8	4.1	6						
		Mean	**5.6**	**4.6**	**4.7**	**80.48**	**70.04**	**60.32**			**64.2**

Discussion

Definitive chemoradiation is a standard of care for the treatment of locally advanced carcinoma cervix. Brachytherapy plays a critical role in determining clinical outcomes in these cases and merits a detailed pre-planning workup after completion of EBRT to the primary. Concurrent chemotherapy plays a crucial role with a 10 % OS benefit when given given along with EBRT.**[**5-8**]** Dual treatment modality is usually tiresome for many of the patients more so in the peripheral setups with limited awareness and literacy rates. To worsen the situation special scenarios like high risk cases for anaesthesia, difficult uterine anatomy, logistic and socio-financial issues add to the non-compliance and delay in the treatment eventually prologing the OTT. Cervical cancer especially squamous histology is a fast proliferating tumor and needs short OTT for better clinical outcomes. Fyles et al. studied 830 patients of cervical cancer, they studied the effect of prolongation of OTT beyond 30 days, on local control and survival. They have reported 1 % loss of tumor control per day prolongation of OTT. **[**9**]** Stage subgroup analysis showed that the effect is predominantly observed in stage III/IV relative to that in stage I/II. Lanciano et al.'s study of cervical cancer on 837 patients treated with radiation therapy showed that local recurrence within 4 years of completion of treatment increased from 6 to 20 % when the OTT was increased to 6–10 weeks (P = 0.0001). This translated into significantly decreased rate of survival .**[**10**]** Girinsky et al. studied 386 patients of cervical cancer treated with radiation therapy. They reported relative risk of local recurrence has increased by a factor of 2.4 when OTT was increased up to 62 days. 1.1 % of loss of pelvic tumor control per day prolongation of treatment time is observed. 10 year-recurrence-free survival rate also decreased **[**11**]**. Perez et al. studied 1,227 patients of cervical cancer treated with radiation therapy. They showed a strong correlation between OTT and clinical tumor stage except for patients with stage I A tumor size being < 3 cm **[**12**]**. Delaloye et al. studied 360 patients of cervical cancer stages I B to III B treated with external RT and brachytherapy. They observed 5-year survival rate of 61 % when OTT was <60 days compared with 53 % when OTT was more than 60 days (P = 0.03) and 50 % increase in death rates for longer therapy group. **[**13**]** It is finally concluded that the shorter treatment duration is a factor associated with the longer survival in cervical cancer. Considering this scenario dose-fractionation and timing of ICA brachytherapy takes a driver's seat in determining the clinical outcome. A variety of dose/fractionation schedules are used in clinical practice for HDR brachytherapy. The most common fractionation schedules in the United States are 5–6 Gy × 5 fractions. However, shorter regimens are also in use, including 7 Gy × 4, 8 Gy × 3, and 10 Gy × 2.53,54 Hesitation for adopting higher doses per fraction comes from studies which suggest higher rates of complications with doses beyond 7 Gy per fraction **[**14**]** Intracavitary brachytherapy fractions are typically delivered 1–2 times per week. For template-based interstitial implants, the entire treatment is commonly done during one insertion, given the complexities involved with proper placement of the brachytherapy catheters. Fractions may be delivered twice-daily, separated by 6 hours, with the total brachytherapy course delivered over 2–3 days.

Direct comparisons between dose/fractionation schedules for cervical brachytherapy are limited. [15-17] A variety of brachytherapy prescriptions will be used at the discretion of individual institutions. Therefore, the results of this study will provide the best information yet on the merits of different fractionation options, in the era of adaptive, image-guided brachytherapy.

In the absence of convincing outcomes data, most fractionation schemes are influenced by practicalities and resource constraints. Fewer insertions are associated with less anesthesia, less chance for operative complications, less demand for operating room time, shorter overall treatment time, with the potential for less repeat imaging and lower use of treatment planning resources. The potential disadvantages include requirements for inpatient care, prolonged patient immobility and its attendant risks, and uncertainty associated with applying a single treatment plan for multiple fractions. Finally, interstitial and intracavitary brachytherapy have not been compared using similar fractionation schedules; however, slightly lower doses are recommended by the ABS, when using interstitial approaches.[18] This is mostly related to issues with meeting rectal constraints when treating larger volumes, as is often the case with interstitial. Our limited sample size study justifies the use of altered fractionation schemes atleast on aforementioned special occasions with equivalent clinical outcomes and toxicity profile across three different fractionation schedule with an added advantage of reducing the OTT leading to better local control. It is very much feasible and may help in improving the patient compliance in remotely placed tier II city centres like ours wherein drop out rates are still a major concern. Nevertheless, owing to a small sample size we suggest larger studies in these regards for further in depth understanding of the same.

Conclusion

Better clinical outcomes with reduced OTT and equivalent toxicity profiles are feasible with altered fractionation schedules for ICA brachytherapy if adequate inter-fraction immobilization is maintained and may be advisable for patients with high risk for anaesthesia especially in the third world resource limited settings with remotely located centres wherein logistics and socio-financial constraints still play a critical role in the treatment compliance.

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