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Compliance with bladder protocol during concurrent chemoradiation for cancer of the cervix and its impact on enteritis: A prospective observational study

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ABSTRACT

Aim: This prospective study aims to assess the compliance with bladder protocol and the correlation with enteritis during pelvic radiation.

Background: Bladder protocol is routinely used for patients undergoing pelvic radiation to reduce radiation enteritis. It is very difficult to maintain constant volume especially in the last two weeks due to radiation enteritis and cystitis.

Materials and methods: Histologically proven 35 cervical cancer patients treated with concurrent chemoradiation in a tertiary care center were the subjects of this prospective study. Following CT simulation and after every fraction, patients were asked to void urine in a calibrated urine container and the volume was documented. Patients were assessed for the highest grade of radiation enteritis weekly as per common toxicity criteria. The mean voided urine volume was correlated with the radiation enteritis.

Results: The mean urine volume at planning CT scan was 295.85 ± 300 ml (SD) with a range of 75–650. At the end of treatment, it was reduced to 233.14 ± 250 ml (range 50–400 ml), a reduction by 21% ($p < 0.001$). The maximum grade of enteritis was grade I (11%), II (11.4%), III (3–29%) in week 1,2 and 3–5, respectively with a p value of <0.001. A mean urine volume of 230 ml was associated with grade III enteritis in the third week.

Conclusions: Urine output volume measured using a calibrated container is a simple, efficient and practical method to monitor bladder distension thereby reducing enteritis in cervical cancer patients treated with concurrent chemoradiation.

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1. Background

The standard treatment for carcinoma cervix from Stage IB2 onwards is concurrent chemo radiation as per National Cancer Institute (NCI) Alert 1999.[1] Radiation therapy along with chemotherapy leads to various acute toxicities, the important ones being radiation enteritis and haematological toxicities. Kirwana et al. observed a twofold increase in acute GI toxicity with concurrent cisplatin adminstration.[2] There are various methods to minimise irradiated small bowel volume, like treatment in a prone position, using a belly board and with distended bladder, amongst others. Tae hyun kim et al. have studied the effect of distended bladder and observed that the irradiated small bowel volume was reduced from 82 to 48% for patients undergoing preoperative radiotherapy for rectal cancer.[3]

Pinkawa et al. conducted a prospective study on prostate cancer correlated bladder volume with questionnaire based assessment of enteritis. A larger initial bladder volume reduced enteritis from 22% to 5% on the last day of radiation.[4]

L.M. Mullaney et al. showed a supine position with distended bladder tends to push the small bowel out of the radiation field and hence can lead to decreased small bowel toxicity.[5] According to the protocol, 30 min prior to simulation CT scan as well as daily during radiation treatment, the patient will be instructed to evacuate the bladder followed by consumption of 500 ml of water. Our observation is that with progress of the treatment, patients may have acute cystitis and enteritis, it may be difficult to maintain the same bladder distension and hence compliance with the bladder protocol is difficult.

With cumulative radiation doses, enteritis increases and is maximum in the last two weeks of radiation. Due to enteritis associated dehydration, it is very difficult to maintain the same bladder volume for radiation. The decrease in bladder volume will in turn increase the amount of bowel in the irradiated area, which may further increase enteritis. Jee et al. observed a reduction in the median bladder volume by 38% at 6 weeks of radiation therapy which was statistically significant among patients with rectal cancer undergoing concurrent chemoradiation.[6]

Many authors have looked at the compliance with the bladder protocol mostly for cancers of the prostate and rectum. There are different methods to assess the bladder volume, such as ultrasound Ahmad,[7] Stam et al.[8] and CT scan Pinkawa et al.[4], Haiqin et al.[9] Doing these on all days of radiation is cumbersome and financially not feasible. A simple method to measure the urine volume is to collect the urine in a calibrated container immediately after every fraction and document the reading. Hence, this study was designed with an aim to correlate the measured value with the degree of radiation enteritis.

2. Materials and methods

This prospective observational study was conducted on 35 histopathologically proven cases of carcinoma cervix treated with concurrent chemo radiotherapy from May 2014 to April 2015. Based on Ahmad et al. in a study conducted on interfraction bladder filling variations, it was found that the mean bladder volume reduced by 71% at week 3. With a power of 90% and significance level of 95%, the minimum sample size required for the present study was estimated to be 35. Patients with postoperative cervical cancer, uterine prolapse and bladder pathology, such as hypotonic bladder and incontinence, were excluded from the study.

Patients were instructed to evacuate the bladder followed by consumption of 500 ml of water. After 30 min, contrast enhanced CT of the abdomen and pelvis scan was done with 5 mm cuts (from L1 vertebra to mid-thigh) with 80 ml of iodinated intravenous contrast. Following the scan, the patient was asked to void urine in a calibrated urine container and the volume was documented.

External Beam Radiation Therapy was delivered with 3D conformal technique to a dose of 45 Gy in 25 fractions (Fr), 5 fractions per week over 5 weeks along with weekly cisplatin 40 mg/m^2 for 4–5 courses. After each fraction, voided urine was measured and documented. Variations in volume of urine (hereafter also referred to as bladder volume) were measured. Patients were assessed once weekly for the highest grade of radiation enteritis weekly as per common toxicity criteria (CTC version 4.0) and documented.

The mean bladder volume per week was calculated which was correlated with the highest grade of radiation enteritis for that week.

3. Statistical analysis

Descriptive statistical analysis was carried out in the present study. Results of continuous measurements are presented on Mean ± SD (Min–Max) and results of categorical measurements are presented in number (%). Significance is assessed at a 5% level of significance. Spearmans correlation was used to find the correlation between the amounts of urine output with the grade of enteritis. Fischer exact test was used to find the significance in difference of proportion between different grades of enteritis with respect to week. Repeated measures of anova was used to compare the measurement of urine output from the baseline to the last day of treatment and for the week wise comparison of urine output.

4. Results

The patient characteristics of this prospective observational study are as shown in Table 1. All patients received the

Table 1 – Patient characteristics.

	Range (24–62 years)	No: 35 (%)
Age	20–30	1 (2.85)
Mean: 47 years	31–40	10 (28.57)
	41–50	13 (37.14)
	51–60	8 (22.85)
	61–70	3 (8.57)
Stage (FIGO)	II A	20 (57.14)
	II B	13 (37.14)
	III B	2 (5.71)

Table 2 – Table showing day wise bladder volume measurements.

	Mean	Std. deviation	Minimum	Maximum
Volume at simulation	295.86	119.61	75	650
Contoured bladder volume in cc	314.26	127.35	89	630
Day 1	325.29	130.74	75	750
2	317	138.17	100	600
3	330.86	129.13	100	600
4	346.57	153.07	50	800
5	320	142.54	50	600
6	338.71	147.56	50	650
7	357.14	154.55	75	800
8	314.29	176.12	50	800
9	325	131.4	50	700
10	352.86	149.83	100	750
11	321.43	124.97	75	600
12	314.57	130.37	50	730
13	297.57	124.97	50	600
14	274.57	118.67	50	600
15	307.71	120.66	80	550
16	298.14	116.3	50	600
17	307.14	105.51	80	500
18	285	115.85	50	500
19	285.29	114.92	50	550
20	266.57	102.87	60	450
21	295.57	98.733	50	450
22	262.29	93.182	50	400
23	254.86	106.73	50	500
24	245.71	84.341	50	400
25	233.14	87.842	50	400

planned external radiation and minimum 4 courses of concurrent cisplatin chemotherapy and are available for analysis. All patients followed the bladder protocol on every day of radiation. The overall treatment time range was 33–38 days and there were no treatment interruptions observed in our study

4.1. *Urine volume measurements*

The measured urine volume is as shown in Table 2. The mean urine volume at planning CT scan was 295.85 ± 300 ml (SD) with a range of 75–650 ml and the contoured bladder volume was 314.25 ± 345 cc (range 89–630 cc). At the end of treatment, it was reduced to 233.14 ± 250 ml (range 50–400 ml), a reduction by 21%. Using repeated measures of annova test the volumes at the baseline were compared to the last day of treatment and it was found that there was a significant difference in the mean bladder volumes across the various time periods ($p < 0.001$).

The mean urine volume (shown in Fig. 1) at the first week was 327.94 ± 118.29 ml (range 75–566 ml). During the treatment, the mean volume of 337.60 ± 124.95 ml, increased up to week 2, later it decreased to 303.23 ± 99.63 ml in week 3, 288.43 ± 85.90 ml in week 4, and 258.31 ± 75.03 ml in week 5, a reduction by 13% from the planning CT scan. Over the weeks, there was a significant difference ($p < 0.001$) between the values of the mean urine volumes.

4.2. *Assessment of radiation enteritis*

Fig. 2 shows that for the first week, the maximum grade of enteritis was grade I (11.4%), in week 2, the maximum grade was grade II (11.4%), whereas in week 3 (2.9%), 4 (8.6%) and 5 (28.6%), the maximum grade was grade III followed by grade II, grade I, grade 0 with a p value of <0.001.

4.3. *Correlation of bladder volume with enteritis*

The mean volumes were compared every week across the various grades and it was found that there was a significant decrease in the bladder volumes over the course of treatment, whereas the grade of enteritis significantly increased.

Spearmans correlation showed negative value (r −0.414, $p < 0.001$), (r −0.369, $p < 0.001$), (r −0.261, $p < 0.001$), (r 0.009, $p < 0.9$) and (r −0.196, $p < 0.009$) for week I, II, III, IV and V, respectively. As the bladder volume decreased, the grade of enteritis increased or vice versa with a significant p value (<0.001), except in week 4.

In our study, the mean overall bladder volume significantly decreased at the end of treatment, whereas the grade of enteritis increased, the maximum grade was III. The mean bladder volumes associated with maximum grade of enteritis were 153 cc in week 1, 252 cc in week 2, later 230 cc, 213 cc and 212 cc in week 3, 4 and 5, respectively (Table 3).

5. Discussion

This prospective study was conducted on 35 cervical cancer patients treated with concurrent chemoradiation using the bladder protocol. Similar studies using the bladder protocol have been done by, O'Doherty et al.,[10] Hynds et al.,[11] Stam et al.[8] and Jee et al.[6] to study the importance of full bladder. However, they have included patients of different primaries such as the prostate, rectum. R. Ahmad et al. assessed cervical cancer and, as such, their study was similar to our work.

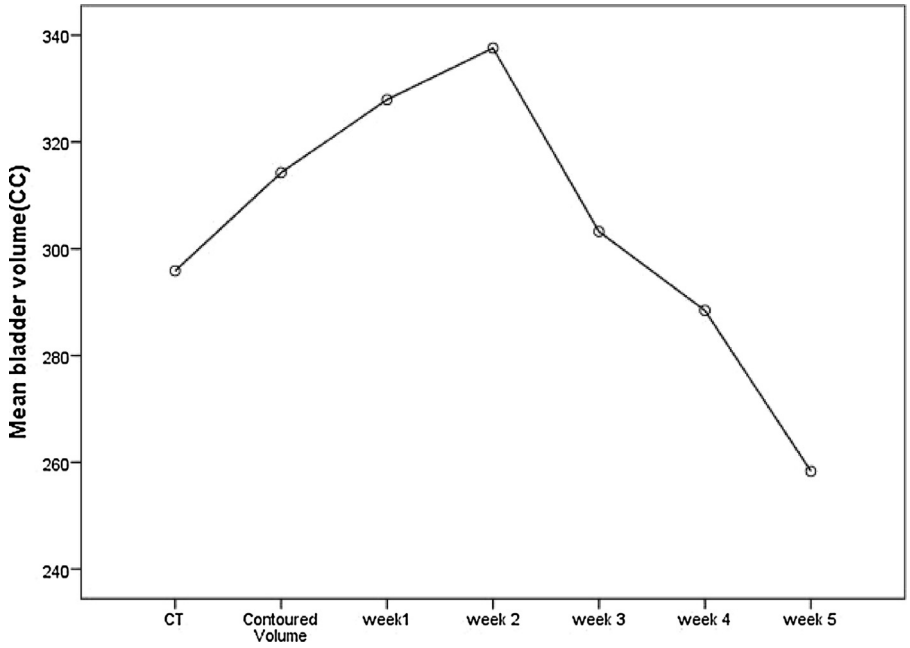

Fig. 1 – Graph showing mean urine output week wise.

Table 3 – Comparison of bladder volume with respect to the grade of enteritis.

Mean bladder volume cc (*n*)	Grade 0	Grade I	Grade II	Grade III	Grade IV	*p* value
wk1	350.47 cc (31)	153.25 cc (4)	0	0	0	0.000
wk2	375.16 cc (18)	290.53 cc (13)	252.5 cc (4)	0	0	0.000
wk3	357.99 cc (7)	315.74 cc (12)	272.39 cc (15)	230 cc (1)	0	0.003
wk4	340 cc (1)	258.85 cc (7)	304.28 cc (24)	213.32 cc (3)	0	0.004
wk5	264 cc (1)	200 cc (2)	284.17 cc (22)	212.5 cc (10)	0	0.000

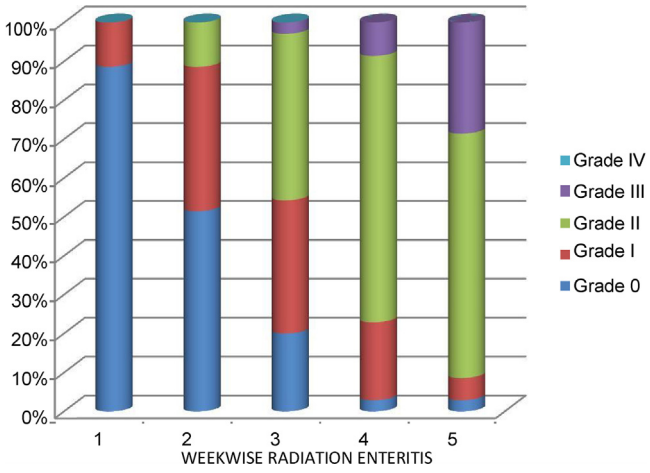

Fig. 2 – Bar chart showing grades of enteritis during radiation.

5.1. *Bladder volume measurements*

Measuring bladder volume has been done by using different methods like ultrasound scan (R. Ahmad et al.[7], O'Doherty et al.[10], Hynds et al.[11], Stam et al.[8], Jee et al.[6] and CT scan (Nakamura et al.[12], Fiorino et al.[13], Pinkawa et al.[4], Haiqin et al.[9]). We wanted to keep it simple and practicable and, therefore, a calibrated urine container was used to collect and measure the urine output.

R. Ahmad et al. conducted a study on cervical cancer patients treated with the bladder protocol, patients were instructed to drink 500 ml of water one hour prior to simulation and then bladder volume was measured by US scan immediately after the planning CT scan and twice weekly during RT. The mean bladder volume at planning of 378 ± 209 ml (1SD) reduced to 109 ± 88 ml (1SD) in week 6, a reduction by 71% was observed.[7] The urine output volume in our study was 295.14 ± 250 ml by the end of treatment a reduction by 21%. The smaller volumes in our study are probably due to the 30-min protocol. As the treatment progresses, patients may not maintain the full bladder because of longer time in their study and, hence, a greater reduction of 71% was observed.

Stam et al. investigated the use of biofeedback to optimise bladder filling. Sixteen prostate patients were given a biofeedback protocol to achieve a more constant bladder volume with a personal drinking advice every treatment day. With this drinking instruction, the results still showed a 19% bladder volume decrease during the whole treatment period compared to 31% in the control group (without biofeedback), which was not statistically significant. The use of a biofeedback protocol yields little reduction in bladder volume variation.[8] This was like our observation; however, we did not use any biofeedback protocol. The mean bladder volume at the time of planning was 282 ml and on the last day of treatment the

mean value was 165 ml, whereas in our study, at planning CT scan it was 295.85 ml and on the last day it was 233.14 ml. This difference was probably due to increased overall treatment time (74 Gy/37Fr/51 days) when compared to our study (45 Gy/25 Fr/35 days).

5.2. *Correlation of bladder volume with enteritis*

While all the above studies had different bladder protocols and showed bladder filling variations during radiotherapy, they are not correlated with enteritis. Studies that correlated with enteritis are from Pinkawa et al.[4], Haiqin et al.[9], but these related to prostate cancer, and rectal cancer patients. Pinkawa et al. conducted a prospective study on prostate cancer.[4] The patients were asked to have a full bladder for the planning CT scan and for each radiotherapy fraction and they assessed their enteritis using a questionnaire before, on the last day of radiotherapy, at 2 months and at 16 months after radiotherapy. A larger initial bladder volume was associated with a lower rate of problems with the bowel habits, 22% vs. 5% on the last day of radiation, 21% vs. 5% at 2 months. Their assessment was patient rated whereas in our study, physician assessed grading was done.

Haiqin et al. carried out a prospective study on postoperative rectal cancer patients.[9] All patients were asked to empty their bladders and drink 800 ml before the CT scan and RT. A self-assessment scale of 1–4 for bladder comfort was used. Repeat scan was done after four weeks of radiation. There was a significant correlation between the reduction in bladder volume and increase in the bowel volume. However, they only performed a dosimetric analysis and no clinical correlation was studied. In our study, there was a reduction in the bladder volume over the course of radiation which significantly correlated with the grade of enteritis ($p < 0.001$).

To our knowledge, this is the first study to consider both compliance with the bladder protocol for cervical cancer and correlation with enteritis. Moreover, it can be used in developing countries where more advanced investigations, like daily CT scan and Ultrasound, are neither practical nor economical. Also, it is very important to reduce enteritis to maintain the overall treatment time. Monitoring the bladder protocol will help us to identify patients who are not compliant and can be counselled much before they develop enteritis. Our observations showed that there may be some spillage of urine during collection and, hence, measured volume may not be precise. Secondly, apart from measuring and documenting, it is very important to monitor the patients throughout the treatment. However, this was overcome by explaining the patient the procedure of collection both at the beginning and interacting with them during weekly radiation.

6. Future directions

In the era of IMRT, it becomes more important that constant bladder distension is maintained on all days of treatment so that only the accepted dose reaches the bowel. Daily monitoring will help us to identify patients who cannot stick to the protocol and in whom replanning can be done to improve tolerance to treatment.

7. Conclusions

This study helped us to understand the concerns of the bladder protocol. Collecting urine in a calibrated container and measuring daily volume is a simple and feasible method, especially in developing countries where daily ultrasound, CT based measurements are practically difficult. Daily measurement and interaction with the patients will help to maintain constant bladder distension throughout the course of treatment thereby reducing enteritis as much as possible.

Conflict of interest

None declared.

Financial disclosure

None declared.

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