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A PROSPECTIVE CLINICAL STUDY ON THE BENEFIT OF ADDING CHEMOTHERAPY TO BRACHYTHERAPY IN PATIENTS WITH INCOMPLETE RESPONSE TO EXTERNAL BEAM IRRADIATION WITH CONCURRENT CHEMOTHERAPY IN LOCALLY ADVANCED CASES OF CARCINOMA CERVIX

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Keywords:
cancer cervix, brachytherapy, concurrent chemotherapy.

Abstract

Introduction: Concurrent chemoradiation followed by brachytherapy is the standard treatment of carcinoma cervix by radiotherapy. Efficient brachytherapy is all the more important in Indian scenario where bulky residual disease is mostly found after external radiotherapy. Our study investigates the feasibility and tolerability of High Dose Rate Brachytherapy (HDR-BT) combined with concurrent cisplatin against HDR-BT alone which is considered the traditional standard of care.

Materials and Methods: Carcinoma cervix patients who have undergone 'partial response' or 'stable disease' to external beam radiotherapy have been randomized into two arms in this study: Concurrent brachytherapy(CBT arm) where weekly 7Gy HDR X 3 fractions was delivered with weekly 40mg/m2 cisplatin given few hours prior to brachytherapy and brachytherapy(BT) alone arm with same HDR schedule.

Results: There were significantly higher complete responses in CBT arm 8 weeks post brachytherapy in CBT arm (59% vs 33.3%, p= 0.038). Systemic toxicities, viz. dermatitis, mucositis, diarrhea, anemia were also significantly higher in CBT arm. Rectal, vaginal and bladder toxicities were also higher in CBT arm, although not significant.

Conclusion: CBT is a feasible approach with acceptable higher toxicties.

Introduction

Concurrent chemo radiation (CRT) has been traditionally accepted as the gold standard of treatment for cervical cancer patients following the National Cancer Institute (NCI) alert in 1999[1] and the supportive meta-analyses of Greene et al [2] and Vale et al [3].It is worth noting that stage specific survivals drop with higher stages of the disease [4], which is related to greater incidences of local and distant failures in the same. Quite obviously, this is mostly due to the presence of bigger residual disease in higher stages after CRT and efficient brachytherapy (BT) is our only defense against such treatment failures. Since brachytherapy is indispensable for the curative treatment of cervical cancers making it more efficient may possibly help in improving treatment results [5, 6]. The radiation tolerance of the paracervical triangle [7] and adjacent normal structures limits dose escalation beyond traditional brachytherapy fractionation schedules [8] even in this volumetric era of brachytherapy planning [9, 10]. Extrapolating the benefits of concurrent chemotherapy with external beam radiotherapy (EBRT), the addition of cisplatin to brachytherapy may possibly enhance its potential to cure residual disease post CRT. In light of this hypothesis, our study investigates this approach of concurrent brachytherapy (CBT) in patients who have residual disease post CRT.

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Materials and methods

1. Aims and objectives of this study:

i. Clinical assessment of tumor response after adding brachytherapy with or without chemotherapy (i.e. CBT vs. BT alone) in cervical cancer patients undergoing clinically incomplete response (stable disease or partial response) to CRT.

ii. Assessment of acute toxicities and toxicities during follow-up in these two groups, CBT vs. BT alone - both systemic and local, i.e. cervix and vagina, bladder and rectum.

2. Study area: Department of Radiotherapy, Medical College, Kolkata, India.

3. Study period: September 2013 to September 2015.The patient accrual phase was from September 2013 to May 2015.

4. Study design: A prospective single institutional randomized study.

5. Inclusion criteria:

a. Biopsy proven cases of locally advanced carcinoma cervix defined as Stage IB2 to Stage IVA as per FIGO staging [11], who have undergone clinically defined Incomplete response (i.e. Partial Response or Stable Disease) to EBRT - 50 Gy in 25 fractions over 5-7weeks (a maximum of 2 weeks of planned/unplanned break was allowed) given in Cobalt-60 teletherapy machine (Theratron780C, Kirloskar Medical Theratronics ,Ottawa, Ontario, Canada) with concurrent three weekly cisplatin (75mg/m^2 body surface area). Notably, clinical responses were defined as following:

Complete Response- Complete regression of lesion.

Partial Response- Regression in diameter of lesion more than 50%.

Stable disease- Regression in diameter of lesion less than 50%.

b. ECOG performance status 0-2[12].

c. Adequate hematologic, hepatic and renal function (Haemoglobin >10gm/dl, Absolute neutrophil count (ANC)>1500, Platelet count>100,000, Creatinine clearance>50ml/min, Serum albumin>3.5mg/dl, Serum bilirubin<2.5 mg/dl, and normal rest of the Liver Function tests.

6. Exclusion criteria:

a. Prior History of abdominal/pelvic radiotherapy .

b. Untreated abdominal/pelvic disease.

c. Uncontrolled co-morbidities like diabetes, hypertension, kidney or liver disease

d. Pregnancy.

7. Study technique:

Patients meeting above criteria were treated with conventional (2-D planning) radiotherapy using four-field box technique- upper borders, L4-L5 junction; lower borders- lower border of obturator foramen; lateral borders of anterior and posterior fields- 1.5 cm lateral to bony pelvis walls on either side; anterior borders of lateral fields- anterior border of symphysis pubis and posterior borders of lateral fields- covering sacral hollow fully. Patients were assessed for clinical response 2 weeks after the completion of CRT (as scheduled above). Incomplete responders to CRT were randomized by computer generated table of random numbers [13] into two arms: standard arm- BT alone (weekly fraction X 3 weeks) and experimental arm- CBT (40mg/m2 cisplatin administered IV one day prior to weekly BT fractions X 3weeks). We have followed our institutional high dose rate brachytherapy schedule of 7Gy, prescribed weekly for 3 weeks, at revised point A [14]. Following our institutional protocol, central residual disease (i.e., residual over cervix, uppermost vagina or medial-most parametria) with relatively preserved vaginal anatomy were treated with Intracavitary brachytherapy (ICBT) and bulky lateral parametrial residuals or distorted vaginal anatomy mandated use of Interstitial brachytherapy (ISBT). The HDR Brachytherapy machine in our department uses remote after-loading system with Iridium 192 isotope (Gamma med Plus- Varian medical Systems, Palo Alto CA) and the HDR treatment planning system (TPS) is enabled with Eclipse Brachyvision software .The final clinical response assessment to radiotherapy was done 6 weeks post treatment completion.

8. Toxicity monitoring during follow-up:

Patients were followed up for treatment induced toxicities shortly after brachytherapy and thereafter every 3 monthly throughout the period of study. The CTCAE v 4 [15] was used for toxicity grading and management. In each visit patients underwent full gynecological examination along with detailed clinical history. Radiation proctitis and rectal complications were managed by pain-killers, laxatives, sucralfate suppositories and/or hydrocortisone enemas. Patients with severe symptoms were referred to surgery for cauterisation. Bowel irregularities were managed

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conservatively. Haematuria due to radiation cystitis was managed with bladder irrigation or cystoscopic cauterization/ sclerotherapy if severe. Cervico-vaginal toxicties like dyspareunia, stenosis were managed with pain-killers, muscle relaxants, vaginal dilators and counseling on regular sexual intercourse with partner. Haematological toxicities were managed with transfusion of relevant blood components and supportive measures. Other systemic toxicities like neurodeficits were also managed conservatively. Local and distal recurrences encountered during follow-up were handled with salvage chemotherapy, palliative radiotherapy and best supportive care.

9. Statistical analysis:

All calculations were performed with the International Business Machine Statistical Package for the Social Sciences software version 20 (IBM SPSS, IBM Corporation, USA) **[16].** Chi-square test was used to compare the effect of CBT with BT alone based on Final Clinical Response-Complete response (CR), Partial response (PR), Stable disease (SD) and Progressive disease (PD). Comparison of toxicities between the two arms was done by simple frequency distribution of mild-to-moderate (<Grade 3) and severe (>= Grade 3) toxicities and Chi-square analysis for significant differences in distribution amongst the arms.

Results

An overview of patients accrued and analyzed can be appreciated from the consort diagram shown in Figure 1 shown below.

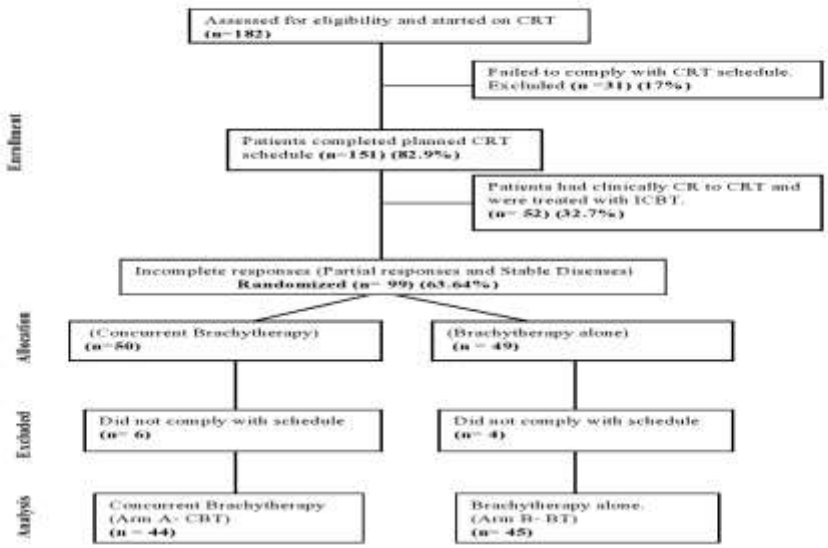

Figure 1: Consort diagram.

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The results can be briefly described under the following headings

a) Demographic variables: The median age of patients was 49 years (range 27-66 years). The most common presenting complaints were irregular and continued vaginal bleeding and white discharge found in 86.8% (158) and 78 % (142) patients respectively. The median age of marriage was 21 years (range16-33 years) and hardly a quarter of patients had ever practiced some form of contraception. Most of the patients (66%) came from a poor socioeconomic background. Squamous cell carcinoma (SCC) was the commonest histopathological variant observed in 87.9% (160) patients, followed by adenocarcinoma in 8.7 % (16) patients. A moderate degree of differentiation on histopathology was observed in most (64.6%) patients. The majority of patients (52.7%, 96) were postmenopausal. FIGO stage IIB was the commonest clinical stage, observed in 39.5% (72) patients followed by Stage IIIB in 33.5% (61) patients.

b) Comparison of CBT vs. BT alone in terms of clinical response 8 weeks post brachytherapy:

Figure 2 shows an overview of incomplete responses (PR or SD) to CRT entering each arm and clinical response (CR, PR or SD) assessed post BT.

	Arm A(CBT) n=44			Arm B(BT alone) n=45		
	Partial Response	Stable Disease	Complete Response	Partial Response	Stable Disease	Complete Response
Prior to BT n (%)	42 (95.4%)	2(4.5%)	0	41(91.9%)	4(8.8%)	0
Post BT n (%)	16(36.3%)	2(4.5%)	26(59%)	24(53.3%)	6(13.3%)	15(33.3%)

Figure 2: Final Clinical response 8 weeks post Brachytherapy.

The cross tabulation method on Pearson Chi-square analysis showed significant differences (p=0.038 with 2 degrees of freedom) in CR, PR and SD in between two arms. Notably, there was no PD in either arm. Thus CBT appears to elicit better clinical response in our study.

c) Comparison of treatment induced toxicities:

The acute toxicities of CBT arm was most pronounced shortly after treatment completion. Hence, for convenience we have divided toxicity analysis in two categories- one week post brachytherapy and toxicity during follow-up (acute and late included):

1) ***Toxicity within 1 week post brachytherapy:***

The only vaginal toxicities encountered were inflammation and dryness found in 5(11.3%) and 16(35.5%) patients in CBT arm, while 4(9%) and 13(29.5%) patients were in BT arm respectively. No patient had any cervical toxicity. 8(17.7%) patients in CBT arm witnessed rectal pain (grade 1- 7 patients, grade2-1 patient), while 7(15.9%) patients (Grade 1-6 patients, grade2- 1 patient) had so in BT alone arm. Dysuria was the only bladder toxicity observed, 6 (13.3%) patients (Grade 1in 5 patients, Grade 2 in 1 patient) in CBT arm and 3(6.8%) patients (Grade 1 in 2 patients, grade 2 in 1 patient) in BT arm. None of the differences in above toxicities were significant. However, other toxicities like dermatitis, mucositis, diarrhea, anemia were significantly higher in CBT arm ($p<0.001$ by Chi square analysis) as tabulated in Figure 3 as shown below.

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TOXICITIES	SKIN	MUCOSITIS			DIARRHOEA			CONSTIPATION	ANAEMIA			NAUSEA AND VOMITTING		
ARMS /GRADES	G1-G3	G1	G2	G3	G1	G2	G3	G1-G3	G1	G2	G3	G1	G2	G3
CBT(44 PATIENTS)	NONE	11	2	NONE	15	12	8	NONE	19	14	11	21	14	9
BT (45 PATIENTS)	NONE	4	NONE	NONE	7	2	1	ONLY 1 HAD GR 1.	6	3	NONE	4	1	NONE

Fig 3: Systemic Toxicities 1 week post Brachytherapy.

In fact no patient in CBT arm was spared of these systemic toxicities. Adequate fluid replenishment, anti-secretory agents, blood transfusion, antibiotics and other supportive measures were generously administered after admitting the patients in Indoor department. All of them revived well after such treatment.

2) Toxicity during follow-up:

The median follow-up period was 11.1 months (Standard deviation -6.17, range: 1-22 months). For the purpose of comparison between the two arms, the peak time of appearance, i.e. median months of appearance of toxicity and the frequency distribution of lesser than CTCAE Grade 3 toxicities and greater than or equal to Grade 3 toxicities in each category were considered. Hence, acute (<6 months) and late (> 6 months) toxicities weren't distinguished. Comparison was again done by Chi-square tests. Vaginal dryness was the most common toxicity during follow-up followed by rectal pain/proctitis and dysuria. Frequency distribution of vaginal, rectal and bladder toxicities in the two arms are shown below in Figures 4- 6, and the median times of appearance of these toxicities are depicted in Figure 7 .There wasn't any discernable cervical toxicity. There were no evident haematological or nephrological toxicities. Notably, one patient in CBT arm developed tinnitus at around 10 months of follow-up. History and clinical tests excluded other neurological causes and most probably it was cisplatin-induced, although we are not sure.

As seen from Fig4-6, the prevalence of toxicity was mostly higher in Arm A than in Arm B. However, none of the differences in between two arms achieved a significant value in Chi-square tests ($p=0.43$ for vaginal toxicities, $p=0.25$ for rectal toxicity and $p=0.35$ for bladder toxicities).

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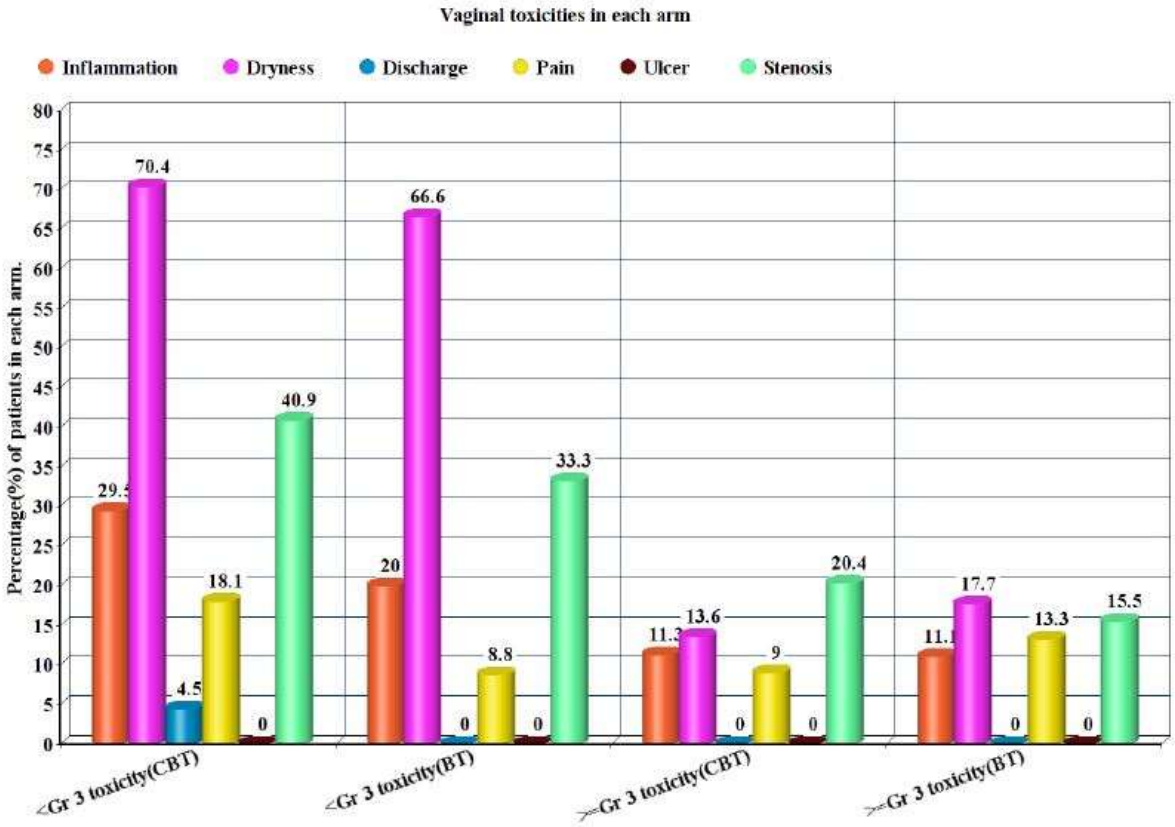

Figure 4: Vaginal toxicities during follow-up.

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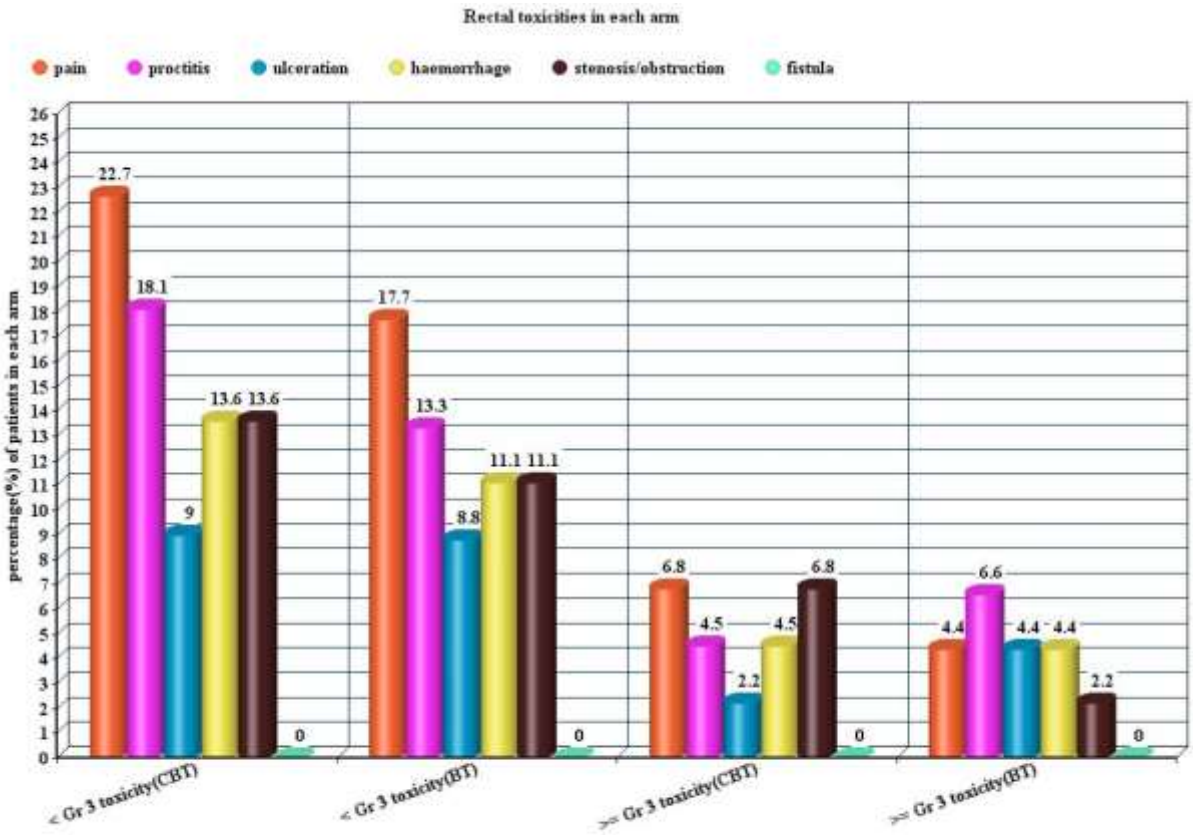

Figure 5: Rectal Toxicities during Follow-up.

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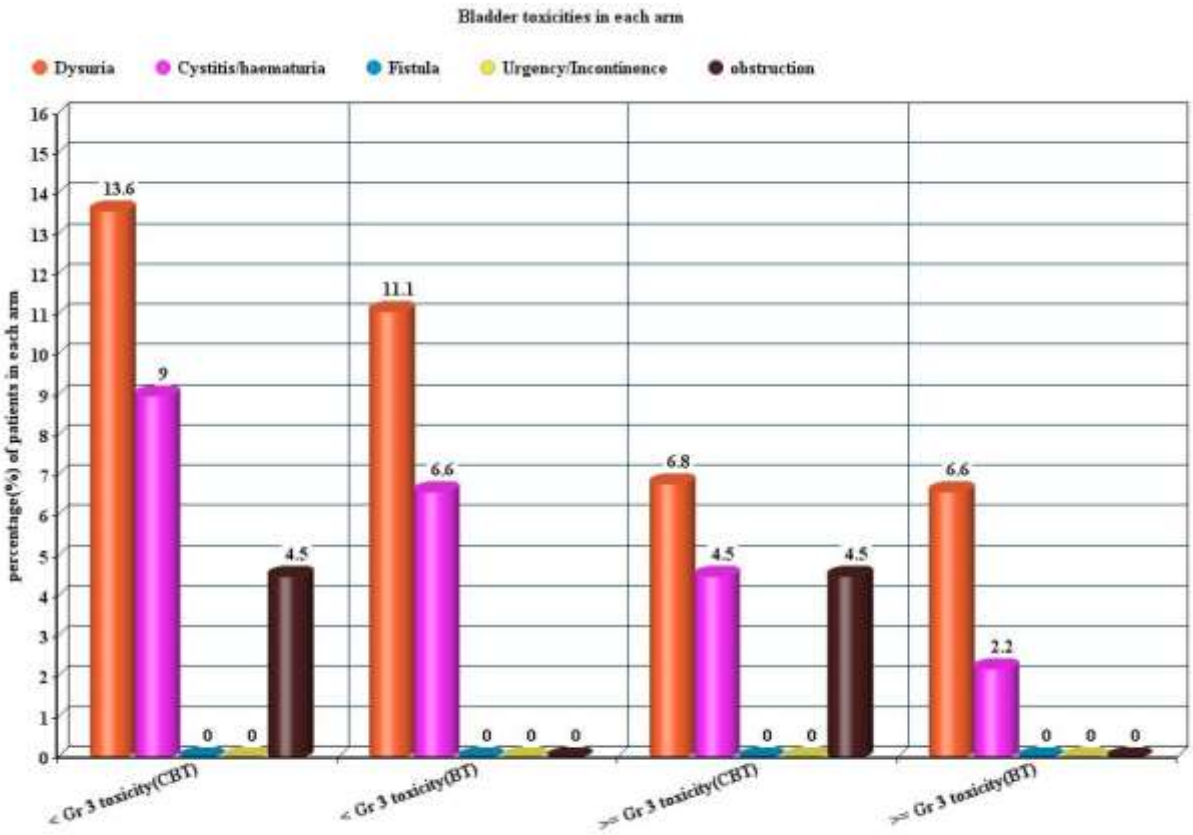

Figure 6: Bladder toxicities during follow-up.

TOXICITIES	Median time of appearance(CBT arm)(in months)	Median time of appearance(BT alone arm)(in months)
< Grade 3 Vaginal toxicity (chiefly, dryness)	5.2	5.8
≥Grade 3 Vaginal toxicity (chiefly, dryness)	7.8	9.1
<Grade 3 Rectal toxicity (chiefly, proctitis)	3.3	4
≥Grade 3 Rectal toxicity (chiefly, proctitis)	4.5	6
<Grade 3 Bladder toxicity (chiefly, dysuria and cystitis)	14.3	16.5
≥Grade 3 Bladder toxicity (chiefly, dysuria and cystitis)	15.3	17.2

Figure 7: Median time of appearance of vaginal, rectal and bladder toxicities in each arm.

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Discussion

As discussed above, stage of disease defines survival [4] and it is directly related to residual disease present after EBRT. An eminent Indian study on Response to EBRT as a prognostic determinant of Over-all and Disease-free survival (OS and DFS) was published in 2004 by Saibishkumar and Patel F et al [17]. This retrospective study included 556 patients of cancer cervix stage IIIB treated between 1996 and 2001 with EBRT (46Gy/23fx/4.5 weeks) followed by intracavitary radiotherapy (ICRT). At the end of EBRT, response to EBRT was grouped as 'no gross residual tumor' (NRT) or 'gross residual tumor' (GRT). At the end of EBRT, 393 patients (70.7%) attained NRT response. NRT responders had significantly better 5 year pelvic control, disease free survival (DFS) and overall survival(OS) than those who had a GRT response (75.6 vs. 54.6%; 60.6 vs. 31.9% and 62.6 vs. 33.7%, respectively; all P values <0.0001).

Owing to lack of awareness, adequate surveillance programmes and poorer socio-economic conditions, Indian patients present with greater tumor bulk for similar stages as compared to that in western population. Quite naturally, we have bigger residual tumors post CRT. So, we are all the more dependent on brachytherapy for curative outcome. In our study, we found only 32.7% patients to undergo a clinically CR after CRT. Since dose constraints of adjacent organs limits dose escalation beyond conventional HDR fraction sizes, the hypothesis of making brachytherapy more efficient by combining it with radio-senstising cisplatin was formulated and this study was conducted.

Literature search shows that studies on concurrent brachytherapy are really limited in number. The efficacy of concurrent brachytherapy alone (i.e., no external radiotherapy) was evaluated in a pilot study by E Koumentakis et al [18]. 36 women with locally advanced cervical cancer (FIGO IIA to IIIA) received two Cs-137 MDR applications, 1 week apart delivering a dose to point A of 20-25 Gy with each implant. Continuous cisplatin (80mg/m^2) and carboplatin (300mg/m2) were given during first and second applications respectively. Macroscopically complete response was observed in 25% of patients and 27.7 % patients had pathological complete response in resected surgical specimens. Another study by Eduard Vrdoljak et al [19] on concomitant chemo-brachytherapy enrolled sixty-two cervical cancer patients who received external radiotherapy (50 Gy in 25 fractions), followed by two low-dose rate brachytherapy applications along with concurrent ifosfamide (2 g/m^2) and cisplatin (75 mg/m2) .After the completion of radiotherapy, four cycles of consolidation chemotherapy with the same drug combination were administered. All the patients were reported to have achieved a complete response. The German study by Strauss et al [20] reported a 92.3% complete response rate in 27 patients treated with external radiotherapy followed by HDR brachytherapy fractions with weekly concurrent cisplatin. In our study, clinical response assessed 6 weeks after brachytherapy showed significantly greater complete responses with concurrent brachytherapy, 59% in CBT arm and 33.3% in BT arm. Also, CBT arm witnessed significantly lesser partial responses (36.3%) compared to BT arm (53.3%) (as shown in Figure 2). The inferior complete response rates in our study may be due to higher disease bulk, stage per stage, compared to German patients, although we are not sure of any reason behind it. No study has been conducted so far comparing CBT with BT alone to the best of our knowledge. The results of our study are quite encouraging considering it to be the first of its kind.

More than response, we were interested in the tolerability of concurrent chemotherapy with brachytherapy considering patients were already exposed to chemotherapy during external radiotherapy. In the study by Strauss et al. [20-24 latest article] acute grade III hematological toxicities were seen in 29.6% of patients. In our study also 25% patients of CBT arm experienced Gr III anemia. As described in results, greater incidence of systemic toxicities like mucositis, diarrhoea, nausea and vomiting in CBT arm are clearly due to higher cumulative dose of cisplatin received by these patients. The median time of appearance of bladder, rectal and vaginal toxicities were earlier in CBT arm; however, there were no significant differences in their frequencies in between the two groups. Rectal toxicities greater than or equal to Grade 3, chiefly pain and proctitis were observed in 6.8% and 4.5% of CBT patients (Fig 5). This agrees with 7.4% rate of serious late rectal toxicities found in the German study [20]. Coming to bladder toxicities, dysuria and cystitis lesser than Grade 3 were observed in 13.6% and 9% patients respectively in CBT arm, at a median time of 14.3 months. These results are supported by the latest Indian study on concurrent brachytherapy [21], where 15% patients suffered Grade I and II toxicities at around 12 months of follow-up.

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Conclusions

Since Indian radiation oncologists are faced with bulkier cervical tumours than their stage matched foreign counterparts , bigger residuals post concurrent external beam radiotherapy are a common finding and brachytherapy is our only stronghold against the obvious high risk of relapses. Combining brachytherapy with concurrent chemotherapy is not a standard recommendation, but worth experimenting given the radiosensitising effect of cisplatin on radiotherapy. At the same time, cumulative toxicity of cisplatin given with external radiotherapy and brachytherapy becomes the major concern with such an approach. We have found higher percentage of complete responses post brachytherapy in this study as well significantly increased systemic toxicities with concurrent brachytherapy. Loco-regional toxicities were also earlier with concurrent brachytherapy. Despite the encouraging results on the efficacy of concurrent brachytherapy, our study has few limitations too. It is well known that response to brachytherapy often takes months; hence, response assessment as early as 6 weeks post brachytherapy may not be representative of eventual clinical response. Recording of response during follow-up visits might have given a conclusive picture. Also, the median follow-up period of 11.1 months is quite small for any definitive conclusion. Lastly, we had very small study groups in either arm. For all these reasons, further studies on concurrent brachytherapy are required to arrive at any standard conclusion. Till then, this study upholds an interesting approach that can be regarded as feasible and tolerable for cervical cancer patients.

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