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Research Article

Comparison of compliance and response rate of radiotherapy alone vs. chemo radiotherapy in stage IIIB carcinoma cervix patients having obstructive uropathy

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ABSTRACT

Background: Carcinoma cervix is the second most common malignancy among females of India [(1)]. The low incidence rate in developed countries is because of well-developed screening programs and awareness among women. But in developing countries like India, because of lack of health awareness and lack of proper screening facilities, patients usually present in advanced stages. They also have a lot of associated co-morbidities like obstructive uropathy with or without deranged RFT, anaemia, poor nutrition, tuberculosis, diabetes, hypertension, multiple genital infections etc. The standard treatment of advanced carcinoma cervix is radiotherapy with weekly cisplatin as radio-sensitizer but it has been observed that a lot of patients are not able to tolerate toxic side effects of concurrent chemo radiotherapy.
Methods: We have chosen only one co-morbid condition i.e. obstructive uropathy with or without deranged RFT because of small sample size. So the aim of this study was to compare the compliance and response rate of concurrent chemo radiotherapy versus radiotherapy alone in patients of locally advanced carcinoma cervix having obstructive uropathy with or without deranged RFT.
Results: Only 36% (n=9) patients in the RT+CT group received the complete planned five cycles of weekly cisplatin. Average number of cycles of cisplatin missed in the chemo-radiotherapy group was one (range 0-3). Compliance was better in the RT alone group. The average time in the RT alone group to complete radiotherapy was 57.72 days and in RT+CT group was 60.72 days. In the RT alone group the treatment time was prolonged by an average of 1.72 days (range 3-6) while in the CT+RT group it was prolonged by 4.72 days (range 2-14).
Conclusions: It is hereby concluded that radiotherapy alone for locally advanced squamous cell cervical carcinoma patients having associated co morbid conditions like deranged RFT had a better compliance then with the concurrent chemoradiotherapy regime.

Keywords: Carcinoma cervix, Obstructive uropathy, Co-morbidities, Radiation alone, Chemoradiation, Compliance, Response rate

INTRODUCTION

Carcinoma cervix is the second most common malignancy among females of India.[1] According to GLOBOCAN 2012 database,[2] the incidence of this cancer in India is 1, 23,000, and the 5 year prevalence is 3,09,000. The age-adjusted incidence is 27 per 1,00,000 women which is the highest relative to all other types of cancer.

Cervical cancer is the fourth most common cancer in women, and the seventh overall worldwide, with an estimated 528,000 new cases in 2012. There were an estimated 266,000 deaths from cervical cancer worldwide

in 2012, accounting for 7.5% of all female cancer deaths. Mortality is more in the less developed countries (87%).

The low incidence rate in developed countries is because of well-developed screening programs and awareness among women. But in developing countries like India, because of lack of health awareness and lack of proper screening facilities, patients usually present in advanced stages.[35]

At our centre, Department of Radiotherapy, RNT Medical College, Udaipur, it is the most common cancer among females. In year 2011, total cases of carcinoma cervix were 480 which accounts for 30% of total cancer cases and 50% of all female malignancies. Patients usually present in advanced stage of cancer because of their illiteracy and unawareness. They also have a lot of associated co-morbidities like obstructive uropathy with or without deranged RFT, anaemia, poor nutrition, tuberculosis, diabetes, hypertension, multiple genital infections etc. The standard treatment of advanced carcinoma cervix is radiotherapy with weekly cisplatin as radio-sensitizer[7,8,9] but it has been observed that a lot of patients are not able to tolerate toxic side effects of concurrent chemo radiotherapy. This ultimately leads to break in radiotherapy treatment schedule and adequate compliance is not expected. A successful treatment schedule without the unplanned interruption is an important factor affecting the best result of treatment.[14,15] With the above mentioned co-morbidities, radiotherapy alone may be a better option to complete treatment with good compliance. We have chosen only one co-morbid condition i.e. obstructive uropathy with or without deranged RFT because of small sample size. So the aim of this study was to compare the compliance and response rate of concurrent chemo radiotherapy versus radiotherapy alone in patients of locally advanced carcinoma cervix having obstructive uropathy with or without deranged RFT. As has been already established, the standard protocol for treating locally advanced carcinoma cervix is radiotherapy with weekly cisplatin. Acute haematological and gastrointestinal toxicity is significantly higher in the concomitant chemo radiation group. Despite the fact that weekly cisplatin during radiation is well-tolerated, its nephrotoxicity is of particular concern in a patient population that frequently harbour renal dysfunction as a consequence of ureteral obstruction by the disease spreading to the pelvic wall or to the bladder. A lot of studies have proven that the associated co-morbidities reduce tolerance to this protocol leading to break in the radiotherapy treatment schedule. Many studies support this point.

Since it is very important to complete the entire treatment within the planned time without any unwanted gaps in the radiotherapy schedule. It can be observed in many trials that CT+RT is associated with more toxicity in patients especially those having associated co-morbid conditions. So it is more difficult to complete the treatment without any interruption in the concurrent chemoradiation group. Therefore, RT alone may be a better option in such patients.

METHODS

The Study Centre

RNT Medical College and Hospital, Udaipur, Rajasthan.

The Study Population

All patients included in the study were histo-pathologically proven squamous cell carcinoma the cervix FIGO Stage IIIB having obstructive uropathy with or without deranged RFT**.** Obstructive uropathy was diagnosed by USG. Patients with hydronephrosis upto Grade 3 were included in the study. Patients with this condition were equally randomized in the RT alone and RT+CT group. Urological intervention (PCN or DJ stent) was done in patients those presented with deranged RFT and treatment was started once RFT was within normal limits. RFT was monitored every week before weekly cisplatin

Inclusion Criteria

1. Age >30yrs or <70yrs
2. ECOG PS upto 02
3. Non-pregnant women
4. Fresh cases who have not received any anticancer treatment in the form of chemotherapy or radiotherapy earlier.
5. Stage IIIB with obstructive uropathy with or without deranged RFT.

Exclusion Criteria

1. Age <30yrs or >70yrs
2. Patients who have been previously treated
3. Pregnant women.
4. ECOG 04
5. Pathology other than squamous cell carcinoma
6. Patients having serum potassium level >6.5 were not included because of the risk of cardiac instability.

A number of other co-morbidities were also observed like anaemia, poor nutrition–weight<40kg, diabetes, hypertension–moderate to severe, tuberculosis-active disease, genital infections, g.i.t infections causing vomiting, diarrhoea and dehydration. But because of small sample size these were not taken into consideration for this study.

Pretreatment Evaluations

A Proforma was made for each patient in which history of symptoms along with patient's general, systemic and local examination findings and reports were entered.

The pattern of clinical work up was –

(a) Detailed history of patient including age, presenting complaint, duration of symptoms, menstrual, obstetrical, personnel history & any significant past history.
(b) General physical examination and systemic examination: The assessment of general condition was done by using ECOG Performance status and state of nutrition, anaemia, state of genital hygiene, clinical evidence of any lymphadenopathy, clinical examination of other organ to exclude any evidence of distant metastasis or any other associated pathological condition was recorded. Per abdominal examination for any lump or scar mark. The examination of cardiovascular system, respiratory system, gastro-intestinal tract and central nervous system was done routinely.
(c) Detailed local examination: Local examination of introitus, labia majora & minora, vulva and perineal area along with both groins and inguinal region. Per speculum examination of cervix and vagina. Per vaginal examination to know status of fornices, both vaginal wall and cervix. Per rectal examination for rectal mucosa, endocervical disease, parametria and utero-sacral ligament.
(d) Investigations: Laboratory Studies (within 2 weeks preregistration)

- Complete Haemogram
- Blood Urea, Serum Creatinine
- Liver Function Test
- Serum electrolytes

Required Imaging Studies

- Chest x-ray
- USG abdomen and pelvis

Optional Studies

- CECT/MRI of Abdomen and Pelvis
- Cystoscopy and
- Proctoscopy was done for accurate staging and when clinically indicated

When all investigations other than RFT were within normal limits, patient's consent was taken after explaining the nature of disease, its treatment and side effects in her own vernacular language.

Staging

All patients were staged according to the FIGO staging system.

Randomisation

The cases were randomly distributed among RT alone group and RT+CT group on the basis of odd and even number.

Arm CT+RT (Control arm) - 30 patients planned for concurrent chemo- radiotherapy. Injection cisplatin 35-40mg/m^2 was given every week in infusion form before one hour to teletherapy fraction to a maximum of five cycles.

Arm RT ALONE (Case arm) - 30 patients planned for radiotherapy alone.

Symptomatic Treatment

All the patients having Hb<10g% were given oral and parenteral iron and folic acid supplements while those having Hb<8g% were given blood transfusions before starting the treatment and also during radiotherapy according to the need. The nutritional status of patients was improved and any genital or g.i.t infections were treated with the appropriate antibiotics. Any electrolyte imbalance if present was corrected. DJ stenting or PCN was done in the patients having deranged RFT in both the study and control group before starting the treatment.

Radiotherapy Treatment Protocol Schedule

Teletherapy (EBRT) was given for five days in a week from Monday to Friday by teletherapy machine ATC-C/9 using Co-60 source by SAD technique by AP/PA portal using conventional simulation. Brachytherapy (ICRT) was given by Eikert and Zeigler HDR machine using Co-60 source. The upper border of the pelvic field was at the L4-L5 junction; the lower border was at the lower most part of the obturator foramen, which was modified according to the vaginal extent the disease. The lateral borders were kept 2.0 cm beyond the widest part of pelvic brim.

External Beam Radiotherapy dose of 50Gy in 25 fr @ 200cGy/fr followed by 4 sessions of ICRT (6Gy/session) was given. After one week of completion of EBRT if found suitable HDR Brachytherapy application was done every fourth day and patients found unfit for brachytherapy EBRT were continued till 60-65Gy according to departmental protocol.

Total dose to Point A
EBRT =50Gy
ICRT =6Gyx4sessions=24Gy
EQD2=32Gy

Observation During Radiotherapy

All patients were investigated once weekly during the treatment. Haemogram and biochemical investigation was done and noted before giving every cycle of chemotherapy. Any delay causing treatment interruption was noted and necessary gap correction for radiotherapy was done. Chemotherapy was withheld during radiotherapy interruptions. Only the patients completing the complete schedule of radiotherapy were evaluated for response and follow up.

Response was assessed by local examination.

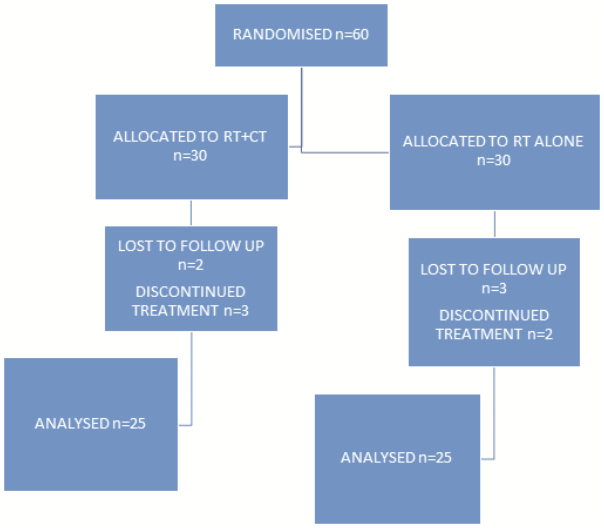
Acute mucosal and skin toxicity was assessed as per the RTOG/EORTC Acute Radiation Morbidity Scoring system.

Chemotherapy induced toxicity like nausea, vomiting, renal and haematological toxicities were assessed as per the Common Terminology Criteria for Adverse Events version 4.02.

The results of RT alone group were analysed & compared with RT+CT group in terms of various aspects like compliance, side effects, tumour response, & local disease status. The data thus collected are analysed by using Chi-square test for co-relation using Medcalc version 12.3.0.0.

Evaluation After Completion of Treatment

At the one month of completion of treatment patients were assessed for toxicity and at three months for response. Comparison of response rate was done after one year.



RESULTS

In the control group concurrent chemo radiotherapy was given while in the study group radiotherapy alone was given. Patients were equally randomised in the two groups on the basis of their age, stage, ECOG-PS and comorbid condition by odd and even number method.

Both the groups were well randomised in age wise distribution. The age wise distribution of patients in both the groups is summarized in Table 1, which shows that the patients were in the age group of 30-70yrs. 56% patients in RT alone group and 60% in RT+CT group were in their 4th and 5th decade of life. Mean age of presentation was 46.92 and 47 years for RT alone & RT+CT group respectively (Figure 3).

Table 1

AGE (yrs.)	RT alone	RT+CT
30-40	9	9
41-50	7	6
51-60	7	8
61-70	2	2

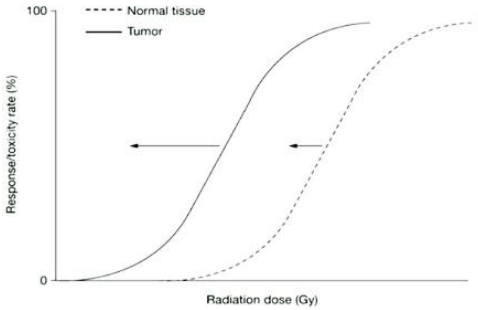


Figure 1: Schematic dose-response curves for tumour and normal tissue damage with radiation. The offset between the two curves indicates the therapeutic range. Chemo radiotherapy leads to a shift of both curves to the left, ideally with a stronger shift of the tumour curve (as indicated by the longer arrow), increasing overall efficacy of treatment (radiation enhancement).

Table 2 shows the distribution of patients according to ECOG performance status. Both the groups were well randomised according to ECOG-PS status. 8% patients in both groups have ECOG-PS of 01. 36% patients in RT alone group and 40% in RT +CT group have score of 02. 56% in RT alone and 52% in RT+CT group have a score of 03 (Figure 5).

Table 2

ECOG-PS	RT alone	RT+CT
01	2	2
02	9	10
03	14	13
04	0	0

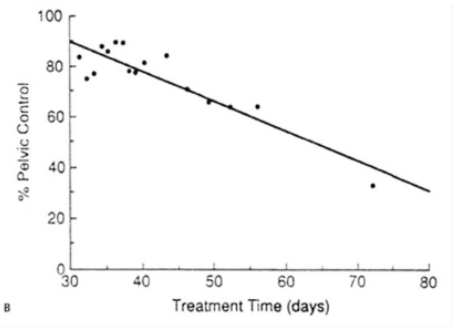
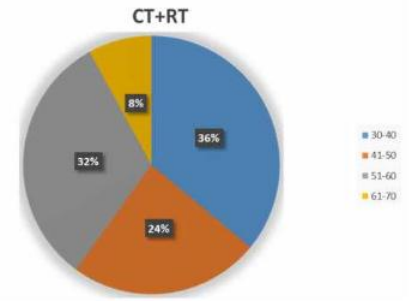


Figure 2: Pelvic control as a function of treatment time for 621 patients treated with a total dose of 85 Gy. (44).

Out of 25 RT + CT patients, nine had deranged RFT for which six had to undergo DJ stenting and PCN was done in two patients. RFT was monitored every week before weekly cisplatin. Out of the 25 patients in RT alone group, six patients had deranged RFT for which five needed DJ stenting and one needed PCN before the start of treatment. Invasive procedures were required more in RT+CT group because RFT needed to be normal to deliver weekly cisplatin on time.

Table 3

	RT Alone	RT+CT
Dj Stent	5	6
Pcn	1	3
No Urological Intervention	19	16



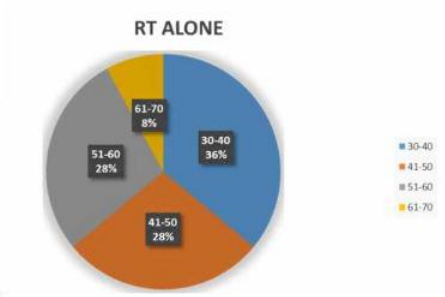


Figure 3

Table 4 shows leukopenia observed among the RT alone and RT+CT group. In patients receiving cisplatin along with RT 40% patients had Grade 1, 24% Grade2, 20% Grade 3 and 1% grade 4 leukopenia while in patients on RT alone only 8% experienced grade1 toxicity

Table 4

Leukopenia Grade	RT alone	RT+CT
0	23	3
1	2	10
2	0	6
3	0	5
4	0	1

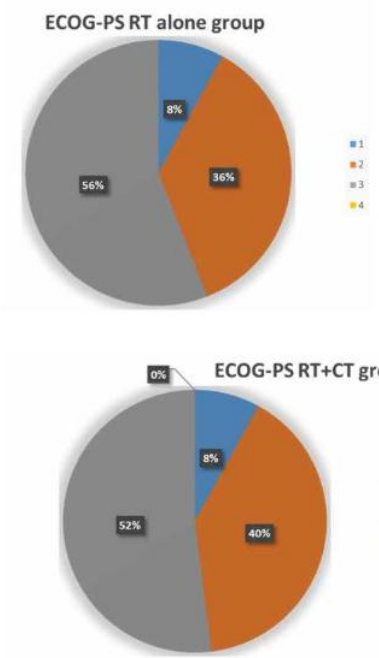


Figure 4

Table 5 compares haemoglobin toxicity among RT alone and RT+CT group. Among patients given cisplatin, 32% had Grade 1, 28% grade 2, 24% grade 3 and 1% grade 4 anaemia. In the RT alone group, 40% patients had grade 1 anaemia only.

Table 5

Anaemia Grade	RT alone	RT+CT
0	15	3
1	10	8
2	0	7
3	0	6
4	0	1

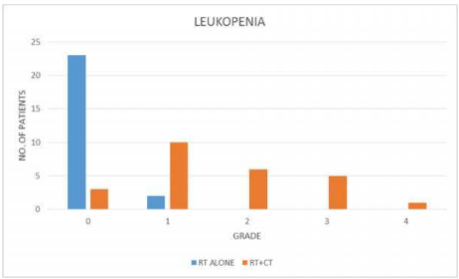


Figure 5

Table 6 compares platelet toxicity observed in RT alone and CT+RT group. In RT+CT group, 32% had grade 1, 16% grade 2 and 8% grade 3 thrombocytopenia. In the RT alone group only 8% had grade 1 toxicity.

Table 6

Thrombocytopenia Grade	RT alone	RT+CT
0	23	11
1	2	8
2	0	4
3	0	2
4	0	0

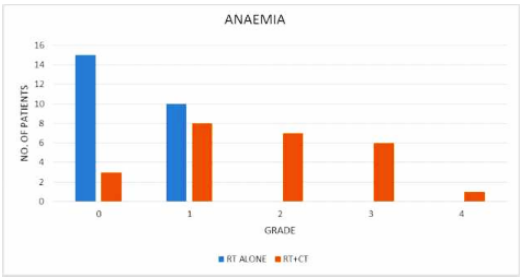


Figure 6

Table 7 compares radiation skin reactions among RT alone and RT+CT group. In RT+CT group, 44% had grade1, 36% grade 2, 16% grade 3 and 1% grade 4 skin reaction while in RT alone group, 76% had grade1 reaction only, 20% had grade 2 and 1% had grade 3 reaction. Grade 4 reaction seen in the RT+CT group patient was because of the obese patient having more AP separation leading to ulceration in the sacral region at 44 Gy EBRT dose only.

Table 7

Skin Reactions	RT alone	RT+CT
1	19	11
2	5	9
3	1	4
4	0	1

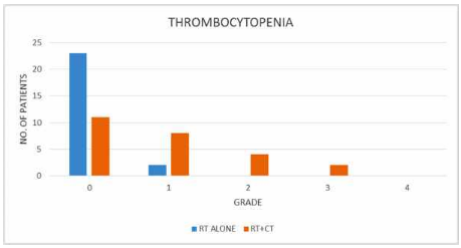


Figure 7

Table 8 compares gastro-intestinal mucosal reactions among RT alone and RT+CT group. In RT+CT group, 60% had no mucosal reaction, 32% had grade1 and 8% grade 2 reaction. In RT alone group, 82% had no mucosal reaction and only 16% had grade 1 reaction.

Table 8

Mucosal Reactions	RT alone	RT+CT
0	21	15
1	4	8
2	0	2
3	0	0
4	0	0

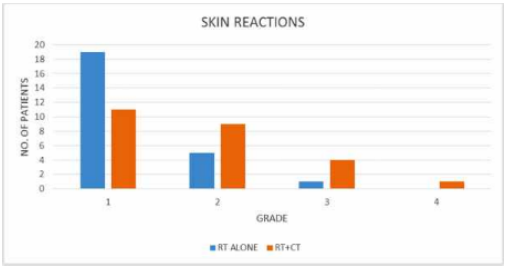


Figure 8

Table 9 compares upper GI toxicity in the RT alone and RT+CT group. In the RT alone group, 48% had grade 1 nausea and vomiting, 36% grade 2 and 8% grade 3. In the RT+CT group, 28% had grade 1 reaction, 32% grade 2 and 3 while 8% had grade 4 reaction.

Table 9

UPPER GI	RT alone	RT+CT
0	2	0
1	12	7
2	9	8
3	2	8
4	0	2

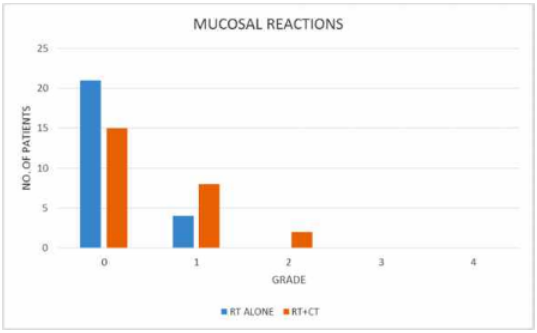


Figure 9

Table 10 compares lower GI toxicity in the two groups. In RT+CT group 20% had grade1, 28% grade 2, 32% grade 3 diarrhoea. In the RT alone group, 48% had only grade1, 8% grade 2 and grade 3 reaction.

Table 10

Lower GI	RT Alone	RT+CT
0	9	5
1	12	5
2	2	7
3	2	8
4	0	0

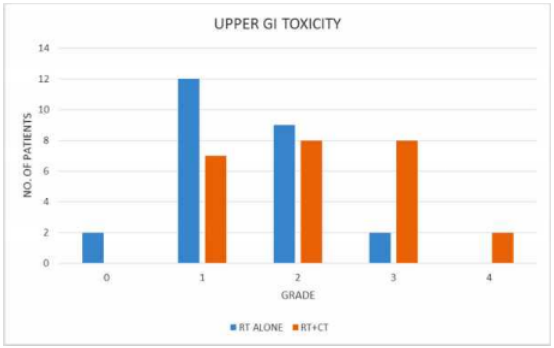


Figure 10

Table 11 compares liver function toxicity among the RT alone and RT+CT group. There is no significant difference between the two groups

Table 11

	S. bilirubin	SGOT	SGPT	Alk. Phos.
RT Alone	2	1	2	1
RT+CT	3	1	2	1

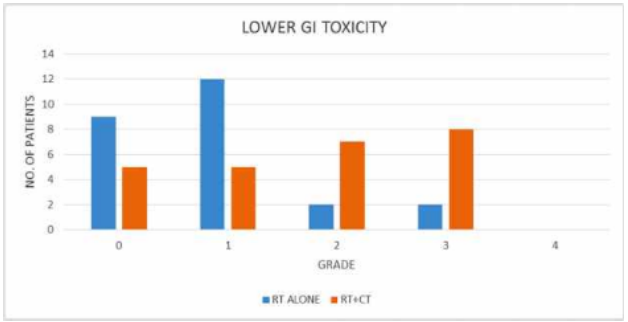


Figure 11

Table 12 shows the no. of chemotherapy cycles missed by the patients in RT+CT group. 36% patients did not miss any cycle, 32% patients missed one cycle, 28% missed two cycles and only one patient had to miss three cycles. The chemotherapy cycles missed was because of the deranged RFT and excessive upper GI toxicity and haematological toxicity caused by cisplatin in the RT+CT group.

Table 12

No. of cisplatin cycles missed	No. of patients
0	9
1	8
2	7
3	1

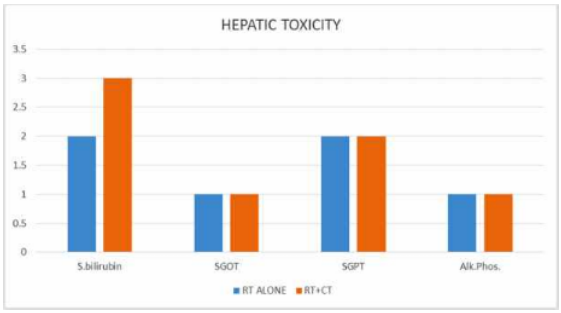


Figure 12

Table 13 compares treatment time prolongation between RT alone and RT+CT group. Ideally treatment should be completed within 8wks. 8 patients in RT+CT group had treatment time prolonged by 1-5 days because of Grade 2 or 3 nausea, vomiting. In 9 patients treatment was delayed by 6-10 days because of the grade 3 diarrhoea for which patient had to be admitted and managed with i.v fluids. One patient developed grade 4 skin reaction. Time was required to get done DJ stenting or PCN of the patients whose RFT deteriorated while on treatment. One patient had a gap of >10 days which was because of dialysis required by that patient to improve renal function

Table 13

Treatment Time Prolongation (Days)	RT alone	RT+CT
0	15	7
1-5	8	8
6-10	2	9
>10	0	1

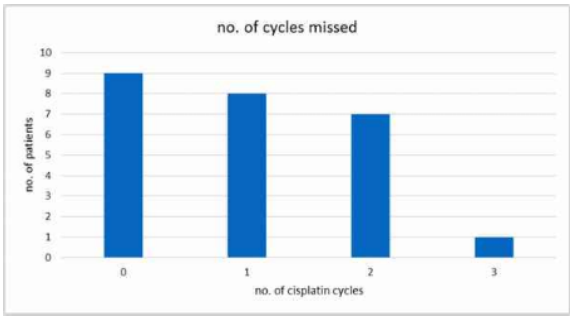


Figure 13

Table 14 compares response among the RT alone and RT+CT group. Response was assessed after one year of completion of treatment by local examination. It was observed that 70% patients in RT+CT group while 68% in the RT alone group were free from disease. Those having disease at one were further managed according to institutional protocol.

Table 14

Local Exam. After One Year	RT alone	RT+CT
Normal	17	18
Disease	8	7

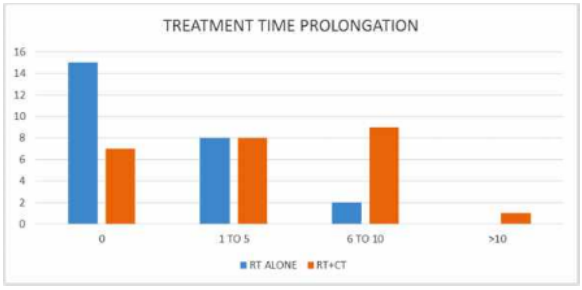


Figure 14

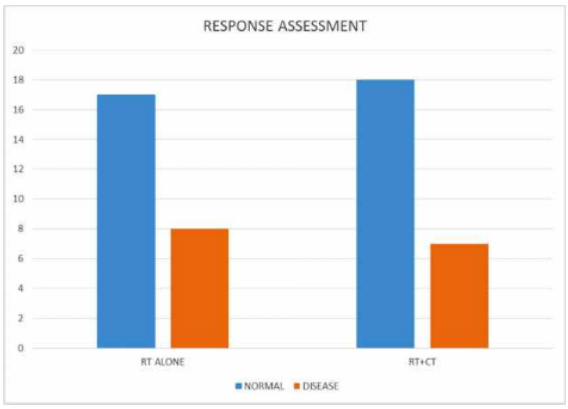


Figure 15

DISCUSSION

The present study was carried out on 60 histopathologically confirmed newly diagnosed cases of squamous cell carcinoma cervix Stage IIIB from October, 2011 to January, 2012. Out of 60 patients, five patients in RT+CT group and five patients in RT alone group were not included because five of them left the treatment and five did not come for follow up at the time of response assessment. So these ten patients were not included in statistical analysis. The aim of this prospective study was to evaluate toxicity, compliance and response of weekly cisplatin concurrent with radiotherapy versus radiotherapy alone in the treatment of locally advanced squamous cell carcinoma cervix patients with associated comorbidity eg:- deranged RFT.

In the present study, 80% patients were from rural background while 20% were from urban background, mostly in their 4th and 5th decade of life having ECOG performance scale of 02 and deranged RFT. Most common histopathological finding was moderately differentiated squamous cell carcinoma.

In the present study, patients in the RT+CT group were given 5 cycles of weekly cisplatin 35-40mg/m^2 along with the EBRT whereas patients in the RT alone group were given radiotherapy alone. Radiotherapy protocol was same in RT alone and RT+CT group i.e. 50Gy by External Beam Cobalt-60, SAD technique by conventional fraction of 2Gy/fr through parallel opposed anterior and posterior fields, along with 4 fractions of HDR brachytherapy each of 6Gy four days apart after completion of EBRT.

In the present study there was statistically significant toxicity difference between the RT alone group and RT+CT group for acute skin reaction, nausea and vomiting, acute diarrhoea, haematological toxicity like anaemia and leukopenia during treatment.

In the present study, among patients receiving cisplatin along with RT 40% (n=10) had Grade 1, 24% (n=6) Grade 2, 20% (n=5) Grade 3 and 4% (n=1) grade 4 leukopenia while in patients on RT alone only 8% (n=2) experienced grade1 toxicity. So there was significant difference (p=0.000) in leukopenia between the two groups. The most common side effect seen is this study is also upper GI toxicity which is more aggravated because of deranged RFT in these patients. In the RT alone group, 48% (n=12) had grade 1 nausea and vomiting, 36% (n=9) grade 2 and 8% (n=2) grade 3 while none of the patients experienced grade 4 toxicity. In the RT+CT group, 28% (n=7) had grade 2 reaction, 32% (n=8) grade 3 and 4 while 8% (n=2) had grade 4 reaction.

In this study, 36% (n=9) patients received five cycles out which only 24% (n=6) completed these cycles in the planned time while in 8% (n=2) of the patients treatment time had to be prolonged to complete these five cycles. This difference from above mentioned randomised trials is because the patients included in the present study have associated comorbid condition of deranged RFT. 32% (n=8) patients received four cycles, 28% (n=7) missed two cycles and only one patient had to miss three cycles.

Response assessment at one year by local examination in our study showed 70% in RT+CT group and 68% response in RT alone group. The difference is statistically insignificant (p=0.779).

Pelvic RT with cisplatin is considered a standard treatment for carcinoma cervix patients in stage 1B2 onwards but in certain proportion of patients having associated comorbid condition like deranged RFT, pelvic RT combined with weekly cisplatin is accompanied by considerable acute toxicity. Administration of the full chemotherapy dose may

be difficult, and the completion of planned radiotherapy on time is generally compromised.

A prospective clinical study was undertaken to evaluate response of the two different protocols in locally advanced squamous cell cervical carcinoma associated with comorbidities, namely concurrent chemoradiotherapy versus radiotherapy alone. The aim of the study was to evaluate toxicity, compliance and response among these two groups.

Toxicity in the form of leukopenia (p=0.000), acute diarrhoea (p=0.008) and vomiting (p=0.006), acute skin reactions (p=0.016) was seen more in RT+CT group then RT alone group.

Only 36% (n=9) patients in the RT+CT group received the complete planned five cycles of weekly cisplatin. Average number of cycles of cisplatin missed in the chemo-radiotherapy group was one (range 0-3). Compliance was better in the RT alone group. The average time in the RT alone group to complete radiotherapy was 57.72 days and in RT+CT group was 60.72 days. In the RT alone group the treatment time was prolonged by an average of 1.72 days (range 3-6) while in the CT+RT group it was prolonged by 4.72 days (range 2-14).

The response of treatment in both the groups was assessed by FIGO criteria. After one year of completion of treatment 68% (n=17) patients of RT alone group and 70% (n=18) of RT+CT group had complete response. The difference in response among the two groups was statistically insignificant (p=0.779).

It is hereby concluded that radiotherapy alone for locally advanced squamous cell cervical carcinoma patients having associated co morbid conditions like deranged RFT had a better compliance then with the concurrent chemoradiotherapy regime. Further study on a larger group of people is needed to prove the results.

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