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Circadian Variations in Patients of Cervical Carcinoma on Pelvic External Beam Radiotherapy

Madisetty Adilakshmi[1], Munagapati Vishnu Priya[2], Pasala Lakshmi Priyanka[3]

Author's Affiliation: [1]Associate Professor, [2]Assistant Professor, [3]Post Graduate, Department of Radiotherapy, MNJIO and RCC, Osmania Medical College, Hyderabad, Telangana 500095, India.

Corresponding Author: Vishnu Priya, Assistant Professor, Department of Radiotherapy, MNJIO and RCC, Osmania Medical College, Hyderabad, Telangana 500095, India.

E-mail: mnjadi1963@yahoo.com

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Abstract

Introduction: The cancer of uterine cervix is one of the leading sites of primary cancers in women around the world. External beam radiotherapy along with Brachytherapy may be routinely administered to cervical cancer patients – stages I B2 to IVA in a curative fashion. Proctitis, a radiotherapy associated toxicity in pelvic irradiation is the main cause of treatment interruptions and discontinuation of treatment. *Aim:* To evaluate any relationship between the severity of acute gastrointestinal mucositis and the time of radiation during a day with respect to circadian rhythm in patients of cervical carcinoma on pelvic EBRT. *Materials and methods:* Prospective randomized 2 arm comparative study. Total of 50 patients were included in the study. Patients with squamous cell carcinoma of the uterine cervix stages IB2 to IVA were randomly allocated to 2 groups-group A and group B. Group A patients received radiation in the morning (8.00-10.00AM) and patients in group B received radiation in the evening (6.00-8.00PM) Each patient was informed about the technique and informed consent was obtained. All patients underwent CT-simulation and 3D conformal treatment planning. *Results:* Incidence and severity of intestinal mucositis is more in the morning arm than in the evening arm. There is no difference in the tumour response rates between the morning and evening arm. Haematological toxicity showed very high significant occurrence ($p < 0.001$) in the CRT arm compared to ART arm. Nausea, dermatological side effects, fever, vaginal discharge and bladder irritation showed no statistically significant difference. *Conclusion:* The final conclusion of this study is there is more incidence and severity of intestinal mucositis in patients receiving RT in the morning indirectly indicating the role of circadian cycle which is most active during early hours on the cell cycle.

Keywords: Cervical Carcinoma; Radiotherapy.

Introduction

The cancer of uterine cervix is one of the leading sites of primary cancers in women around the world. Worldwide, cervical cancer remains the most common gynaecologic cancer and the third-most-common malignancy in women, with over 500,000 women globally developing this tumour and 233,000 dying of the disease every year. In developing countries like India, carcinoma cervix is the leading cause of cancer related death. Unlike many other cancers, cervical cancer occurs early and strikes at the productive period of a woman's life. The incidence rises in 30–34 years of age and peaks at 55–65 years, with a median age of 38 years (age 21–67 years) [1]. Poverty, ignorance and lack of proper screening facilities at the primary care level are the root causes for the presentation of patients at locally advanced stages [2,3].

Since early 1900 radiation has been used in curative management of cervical cancer with combination of EBRT and brachytherapy [4]. External beam radiotherapy along with Brachytherapy may be routinely administered to cervical cancer patients – stages I B2 to IVA in a curative fashion. Exposure to ionising radiation during Radiotherapy to abdominopelvic organs is associated with development of treatment related toxicity. Proctitis, a radiotherapy associated toxicity in pelvic irradiation is the main cause of treatment

interruptions and discontinuation of treatment [4].

The severity of intestinal mucositis in patients undergoing Radiotherapy depends upon number of patient and treatment related variables including age, smoking, variations in position of rectum due to either empty bowel or due to fully loaded rectum, radiation dose and fractionation and may also depend upon time of administration of radiation in addition to other factors [5]. In this study the presence of any correlation between theseverity of acute gastrointestinal mucositis and the time of radiation in cervical cancer patients was prospectively evaluated.

Materials and Methods

This randomised prospective study was conducted from January 2016 to july 2017 on patients receiving external beam radiotherapy (EBRT) for Ca. Cervix at the department of radiotherapy, MNJ institute of oncology and regional cancer centre, Hyderabad, India. Ethical clearance was obtained from the institute's ethical committee. Total of 50 patients were included in the study during this period. Informed consent was obtained according to institutional ethical committee requirements

Inclusion criteria

Site: Uterine cervix

Stages: IB2 to IVA

Age: 30-65 years

Performance status: ECOG PS 0-2

HPE: Well differentiated squamous cell carcinoma.

Haemoglobin>10g%

WBC count > 4000/mm3

Platelets > 100000/mm3

Blood Urea<30 mg%

Serum creatinine<1.5 mg%

Normal liver function tests

Exclusion criteria

Site: spread to other sites inside or outside the pelvis.

Stage: IA1, IA2, IB1 and IVB

Age: younger than 30 years or older than 65 years

Performance status: ECOG 3 and 4 (ANNEXURE-II)

HPE: other than squamous cell carcinoma

Haemoglobin<10g%

WBC count < 4000/mm3

Platelets < 100000/mm3

Blood Urea >30 mg%

Serum creatinine>1.5 mg%

Abnormal liver function tests

Patients previously treated with surgery or radiotherapy

Any co morbid condition or infection where treatment is contra-indicated

Clinical or radiological evidence of metastasis

Any coexisting malignancy

Pregnancy

Participation in any other clinical trial.

Discontinuation of treatment for more than 5 days.

Good clinical practice and informed consent

Study will be conducted after receiving the necessary approval from Ethics Committee, Osmania Medical College. Patient's informed consent will be taken after explaining the nature of the disease, its treatment and nature of the side effects in her own vernacular language. Patient will be counseled about maintaining good perineal hygiene throughout the treatment and to come for weekly follow ups and to contact whenever necessary and for weekly cisplatin in the control arm.

Pre-treatment evaluation

Complete history and physical examination including punch biopsy from the cervical lesion.

Complete blood picture, renal function tests and liver function tests.

Chest x-ray PA view

Ultrasound of the abdomen and pelvis.

CT scan abdomen and pelvis if clinically or on ultrasound there is suspicion of bladder or rectal wall involvement and MRI pelvis if parametrium cannot assessed adequately on clinical examination.

Any other investigation as and when needed.

Treatment:

Patients with squamous cell carcinoma of the

uterine cervix stages IB2 to IVA were randomly allocated to 2 groups-group A and Group B. Group A patients received radiation in the morning (8.00-10.00AM) and patients in group B received radiation in the evening (6.00-8.00PM) Each patient was informed about the technique and informed consent was obtained. All patients underwent CT-simulation and 3D conformal treatment planning.

Process of Randomization

Patients are explained about the whole study and evidence shown to them and they are randomly allocated to one of the 2 groups as per their IP registration number in MNJ cancer hospital i.e. first registered number to the group A and the next to the group B and again the next number to the group A and so on and so forth.

Parametrial Involvement Index:

In FIGO staging of Carcinoma Cervix stratification of stage IIB in terms of prognosis was not done i.e. involvement of medial 1/3 of parametrium on one side was assigned stage IIB, involvement of medial 1/3 of parametrium on both sides was also under stage IIB and involvement of bilateral parametrium just short of pelvic side wall was also included under stage IIB. If parametrial disease was up to pelvic side wall on one side or both the sides it was stage IIIB only.

All these entities have different volumes of disease and response to radiotherapy and presence of any one entity in one group in excess may lead to bias in the results. Hence to circumvent this problem in FIGO staging in this study parametrial involvement score was given. Parametrium was divided into medial 1/3, middle 1/3 and lateral 1/3 and score of 1 for involvement of each on one side i.e. if the patient had involvement of bilateral parametrium in the medial 1/3rds score of 1+1=2 was given, similarly involvement of medial 1/3rd on one side and medial 2/3rds on other side was given a score of 1+2=3. Minimum score was 1 and maximum score was 6 i.e. 3+3 if bilateral parametrium was involved up to pelvic side walls on both the sides. It was made sure that the parametrial involvement index was similar in both the groups and hence the volume of the disease treated in IIB and IIIB was equally distributed among both the treatment groups.

In both group A and group B patients will be given RT in the form of 2 Gy per day for 5 fractions a week to a total dose of 50 Gy in 25 fractions for a span of 5 weeks along with weekly cisplatin in a dose of 40mg/m2 followed immediately by 3 fractions of HDR intra cavitary brachytherapy (ICBT) in doses of 700cGy in 3 fractions achieving a dose of 85Gy equivalent to point A. ICBT was started within a week of the last fraction of EBRT subject to vacancy in the ICBT theatre list.

Radiation technique

Immobilization

Patient is asked to defecate before coming to the hospital and immobilized in a thermoplastic mask in supine position with full bladder i.e. the patient is asked to have 500 ml of water and asked to wait half an hour and the thermoplastic mask is made and the patient is advised to take treatment daily with a full bladder and an empty rectum as on the day of making the thermoplastic mask.

CT-Simulation

Patient is simulated in supine position with hands above the head on a flat couch in the dedicated CT-simulator facility at the institution. Fiducials are used to mark virtual isocenter and it was also useful to reproduce the simulated position while treating. The axial scans are acquired at 3-mm-slice thicknesses.

Contouring

CT images were imported to TPS (Treatment Planning System) and a 3D image was reconstructed. Body contour is marked with green colour and user origin is set in the plane where the fiducials kept during simulation on the external surface are visible. The uterine corpus and cervix are contoured as the CTV (clinical target volume) and PTV (planning target volume) is generated by giving 0.5 cm margin to the CTV, bladder, rectum and the femoral heads contoured in different colours, entire bowel bag coming into the field is contoured with a different colour.

Planning

DRR (Digitally reconstructed radiograph) is generated and then radiation treatment portals were placed using beams eye view. A four field box technique or a 2 field (AP-PA) technique is used based on the separation of the patient. If the patient separation was more than 20 cm four field box technique was used and if it is less than 20 cm two (AP-PA) field technique was used. Borders of the pelvic field used in AP/PA portals are as:

Superior border: CT visualized bifurcation of the common iliac nodes into external and internal iliac nodes which may be as high as L3-L4 interspace.

Inferior border: to cover 2cm below the lowest extent of disease which most of the Times is obturator foramen but in bulky tumours it can be extended to ischial.

Tuberosity or may lie in the vulvar tissue and in such cases inguinal lymph nodes are treated resulting in a wider AP field.

Lateral border: 1.5 cm from the pelvic brim. The dose will be prescribed on the central ray at mid-separation of the coaxial equally weighted beams.

Borders of the pelvic field used in lateral portals are as follows:

Anterior border: vertical line anterior to the pubic symphysis in order to cover the external iliac nodes

Posterior border: entire sacral hollow is included in order to include utero sacral ligaments.

Superior and inferior border is the same as AP/PA portals. 60% of the dose is delivered through AP/PA (30% each portal) portals and 40%(20% each portal) of the dose through lateral portals in four field box technique and 50% through each portal in 2 field AP/PA technique. Major portion of marrow in the iliac fossae and femoral head and neck are shielded with MLCs (multi-leaf collimators). dose to be prescribed at the isocenter of the beams; the maximum and minimum doses in the target volume should be within ± 5% of the dose at the isocenter.

Plan evaluation

After prescribing RT dose, plan was evaluated for dose homogeneity, cold and hotspots in the target area and dose constraints of OARs. Dose distribution maintained between 95% and 107%.

Implementation

Simulated position was reproduced using thermoplastic mask, fiducials. Planning was implemented on treatment machine using EPID (Electronic Portal Imaging Device). Images taken from EPID were matched with DRR in 3 dimensions to reproduce the simulated position

Chemotherapy

Chemotherapy with cisplatin of a uniform dose of 40mg/m2 was given to patients intravenously immediately the next day after the 1st fraction of cisplatin and was ensured that the patient had taken radiotherapy on the day of infusion after 4 hours after cisplatin therapy and even the next day after that. Patient was given tablet zofer 8 mg thrice a day for 5 days as routine anti emetic therapy after cisplatin. Thereafter it was repeated weekly for the entire duration of EBRT.

Cisplatin regimen

Injection Granisetron 3mg IV

Injection Dexamethasone 8mg IV

Injection Rantidine 50mg IV

Injection MgSO4, 1 ampoule in 1 pint 5% D IV over 1 hour

Injection Cisplatin, 50 mg in 1 pint NS IV over 1 hour infusion

Treatment Monitoring

All patients were treated with curative intent with no intended gaps during the external therapy. Hydration, protein and caloric intake and hygiene were adequately maintained for all the patients during the entire treatment course. No enemas or bowel preparations were used during external beam RT. Haemogram and biochemical investigation was done and noted before giving chemotherapy. Patients were given symptomatic treatment such as antimotility drugs and intravenous fluids as and when required. All patients were examined once weekly during the treatment and radiation induced mucositis was assessed by a single observer and graded in terms of diarrhoea using Radiation Therapy Oncology Groups Common Toxicity Criteria. The clinical appearance of the primary tumour and at the initiation of treatment was noted. The regression of primary tumour during the treatment was assessed and noted weekly. Any delay causing treatment interruption was noted and necessary gap correction for radiotherapy was done. Patient completing the full schedule of radiotherapy irrespective of the delay and receiving chemotherapy were evaluated for response and assessed for intracavitary brachytherapy (ICBT) feasibility. 1st fraction of High dose rate (HDR) intracavitary brachytherapy was given within 1 week of completion of external beam radiation as 7Gy per fraction in total 3 fractions with a week gap between each fraction. and patients with parametrial disease after 50Gy of EBRT were boosted to 60Gy with midline block.

Technique of High Dose Rate Intracavitary brachytherapy.

Preparation of the patient

Patient is explained the entire procedure and consent taken. They are admitted the day before the procedure and kept nil per orally from 11 pm of the previous night onwards and given 2 tablets of Bisacodyl at bed time. Anxious patients are given 0.25mg alprazolam 1 hour before sleep. On the morning of the procedure part preparation is done and a soap water enema is given 2hr prior to taking up the patient into the operating room.

In the operating room

Patient is given a sterilized dress and slippers and taken into the operating room Patient is positioned in lithotomy position and sedated with intravenous Pentazocine and intravenous Phenergan. Perineum is cleaned with betadine and normal saline and draped. Per vaginal examination is done and os sounded and central tandem Length decided accordingly. Foleys catheter is inserted. Fletcher suite declos applicator or Henski's applicator is used based on the vaginal anatomy. Adequate anterior and posterior packing with gauze soaked in betadine is done to physically push bladder and rectum away from the tandem and ovoids. Rectal tube is inserted after packing is done and the patient moved on the same couch into CT simulator room and planning CT scan is acquired, imported into 3D TPS and once the plan is approved it is exported to the brachytherapy remote after loading machine with Ir-192 source for treatment. In the meanwhile patient is transferred into the treatment room. After completing the treatment patient is transferred back to the OT and applicator removed and observed for any local bleeding for half an hour and then discharged after prescribing antibiotics, antiemetics and pain killers.

Brachytherapy planning

DRR (Digitally reconstructed radiograph) is acquired and bladder line and rectal line are drawn for reference. Dwell points are prescribed along the central tandem and ovoids and dose of around 700cGy to Point A (a point 2cm lateral to the centre of the uterine canal and 2cm above the mucous membrane of lateral fornix of the vagina in the plane of uterus) is prescribed. Point doses along the bladder and rectal line are seen along the dwell points and dwell point optimization is done in case of any excess point dose to the bladder or rectum. If the excess point dose is not corrected with dwell point optimization repacking is done. Pear shaped dose distribution is typically obtained and any dose below 650cGy and more than 750cGy to Point A is not accepted.

Assessment of toxicity

The acute toxicity was assessed using RTOG acute toxicity criteria weekly during Treatment and at 6 weeks and 3 months after completion of the treatment by a single observer.

Chemotherapy induced toxicity like nausea, vomiting, haematological and other Toxicities were assessed as per the Common Terminology Criteria for Adverse events.

Assessment of Response

Response is assessed as per the RECIST1.1 Criteria after the last fraction of EBRT and after last fraction of HDR-ICBT and after 6 weeks and 3 months

Statistical Analysis

All the data was presented as mean or median and percentages. Data was analysed by using SPSS V 16.0 Software. The mean difference between age and haemoglobin between two groups was assessed by two tailed t Test. Probability $p<0.05$ was considered significant.

Results

Of a total of 50 patients enrolled into the study. 4 patients were excluded as per the inclusion and exclusion criteria and 5 patients had radiation interrupted during the treatment because of reasons other than mucositis, such as haemoglobin<10gm/dl, leukopenia and infection. Thus 41 patients were found eligible with 20 patients in the morning arm (group A) and 21 patients in the evening arm (group B). The overall treatment time of the 2 arms (36.38 vs 35.15) was similar ($p<0.05$). Patients baseline (pre-treatment) characteristics in the 2 groups are summarised in table 1. on comparison, the baseline characteristics of the 2 groups were found not to differ significantly ($p>.05$) The overall radiotherapy-induced mucositis (grade 1-4) in patients of the 2 groups is summarized in table 2. This was found to be significantly higher in the patients in the morning arm than those in the

evening arm. Similarly higher grades of mucositis (grade 3 and 4) was also found to be higher in the patients in the morning arm than the patients in the evening arm.

Other radiation induced toxicity in patients were summarised in Table 3 and on comparison the proportion of toxicity in the patients of the 2 groups did not differ significantly. The proportion of patients showing either complete response or partial response did not differ significantly.

Table 1: Pre-treatment characteristics

Characteristic	Morning arm	Evening arm
Average Age	45.7	44.14
Ecog	1.05	1.1
Hb initial	11.43	11.41
Final HB	11.24	11.21

P Value > 0.05 – not significant
ECOG : Eastern Cooperative Oncology Group

Table 2: Toxicity grades during treatment

Grade	Morning,n=20, No(%)	Evening, n=21, No(%)
I	11(55)	9(42)
II	6(30)	3(14)
III	2(10)	1(4)
IV	1(5)	0(0)
Total	20(100)	14(66)

P value 0.027

Table 3: Toxicity comparision

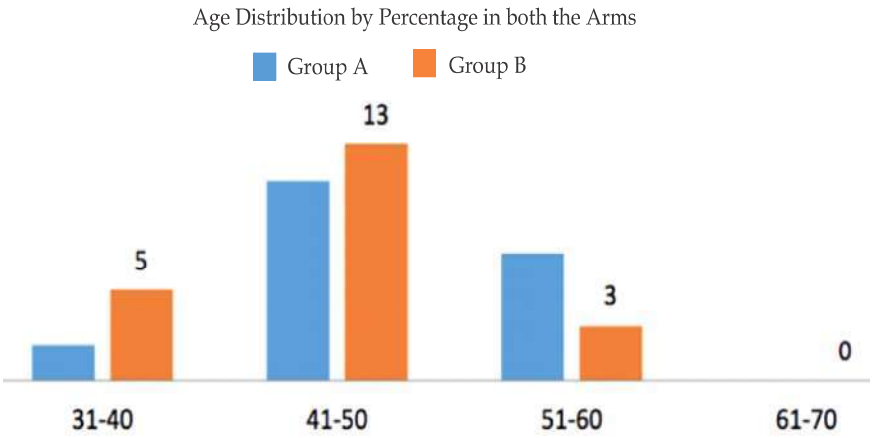
Toxicity	Morning arm,n=20,No(%)	Evening arm,n=21,No(%)	P value
Skin reaction	3(15)	3(14)	0.184
Nausea/vomiting	3(15)	4(19)	0.216
Bladder toxicity	1(5)	0(0)	0.486
Hematological	1(5)	1(4)	0.161
Total	8(40)	8(38)	

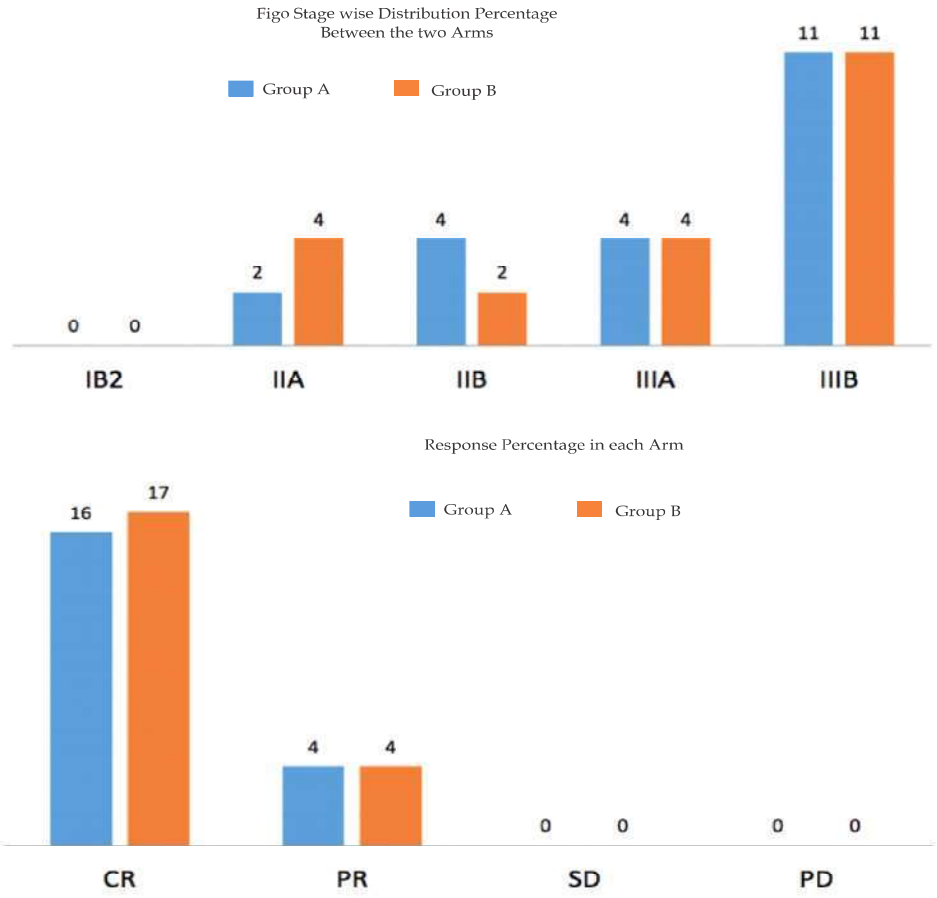
P-value >0.05 not significant

Table 4: Comparision of responses

Response	Group A	Group B	P value
CR	16	17	
PR	4	4	
SD	0	0	0.2
PD	0	0	
Incomplete Treatment	0	0	

CR-Complete response, PR-Partial response, SD-Stable Disease, PD-Progressive Disease





Figo Stage

All the stages were equally distributed between both the arms and majority of the patients were of stage IIIB in both the arms. The percentage of patients in each stage of this study is representative of the stage distribution in the admissions of carcinoma cervix every year in MNJ cancer hospital. Patients of different age groups were equally distributed among both the arms, but p value could not be derived due to less sample size.

Parametrial Involvement Index

Parametrial disease volume was approximately equally distributed in both the arms and majority had parametrial disease up to the pelvic wall in both the arms. Patients of different age groups were equally distributed among both the arms, but p value could not be derived due to less sample size.

Discussion

The hypothesis that the response of the patients who received treatment in the morning or in the evening would be the same was found to be true. Overall (grade I-IV) as well as higher grade (III and IV) diarrhoea was found to be significantly more frequent in the morning arm as compared with the evening arm (overall, 100% vs 66%, $p < 0.01$). The mechanism behind this significant difference is not yet clear. We hypothesized that the significant difference in the incidence of higher grade diarrhoea between the morning and evening arms is indirect evidence of the influence of circadian rhythm on the intestinal mucosa of the human intestine.

A total of 41 patients were finally evaluated in this study. Overall radiation induced mucositis was the primary endpoint, and this study found significant difference in mucositis between patients in the 2 groups at each grade or in radiation-induced toxicity at higher grades.

Mucositis is an important factor determining morbidity and treatment compliance. Prolonging overall treatment time results in a decrease in tumour control of 0.55%-1.4% per day of treatment elongation [6]. According to the law of Bergonie and Tribondeau [7], tissue appears to be more radiosensitive if its cells

are less well differentiated, have greater proliferative capacity, and divide more rapidly. Radiotherapy-associated mucositis is caused by the effect of ionizing radiation on proliferating epithelial stem cells and partly results from damage to endothelial cells [8]. Paris et al. [9] proposed that crypt cell death is an indirect consequence of endothelial cell apoptosis. The lower of the crypt is considered the normal proliferative zone, and the upper is occupied by non-dividing differentiated cells. Terpstra et al. [10] reported that epithelial proliferation is fairly uniform along the entire length of the large and the small bowel.

This randomized prospective trial was conducted to discover any correlation between radiation-related mucositis and the time of radiation. We have evaluated the incidence of grade III/IV mucositis in patients with carcinoma of the cervix treated between 8:00 and 10:00 AM and between 6:00 and 8:00 PM. In our study, we have seen that the patients undergoing radiation in the morning showed a significantly higher incidence of grade III and IV mucositis. The progression trend also suggests that the patients given radiation in the morning exhibited higher grades of mucositis. This lower incidence of grade III/IV mucositis in patients who were treated in the evening may be because of the effect of circadian rhythm in the cell cycle of normal mucosa.

Studies on the effect of radiation on mice have clearly demonstrated that the peak time of day for inducing apoptosis is between 6:00 and 9:00 AM, with the trough occurring between 6:00 and 9:00 PM [11]. Studies of cellular proliferation in the human rectal mucosa have shown the existence of a circadian rhythm of cell proliferation in rectal mucosa, [12] with the highest proliferative activity occurring in the morning between 3:00 and 11:30 AM and the least activity occurring 12 hours later. The difference in the grade of mucositis in the 2 study groups could be explained on the basis of these studies. Klevecz et al. [13] and Smaaland et al. [14] have reported a phase opposition between DNA synthesis rhythms in healthy target organs and in tumour. This might explain the similar response rate achieved in the 2 groups of this study (82.35% in morning irradiated patients and 80.91% in evening irradiated patients).

Conclusion

From this study the following conclusions were made Incidence and severity of intestinal mucositis is more in the morning arm than in the evening arm. There is no difference in the tumour response rates between the morning and evening arm. Haematological toxicity showed very high significant occurrence ($p < 0.001$) in the CRT arm compared to ART arm. Nausea, dermatological side effects, fever, vaginal discharge and bladder irritation showed no statistically significant difference. The final conclusion of this study is there is more incidence and severity of intestinal mucositis in patients receiving RT in the morning indirectly indicating the role of circadian cycle which is most active during early hours on the cell cycle.

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