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Original Research Paper

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CHRONORADIOTHERAPY IN CERVICAL CANCER – INSTITUTIONAL EXPERIENCE

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ABSTRACT

Aim: To evaluate the Chronoradiotherapy in cervical cancer, an institutional experience. **Methods:** This present research study is a retrospective study of electronic medical data from 29 cervical cancer patients and was conducted at the Department of Radiation Oncology at Madras Medical College in Chennai, India, between November 2022 and April 2023. **Results:** Among the 29 cervical cancer study patients the Morning Group (MG) with 14 participants and the Evening Group (EG) with 15. Treatment response assessed by RECIST criteria showed that a higher percentage of complete responses was observed in the evening group (73.3%) compared to the morning group (50.0%), and Partial responses were more common in the morning group, balancing out the complete response differences. The cervical cancer treatment toxicities were assessed by CTCAE showed that the morning group Grade 2 patients exhibited significantly more gastrointestinal toxicity (78.6% in MG vs. 0% in EG, $P < 0.0001$), and in contrast, hematological toxicities were more severe and frequent in the evening group, with up to 80% of Grade 1 or 2 patients (93.3% vs. 7.1%, $P < 0.0001$), highlighting a clear circadian effect on drug or radiation-induced side effects. The Quality of Life (QoL) of the study patients was also analyzed and showed that in the evening-treated patients, the scores for functional status, additional concerns, and total QOL-FACT-Cx (p-value < 0.0001) scores were significantly higher in the evening group than in the morning group. The MDASI scores were lower in the evening group, reinforcing the impression that evening therapy was better tolerated.

KEYWORDS : Cervical Cancer, Chronoradiotherapy, Morning Group (MG), Evening Group (EG), Quality of Life (QoL), External beam radiation therapy (EBRT), Intensity-Modulated Radiation Therapy (IMRT)

INTRODUCTION

Cervical cancer is a form of cancer that begins in the **cervix**, the lower, thin end of the **uterus**. **Human Development Index** levels describe that in **2024**, the United States is estimated to see **13,820 new cases** and **4360 related fatalities**, while the **European Union anticipates 58,169** cases (56% from central and eastern Europe) and **22,989 related deaths**. The **median age** upon diagnosis is **fifty years** [1].

The **FIGO** system is used to stage cervical cancer, with **Stage 0** indicating precancerous cells and **Stage IV** indicating cancer spread to distant organs. The stage is defined by the **tumor's size and extent**, as well as whether it has spread to surrounding or distant areas of the body. The **2018 FIGO** system incorporates several important upgrades for radiologists. **Stage IB1** now has three subgroups depending on tumor size, up from two previously. IB1: 2 cm or smaller, **IB2**: bigger than 2 cm to 4 cm, and **IB3**: larger than 4 cm [2].

External beam radiation therapy (EBRT) combined with **chemotherapy** and **brachytherapy** is the recommended treatment for advanced cervical cancer. Historically, EBRT was administered using a two-dimensional **approach relying mostly on bone features.** This led to three-dimensional conformal radiation therapy, which enables dosage computation and adjustment depending on unique tumor and patient anatomy. Further technological improvements have established **Intensity-Modulated Radiation Therapy (IMRT)** as a common treatment method, owing to its capacity to provide tumoricidal doses to target volumes while limiting undesired radiation dosage to neighboring important structures, hence lowering toxicity [3].

Brachytherapy is a type of **internal radiation therapy** in which radioactive sources are inserted directly into or near a tumor. This allows a **high dosage of radiation** to be administered to the malignant region while reducing exposure to healthy tissues around it. It is used to **treat malignancies such as prostate, breast, cervix, and head and neck**. Magnetic resonance and ultrasound imaging are increasingly used to plan all types of brachytherapy due to their soft tissue contrast**. Image-guided brachytherapy** has led to advancements in applicators and 3D printing, resulting in more consistent and predictable implants. These advancements improve **implant quality and focus radiation to target quantities** while sparing normal tissue. Applicator reconstruction **three-dimensional models** with predefined source paths, enabling automatic detection and automation [4].

The **Karnofsky Performance state (KPS) scale** is a standardized instrument for evaluating a patient's functional state, especially in individuals with cancer or other chronic illnesses and it goes from **100 (normal, no complaints) to 0 (death)** and provides a numerical value indicating a patient's ability to complete everyday activities and the need for assistance. The KPS is used to **predict prognosis**, monitor changes in a **patient's functional ability**, and identify eligibility for clinical trials [5].

Intensity-modulated radiation (IMRT) for cervical cancer has **positive oncological outcomes, acute toxicity, and late toxicity**. There is limited data on therapeutic outcomes with **volumetric modulated arc treatment (VMAT).** The goal of this study is to evaluate the result and toxicity of VMAT to conventional 3D conformal radiation (3DCRT), with a focus on the impact of patient- and treatment-related characteristics on side effects [6].

The Response Evaluation Criteria in Solid Tumors (RECIST) is the **gold standard for assessing therapeutic response in solid tumors**. The morphologic change of tumor size assessed by RECIST is commonly connected with survival length and used as a surrogate endpoint for therapy success. However, morphologic changes alone may not be enough to evaluate response to novel anti-cancer medications in all solid tumors. Over the past 15 years, molecular-targeted treatments and immunotherapies have evolved in cancer treatment to disrupt signaling pathways and decrease cell proliferation. Even without tumor reduction, tumor necrosis or lack of advancement can lead to a positive therapy response [7].

The long-term extension therapy for monotherapy or in combination with anticancer medicines, the adverse events (AEs) were graded according to Common Terminology Criteria for AEs **(CTCAE)** grade ≥3, severe AEs (SAEs), and deaths associated with anticancer treatment [8].

Treatment response is also influenced by the factors that impact radiotherapy, and **cellular dynamics** could improve radio sensitivity in cervical cancer. Circadian rhythm and melatonin concentration are two connected elements. The **circadian cycle is a daily biorhythm that occurs in numerous physiological systems and follows a particular and harmonious pattern**. Numerous investigations have shown a close link between the circadian and cell cycles, which were previously thought to be independent [9].

Peyric et al describe that the **circadian-related radiotherapy** tries to deliver radiation in sync with the body's internal and global clocks, creating a radiosensitive environment [10].

Apart from the circadian cycle, **Melatonin** acts as a **scavenger of OH-containing compounds**, protecting cells from radiation-induced damage. The impact of circadian rhythm and melatonin levels on radiation sensitivity remains unclear in clinical settings [11].

Cervical cancer is the fourth most common malignancy in women globally and the eleventh most common neoplasm in Spain. Treatment optimization has resulted in a 70% 5-year survival rate; however, there are still reports of side effects and complications, and treatments negatively impact **QoL in certain patients' physical, psychological, and societal well-being** [12].

The above published data show us that **any small insight or information** about any cancer patients can bring enlightening changes and enhance their QoL. **All factors**, such as **early identification** of cervical cancer, **early treatment**, **circadian cycle, melatonin,** and **early identification of treatment toxicities**, all together must aid the patients with cervical cancer for good QoL in **enhancing their life line longer with good QoL**. Hence, we have conducted this present research study in the selected study patients with a validated questionnaire, Functional Assessment of Cancer Therapy-Cervix Cancer [FACT-Cx].

Ethical Clearance
As this study is retrospective, ethical clearance was not required; however, the study was conducted under the supervision of the Departmental Head.

Conflicts- None
Funding- None

Inclusion Criteria
Patients with Cervical Cancer

Exclusion Criteria
Patients without Cervical Cancer

MATERIALS AND METHODS
Methodology
Study Design And Setting
This retrospective study was conducted at the **Department of Radiation Oncology** at **Madras Medical College** in **Chennai, India**.

Study Duration And Participants
Between November 2022 and April 2023, electronic medical data from 29 cervical cancer patients were collected after meeting the exclusion and inclusion criteria for this study.

Study Variables
Cervical Cancer
Cervical cancer is a type of cancer that starts in the cervix, which is the bottom section of the uterus that links to the vagina. It is primarily caused by long-term infection with high-risk strains of the human papillomavirus (HPV), a common sexually transmitted virus. Early cervical cancer frequently has no symptoms, but as it advances, signs may include abnormal vaginal bleeding, pelvic pain, and changes in vaginal discharge [13].

Stages Of Cervical Cancer
Cervical cancer stages are assessed by the **FIGO (International Federation of Gynecology and Obstetrics)** staging system and span from Stage 0 to Stage IV, with additional subdivisions. These stages describe the extent to which the cancer has spread.

Stage I- This stage of cancer is confined to the cervix.

Stage II- The cancer has spread from the cervix to nearby tissues but not to the pelvic wall or the bottom portion of the vagina.

Stage III
Cancer has spread to the pelvic wall, the lower 3rd of the vagina, or lymph nodes in the pelvis or abdomen.

Stage IV (A)
The malignancy has progressed to the bladder or rectal mucosa.

Stage IV (B)
The malignancy has progressed to the distant organs [14].

Treatment Modality
External beam radiation therapy (EBRT) is a common cancer treatment that targets and destroys cancer cells with high-energy radiation beams emitted by a machine outside the body. This local treatment concentrates radiation on a specific location, such as the chest for lung cancer, rather than the entire body. The gadget directs radiation beams from a variety of angles, reducing damage to healthy tissue [15].

Brachytherapy
Brachytherapy is a type of radiation therapy that uses a radioactive source inside or near a tumor to treat cancer. It is a type of internal radiation therapy in which seeds, ribbons, or capsules containing a radiation source are inserted into or near the tumor. This allows a higher dose of radiation to be administered directly to the tumor while limiting damage to surrounding healthy tissues [16].

Karnofsky Performance State (KPS)
The Karnofsky Performance State (KPS) is a commonly used measure for determining a patient's functional state, notably in cancer care. It assesses a patient's ability to undertake everyday tasks and care for themselves on a scale ranging from completely independent to completely dependent. A KPS score of 100% indicates normal activity with no complaints,

whereas 0% signifies death [17].

CT-3D-CRT

3D conformal radiation therapy (3D CRT) is a type of radiation therapy that uses three-dimensional pictures, usually CT scans, to determine the shape and size of a tumour. CT or MRI images are utilized to generate a three-dimensional representation of the tumor and surrounding structures. Radiation oncologists utilize this 3D model to arrange radiation beams, with the goal of delivering a high dose to the tumor while sparing adjacent organs and tissues [18].

Cervical Cancer Treatment Responses

Cervical cancer treatment outcomes vary greatly depending on the stage of the disease and the type of treatment utilized (Complete Response, Partial Response) [19].

Cervical Cancer Treatment Responses Assessment by RECIST

The National Cancer Institute.gov defines **RECIST** (Response Evaluation Criteria in Solid Tumors) as a systematic method for assessing a patient's tumor response based on changes in tumor size. It establishes objective criteria for identifying whether a tumor shrinks, remains unchanged, or progresses, resulting in classifications such as total response, partial response, stable disease, and progressive illness [20].

Cervical Cancer Treatment Toxicities

Hematological and gastrointestinal toxicities are prevalent in cervical cancer patients undergoing radiation or chemoradiation therapy, and those receiving concurrent chemoradiation therapy typically acquire higher levels of hematological damage than those receiving just radiation therapy [21].

Cervical Cancer Treatment Toxicities Assessed By CTCAE

CTCAE (Common Terminology Criteria for Adverse Events) grading is a systematic system for categorizing the severity of adverse events (AEs) in clinical trials, mostly in oncology. It classifies AEs from 1 to 5, indicating a range of severity from moderate to fatal [22].

Quality Of Life (QoL)

Quality of life (QoL) refers to a person's subjective perception of their overall well-being, encompassing physical, mental, and social health. It is a multifaceted term impacted by personal beliefs, relationships, health, and circumstances, and it varies greatly from person to person [23].

FACT-Cx

A validated questionnaire for women with cervical cancer, the Functional Assessment of Cancer Therapy-Cervix Cancer [FACT-Cx], was used to assess quality of life. The overall score on the FACT-Cx questionnaire runs from 0 to 168, with higher scores indicating greater QoL [24].

Study Procedure

29 cervical cancer patients treated at Madras Medical College's Department of Radiation Oncology between November 2022 and April 2023 were divided into two groups for this study. Morning Group [8.00 AM-10.00 AM], n=14; Evening Group [7.00 PM-9.00 PM], n=15. The short-term efficacy of radiotherapy was measured using the RECIST Criteria [v 1.1], symptoms by the MD Anderson Symptom Inventory Score [MDASI], radiotoxicity and quality of life after radiotherapy by the RTOG Criteria, and functional assessment of cancer therapy questionnaire-cervix, respectively.

Data Collection

The electronic medical records of the study cervical cancer patients were read carefully, and data such as **age**, **stages of cervical cancer**, **EBRT**, **Brachytherapy**, **KPS**, **CT-3D-CRT**, cervical cancer treatment responses assessed by **RECIST**, cervical cancer treatment toxicities assessed by **CTCAE,** and **QoL** assessed by **FACT-Cx** were selected from the medical records were collected and recorded.

Analysis

The collected and recorded data from the electronic records of the study patients were analyzed after being segregated into the **Morning group (MG)** and the **Evening group (EG)**. Further analyzed to extract the results were plotted and tabulated in the results section.

Statistical Analysis Of Data

The data were shown as mean, standard deviation, frequency, and percentage. Independent sample t tests were used to compare continuous variables. Categorical variables were compared using p-values. Using a two-tailed test, p-values less than 0.05 indicated significance. The basic statistical analysis was performed in Microsoft Excel, and the data were then analyzed further using IBM-SPSS version 21.0. Baseline variables from both intervention groups were examined to determine whether there were any inter-group variations.

RESULTS

29 cervical cancer study patients were studied, analyzed, plotted, and tabulated. **Figure 1** illustrates the distribution of the two intervention groups; patients were fairly evenly split between the **Morning Group (MG)** with 14 participants and the **Evening Group (EG)** with 15, enabling a balanced comparison.

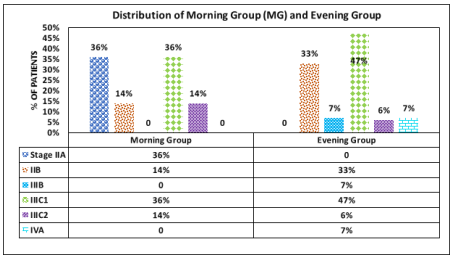

Figure 1: Distribution of Morning Group (MG) and Evening Group (EG)

In terms of treatment response assessed by RECIST criteria (Table 1), although a higher percentage of complete responses was observed in the evening group (73.3%) compared to the morning group (50.0%), the difference was not statistically significant (P = 0.196), suggesting that both schedules yielded comparable tumor shrinkage outcomes. Partial responses were more common in the morning group, balancing out the complete response differences. This implies that Chrono modulated radiotherapy does not significantly alter tumor control, at least based on RECIST-based classifications.

Table 1: Cervical Cancer Treatment Responses Assessed by RECIST

Treatment Response	Study Groups (n=29)		P value
	Morning Group n=14 (%)	Evening Group n=15 (%)	
Complete Response (n=18)	7 (50.0)	11 (73.3)	0.196
Partial Response (n=11)	7 (50.0)	4 (26.7)	

Table 2 presents the cervical cancer treatment toxicities assessed by CTCAE. The morning group exhibited significantly more gastrointestinal toxicity, especially Grade 2 patients who received radiation, experienced enteritis **(78.6% in MG vs. 0% in EG, P < 0.0001)**, suggesting increased bowel

sensitivity to radiation exposure in the earlier part of the day. In contrast, hematological toxicities such as neutropenia, thrombocytopenia, and leucopenia were more severe and frequent in the evening group, with up to 80% of Grade 1 or 2 patients experiencing neutropenia. The nausea/vomiting incidence was also dramatically higher in the evening group **(93.3% vs. 7.1%, P < 0.0001)**, highlighting a clear **circadian effect on drug or radiation-induced side effects**.

Table 2: Cervical Cancer Treatment Toxicities Assessed by CTCAE

Treatment Toxicities and Grading	Morning Group n=14 (%)	Evening Group n=15 (%)	P value
Radiation enteritis			
Grade 1	2 [14.3%]	1 [6.7%]	<0.0001 *
Grade 2	11 [78.6%]	0	
Grade 3	1 [7.1%]	1 [6.7%]	
NO	0	13 [86.7%]	
Neutropenia			
Grade 1	0	3 [20.0%]	<0.0001 *
Grade 2	1 [7.1%]	12 [80.0%]	
NO	13 [92.9%]	0	
Thrombocytopenia			
Grade 1	1 [7.1%]	12 [80.0%]	<0.0001 *
Grade 2	0	2 [13.3%]	
NO	13 [92.9%]	1 [6.7%]	
Leucopenia			
Grade 1	1 [7.1%]	8 [53.3%]	<0.0001 *
Grade 2	0	5 [33.3%]	
Grade 3	0	1 [6.7%]	
NO	13 [92.9%]	1 [6.7%]	
Nausea/Vomiting			
YES	1 [7.1%]	14 [93.3%]	<0.0001 *
NO	13 [92.9%]	1 [6.7%]	

* Statistically Significant

Table 3 expresses the Quality of Life **(QoL)** of the study patients. This table reveals a more favourable subjective experience among **evening-treated patients**. Scores for **functional status, additional concerns, and total QOL-FACT-Cx (p-value-0.0001)** scores were significantly higher in the **evening group, indicating better perceived well-being**. Moreover, the MDASI (MD Anderson Symptom Inventory) scores, which inversely relate to quality of life, were lower in the evening group, reinforcing the impression that **evening therapy was better tolerated**.

Table 3: Quality Of Life (QoL) Of The Study Patients

QoL Assessed by FACT-Cx	Morning Group Mean ±SD	Evening Group Mean ±SD	P value
Physical status	15.50 ± 1.40	15.53 ± 1.60	0.953
Family status	12.50 ± 1.51	13.67 ± 1.68	0.06
Emotional status	12.14 ± 2.25	12.47 ± 1.64	0.66
Functional status	10.07 ± 1.44	11.80 ± 0.94	0.001*
Additional concerns	33.43 ± 3.90	38.27 ± 3.28	0.001*
QOL-FACT Cx	82.36 ± 3.15	91.87 ± 3.64	<0.0001*
MDASI SCORE	40.29 ± 3.24	35.33 ± 3.56	0.001*

* Statistically Significant

DISCUSSION

This current study presented that the two intervention groups were reasonably well distributed, with 14 patients in the **Morning Group (MG)** and 15 in the **Evening Group (EG),** allowing for a balanced comparison. Treatment response was assessed using RECIST criteria, and the evening group had a larger percentage of complete responses (73.3%) than the morning group (50.0%). Whereas a published study by Ramli I et al described that the radiation time was determined by whether the patients were irradiated in the morning (06.00-10.00 am) or afternoon (04.00-6.00 pm). The AM group had a higher 5-year overall survival rate, but the difference was not statistically significant [25]. But our research study is compatible with a few studies published by Smaaland et al, Klevec et al, and Lakatua et al, who explained that the tumor cells divide at a different time than healthy cells. The data suggest that cancer cells are more likely to be in the radiosensitive G2/M phase between 6:00 pm and 12:00 am, while normal cell proliferation occurs in the afternoon [26-28].

Our research study reported that in the cervical cancer treatment, toxicities assessed by **CTCAE** showed that the morning group Grade 2 patients exhibited significantly more gastrointestinal toxicity than the evening group **(78.6% in MG vs. 0% in EG, P < 0.0001)**. Our study is consistent with the study published by Palagudi M et al reported that combined radiation therapy and chemotherapy (CT) had the highest incidence of adverse events (AEs), affecting 56.0% of patients (95% CI: 55-60.1). Most cervical cancer patients (92.5%, 95% CI: 90.2-96.9) experienced gastrointestinal side symptoms [29].

We also reported that the Hematological toxicities, such as neutropenia, thrombocytopenia, and leucopenia, were more severe and common in the evening group, with up to 80% reporting Grade 1 or 2 neutropenia. The incidence of nausea/vomiting was much higher in the evening group **(93.3% vs. 7.1%, P < 0.0001),** demonstrating higher intestinal sensitivity to radiation exposure earlier in the day. In comparison, indicating a **circadian effect on medication or radiation-related adverse effects**. Petre I et al presented that the Lymphocytes, neutrophils, leukocytes, creatinine, thrombocytes, and hemoglobin levels were examined following carboplatin or cisplatin administration in 45 stage III cancer patients. Lymphocytes ranged from Lym 1 to Lym 5. Monitoring these variables assessed how therapies affected patients' immunological function, blood cell count, and renal function. Regularly evaluating these indicators is critical for detecting potential toxicities, managing adverse effects, and optimizing therapeutic outcomes for carboplatin and cisplatin regimens [30].

The current study found that evening-treated patients have a better subjective quality of life (QoL). The **evening group had significantly higher scores for functional status, additional concerns, and total QOL-FACT-Cx (p-value-0.0001),** and Zhou W et al published that the average total FACT-Cx score was 124.45 (range: 70–157). The average FACT-general score was 112.39 (49-150), with an average FACIT-Sp score of 13.9 (2-33.6). 78% of our individuals suffered from sexual dysfunction. Factors linked with QOL in cervical cancer survivors were gastrointestinal problems, health insurance, age, sleep issues, and the number of sequelae. Radiotherapy, age, surgical type, sleep issues, and occupation all affected sexual function [31].

Our present study reported that the lower MDASI (MD Anderson Symptom Inventory) scores, indicating better perceived well-being and reinforcing the impression that evening therapy was better tolerated, our study was compatible with the published by Wang Y et al who presented that the MG and EG both have similar radiation effects. The MG had higher rates of radiation enteritis and diarrhea compared to the EG. However, the EG experienced more severe bone marrow suppression and blood toxicity [32]. Amoh R et al also described that cervical cancer is a major public health concern in Sub-Saharan Africa, with treatment options including chemoradiotherapy affecting patients' **quality of life (QoL).** This study evaluated the quality of life of cervical cancer patients having definitive chemoradiotherapy. QoL ratings were highest in social well-being (17·3/24·0) and emotional well-being (16·8/24·0), but

lower in physical and functional well-being (15·4/28·0 and 12·3/24·0, respectively). The majority of participants (66.7%) rated a **good quality of life**, whereas 6.7% reported a poor one [33]. A study by Hunt T et al also reported that the CLOCK genes regulate gene expression patterns based on circadian rhythms [34].

CONCLUSION

In summary, while tumor response did not differ significantly, the pattern and severity of side effects and **patient-reported outcomes strongly support evening administration of cisplatin-based chromo-radiotherapy** as **more favourable in terms of quality of life** and **manageable toxicity**, although with **increased haematological risk that warrants monitoring**.

This research study presents the **insight that compelling evidence that the body's circadian rhythms significantly influence cancer therapy tolerance**, and **optimizing treatment timing could be a non-invasive, cost-effective method to enhance therapeutic outcomes** in cervical cancer care.

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