RESEARCH
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BEYOND THE TUMOR: COMPARATIVE INSIGHTS INTO BIOCHEMICAL ALTERATIONS IN CERVICAL CANCER PATIENTS UNDER CHEMOTHERAPY AND RADIOTHERAPY

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Abstract
Cervical cancer remains a predominant cause of cancer-related morbidity and mortality among women, with chemotherapy and radiotherapy serving as cornerstone therapies for advanced stages. Despite their established role in tumor control, the systemic biochemical effects of these treatments remain inadequately characterized. This study aims to compare the biochemical alterations in cervical cancer patients undergoing chemotherapy versus those receiving radiotherapy, focusing on critical biomarkers such as immunoglobulins, liver enzymes (SGPT, SGOT, alkaline phosphatase), urea, bilirubin, magnesium, calcium, zinc, iron, fasting glucose, and total protein. These variables were selected for their involvement in immune modulation, hepatic function, metabolic regulation, and mineral homeostasis. To investigate these alterations, a prospective cohort study design was employed, wherein serum samples were collected from patients at baseline and at multiple intervals during their respective treatments. The serum concentrations of the selected biomarkers were quantified using standard clinical assays. Results demonstrated that chemotherapy induced significant elevations in hepatic enzymes (SGPT, SGOT), urea, and bilirubin, suggesting hepatocellular stress and perturbations in metabolic processes.
The findings underscored the differential biochemical pathways engaged by chemotherapy and radiotherapy, elucidating their distinct systemic effects beyond the local tumor response. This comparative analysis offers valuable insights into the broader physiological impacts of these therapeutic interventions, reinforcing the potential utility of serum biomarkers for tailoring personalized treatment strategies in cervical cancer.
Keywords: Cervical carcinoma, chemotherapy, radiotherapy, serum biomarkers, personalized oncology, treatment monitoring, HPV

INTRODUCTION

Cervical cancer remains a major global health concern, particularly in low- and middle-income countries, where barriers such as limited access to screening programs, vaccination, and healthcare services exacerbate the disease burden. According to the World Health Organization (WHO), cervical cancer ranks as the fourth leading cause of cancer-related mortality among women, responsible for an estimated 311,000 deaths annually worldwide. The majority of these fatalities occur in regions with inadequate healthcare infrastructure, where early detection and preventive measures such as vaccination are insufficiently implemented. In 2020 alone, 604,000 new cervical cancer diagnoses were reported globally, resulting in approximately 342,000 deaths, underscoring the persistent and significant impact of this disease on women's health.

Over the past five years, the incidence of cervical cancer-related deaths has remained alarmingly high, despite notable advancements in treatment strategies, including chemotherapy and radiotherapy, which are pivotal in managing advanced stages of the disease. However, while these therapeutic interventions have

undeniably contributed to improved survival rates, they also bring about a range of systemic effects that can severely affect the overall health of patients. Emerging evidence suggests that chemotherapy and radiotherapy induce disruptions across multiple physiological systems, including immune function, liver metabolism, mineral balance, and metabolic processes. These alterations not only complicate treatment management but can also significantly reduce the patient's quality of life and long-term prognosis. Hence, understanding these biochemical shifts is critical to refining therapeutic strategies and enhancing treatment outcomes for cervical cancer patients.

The Critical Role of Biochemical Markers in Cancer Therapy

Biochemical profiling can assist in early detection of treatment-related toxicities, enabling clinicians to adjust treatment regimens promptly to avoid long-term damage. For example, monitoring immunoglobulin levels can provide critical information on the immune system's response to chemotherapy or radiotherapy, while changes in total protein and fasting glucose levels can indicate disruptions in protein synthesis or metabolic pathways, which may lead to adverse side effects such as cachexia or hyperglycemia. The use of these biomarkers in clinical practice has the potential to not only enhance treatment outcomes but also improve patient quality of life by identifying and mitigating the adverse effects of therapy.

Despite their importance, the systematic use of biochemical markers in cervical cancer treatment remains underexplored. Most studies tend to focus on tumor-specific biomarkers, often overlooking the broader biochemical impacts of treatment. Therefore, this study seeks to fill this knowledge gap by comparing the biochemical alterations induced by chemotherapy and radiotherapy in cervical cancer patients, providing a holistic view of the systemic impact of these therapies.

Biochemical Variables of Interest to Assess Systemic in Cervical Cancer Patients

This study focused on a specific set of biochemical markers to evaluate the systemic alterations induced by chemotherapy and radiotherapy in 150 cervical cancer patients, compared with a control group of 50 healthy individuals. These markers were selected for their relevance to critical physiological processes such as immune modulation, hepatic function, metabolic regulation, and mineral homeostasis, all of which were affected by the treatments.

The levels of immunoglobulins (IgA, IgG, IgM) were measured to assess the immune response, as chemotherapy and radiotherapy were known to suppress immune function, leaving patients vulnerable to infections. Liver function was evaluated through the measurement of SGPT, SGOT, alkaline phosphatase, and bilirubin levels. These biomarkers served as indicators of hepatotoxicity, a frequent consequence of cancer therapies, and provided insight into liver injury or cholestasis induced by treatment.

To assess renal function and potential metabolic disturbances, urea and fasting glucose levels were evaluated. Chemotherapy had been associated with renal dysfunction and hyperglycemia, which could further complicate treatment. Additionally, the mineral markers calcium, magnesium, zinc, and iron were assessed to evaluate disruptions in electrolyte balance and nutritional status, as these minerals are crucial for various physiological functions and immune regulation. Finally, total protein levels were measured to determine nutritional adequacy and protein synthesis, as cancer therapies often led to cachexia and muscle wasting.

By analyzing these biomarkers in cervical cancer patients and comparing them with the control group, the study aimed to characterize the systemic effects of chemotherapy and radiotherapy. It sought to identify biochemical markers that could serve as early indicators of treatment-related toxicities and contribute to the development of personalized treatment strategies.

CURRENT RESEARCH GAP

Despite significant advancements in the treatment of cervical cancer, there remains a considerable gap in understanding the biochemical alterations induced by various therapeutic approaches. While existing studies have highlighted the short-term effects of chemotherapy, radiotherapy, and chemoradiotherapy on cervical cancer patients, limited research has comprehensively evaluated the longitudinal

biochemical responses to these treatments across different stages of the disease. Furthermore, most studies have focused on individual markers, without providing a holistic view of how multiple biomarkers interact and influence overall systemic health during treatment.

Another significant gap is the lack of detailed comparative studies examining the biochemical variations in cervical cancer patients treated with different modalities, specifically surgical intervention, radiotherapy, chemotherapy, and chemoradiotherapy. Understanding how these treatments impact immune function, liver and renal metabolism, mineral balance, and nutritional status is crucial for improving patient outcomes. Additionally, research has yet to establish reliable early biomarkers of toxicity that could be used to monitor adverse effects over time, particularly in long-term follow-up.

Moreover, there is an underrepresentation of studies that correlate biochemical changes with clinical outcomes, such as treatment response, survival rates, and quality of life, in cervical cancer patients at different stages. As the systemic effects of cancer treatments are often poorly understood, this research aims to fill these gaps by providing a comprehensive biochemical assessment that could improve patient care and personalized treatment protocols.

KEY RESEARCH GOALS AND INVESTIGATIVE AIMS

This study aims to comprehensively investigate the biochemical alterations associated with various treatment regimens in cervical cancer, with a focus on identifying biomarkers that could facilitate early detection of treatment-induced toxicity and improve personalized care. Specifically, the objectives are as follows -

1. To examine the biochemical changes in cervical cancer patients subjected to distinct therapeutic approaches—surgery for Stage I, radiotherapy for Stage II, chemoradiotherapy for Stage III, and chemotherapy for Stage IV—focusing on markers related to immune function, hepatic metabolism, renal health, and electrolyte balance.
2. To assess longitudinal variations in a selected set of biomarkers, including immunoglobulins (IgA, IgG, IgM), liver enzymes (SGPT, SGOT, alkaline phosphatase), bilirubin, urea, fasting glucose, total protein, and key minerals (calcium, magnesium, zinc, iron), at baseline and follow-up intervals of 1 month, 3 months, 6 months, and 9 months post-treatment.
3. To identify specific biomarkers that could act as predictive indicators of treatment-related toxicity and adverse effects, particularly focusing on hepatic dysfunction, renal impairment, and immune suppression.
4. To compare the biochemical profiles of cervical cancer patients at various stages of the disease with those of a healthy control group, thereby highlighting the distinct biochemical signatures linked to different treatment regimens and disease stages.
5. To explore the relationship between changes in biochemical markers and clinical outcomes, such as treatment efficacy, adverse reactions, patient recovery, and quality of life, with the aim of informing personalized treatment strategies.
6. To develop a set of biomarker-based guidelines for monitoring treatment toxicity and adjusting therapeutic regimens according to individual biochemical responses, thereby optimizing patient management and improving treatment outcomes.

MATERIAL AND METHODS

A prospective, observational study was conducted at multiple hospitals in Jaipur, Rajasthan, India, from 2022 to 2024, involving 150 female patients diagnosed with cervical cancer, ranging in age from 25 to 60 years. The study aimed to evaluate the variations in various biochemical markers, including immunoglobulins, liver enzymes, electrolytes, and other metabolic indicators, across different stages of cervical cancer and corresponding treatment regimens. To serve as a baseline, a control group of 50 healthy age- and sex-matched females were also included.

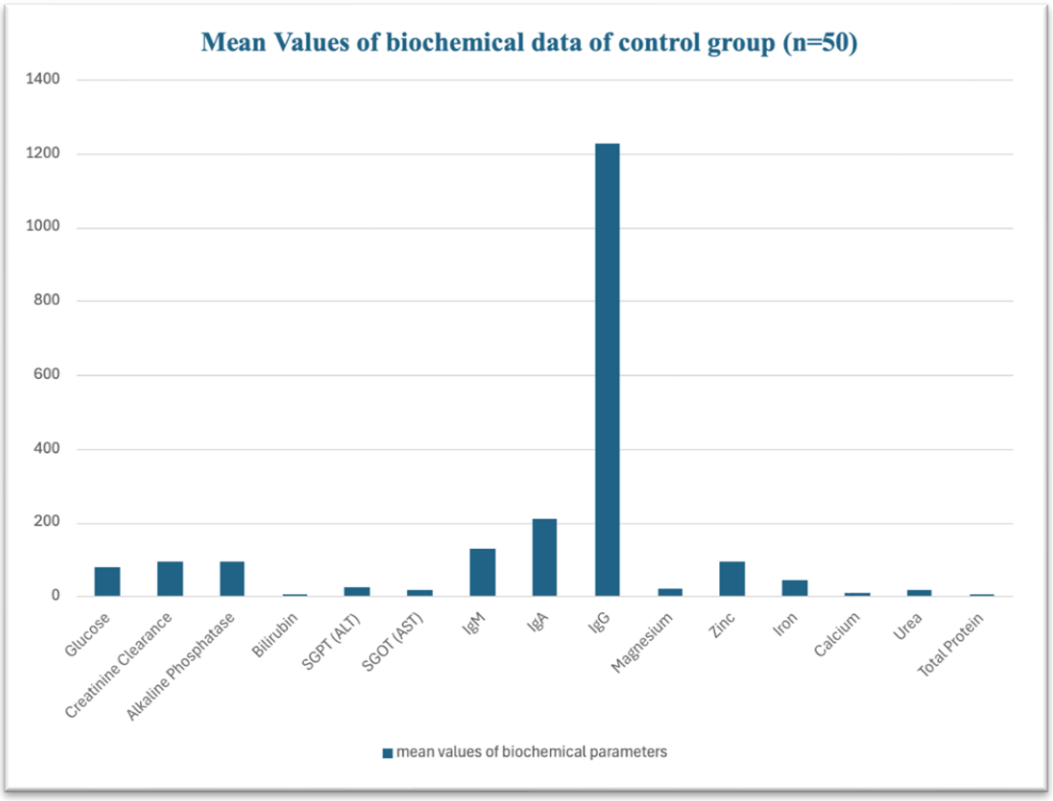

Fig 1. Mean values of biochemical variables in control group

Study Design And Participants

This prospective observational study was conducted between 2022 and 2024 at multiple hospitals in Jaipur, Rajasthan, India, aimed at evaluating the biochemical alterations in cervical cancer patients undergoing different treatment regimens. The study involved 150 cervical cancer patients, categorized into four groups based on the stage of cancer and treatment modality, with the following patient distribution -

1. Stage I (Early-stage Cervical Cancer): 54 patients (36% of total sample), treated with surgery.
2. Stage II (Localized Cervical Cancer): 38 patients (25.3% of total sample), treated with radiotherapy.
3. Stage III (Advanced Cervical Cancer): 42 patients (28% of total sample), treated with chemotherapy and radiotherapy (chemoradiotherapy).
4. Stage IV (Metastatic Cervical Cancer): 16 patients (10.6% of total sample), treated with chemotherapy.

The age group of participants ranged from 25 to 60 years, and all patients had a confirmed diagnosis of cervical cancer, verified by histopathological examination. Inclusion criteria for patients included the ability to provide informed consent and no history of prior cancer treatments. Exclusion criteria included pregnancy, severe liver or kidney dysfunction, autoimmune diseases, or any comorbid conditions that could interfere with the study's findings.

A control group of 50 healthy females (also aged between 25 and 60 years) were included to serve as the baseline for comparison of biochemical markers. These individuals were confirmed to be free from any underlying health conditions through clinical examination and laboratory tests.

Treatment Protocols

1. Stage I (Surgical Treatment): Patients in this group underwent surgical intervention (either hysterectomy or conization) as the primary treatment. Follow-up visits were conducted

at 1 month, 3 months, 6 months, and 9 months after surgery.

2. Stage II (Radiotherapy): Patients received radiotherapy, including both external beam radiotherapy and brachytherapy, as per standard protocols for localized cervical cancer. Follow-up intervals were the same as for Stage I patients.
3. Stage III (Chemoradiotherapy): Patients with Stage III cervical cancer received chemoradiotherapy, combining chemotherapy (cisplatin-based regimens) with radiotherapy. The follow-up schedule mirrored that of other stages.
4. Stage IV (Chemotherapy): The Stage IV cohort received chemotherapy (cisplatin, paclitaxel). Follow-up visits were scheduled at 1 month, 3 months, 6 months, and 9 months.

Sample Collection and Analysis

Serum samples were collected from all participants at baseline (pre-treatment) and at follow-up visits at 1 month, 3 months, 6 months, and 9 months post-treatment. Serum samples (5–10 mL) were drawn by trained phlebotomists using standard aseptic techniques. The blood was allowed to clot for 30 minutes at room temperature, and then serum was separated by centrifugation at 3000 rpm for 10 minutes. The serum was then stored at -80°C for future analysis. The following biochemical markers were analyzed in the serum using widely recognized diagnostic kits, commonly employed in clinical laboratories across India:

Immunoglobulins (IgA, IgG, IgM)

a. Brand: Human Diagnostics
b. Method: Enzyme-Linked Immunosorbent Assay (ELISA) kits for quantifying immunoglobulins.

Liver Enzymes (SGPT, SGOT, Alkaline Phosphatase)

c. Brand: Randox Laboratories
d. Method: Colorimetric assays for liver enzyme activity.

Bilirubin (Total and Direct)

e. Brand: Beckman Coulter or Siemens Healthineers
f. Method: Diazo method for bilirubin quantification.

Urea and Creatinine

g. Brand: Merck
h. Method: Urease and Jaffe method for kidney function analysis.

Minerals (Calcium, Magnesium, Zinc, Iron)

i. Brand: Thermo Fisher Scientific
j. Method: Atomic Absorption Spectrophotometry (AAS) for accurate metal ion determination.

Total Protein and Albumin

k. Brand: Thermo Fisher Scientific
l. Method: Biuret method for total protein and BCG dye-binding method for albumin.

Fasting Glucose

m. Brand: AccuChek (Roche)
n. Method: Hexokinase method

RESULTS

By analyzing a range of biochemical markers, such as liver and renal enzymes, immune markers, glucose metabolism, and mineral levels, the study aimed to assess the physiological impact of these treatments on patients over time. The results offer critical insights into the safety and potential side effects of current treatment protocols, highlighting any short-term biochemical disruptions and their implications for patient health. The data generated will not only help elucidate the immediate effects of treatment but also provide a foundation for future research into long-term outcomes and personalized treatment strategies.

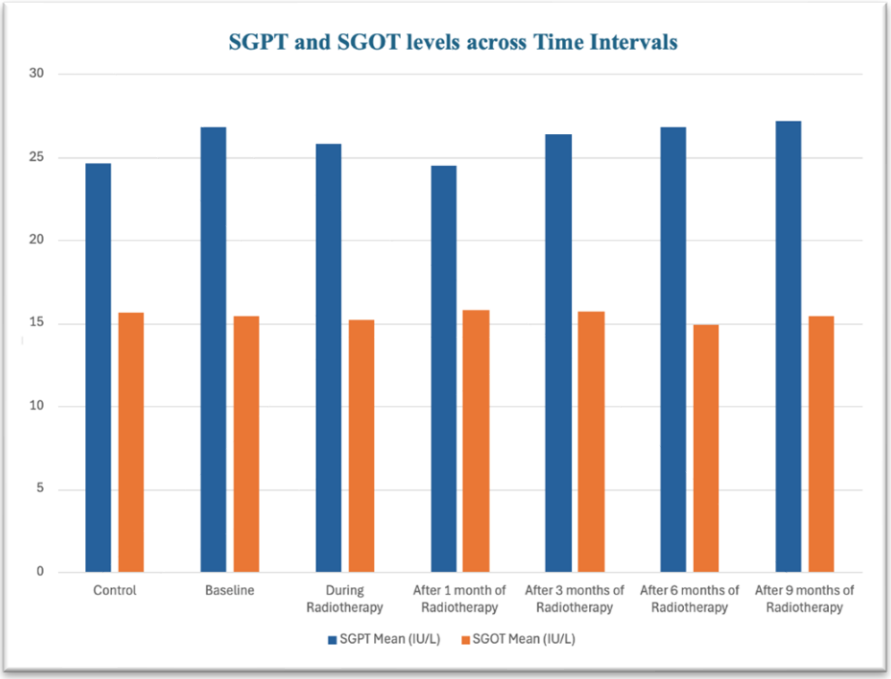

Fig 2.Mean values of SGPT and SGOT in stage II cervical cancer patients

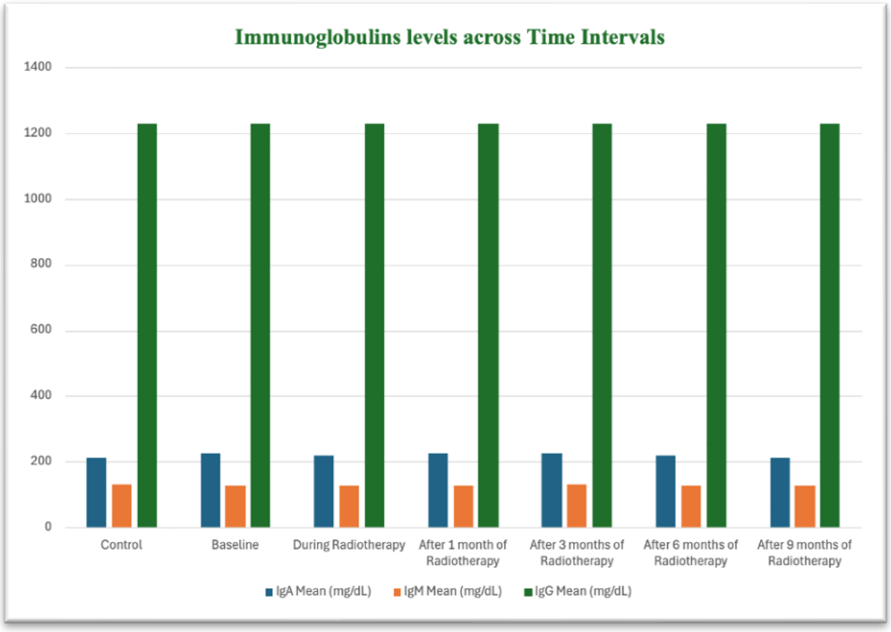

Fig 3. Mean values of immunoglobulins in stage II cervical cancer patients

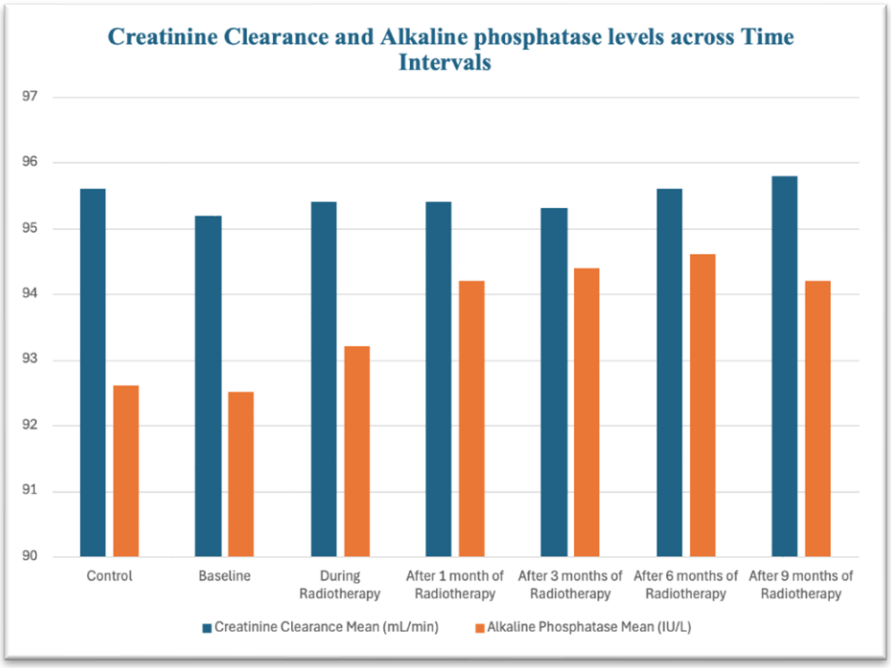

Fig 4. Mean values of creatinine clearance and alkaline phosphatase in stage II cervical cancer patients

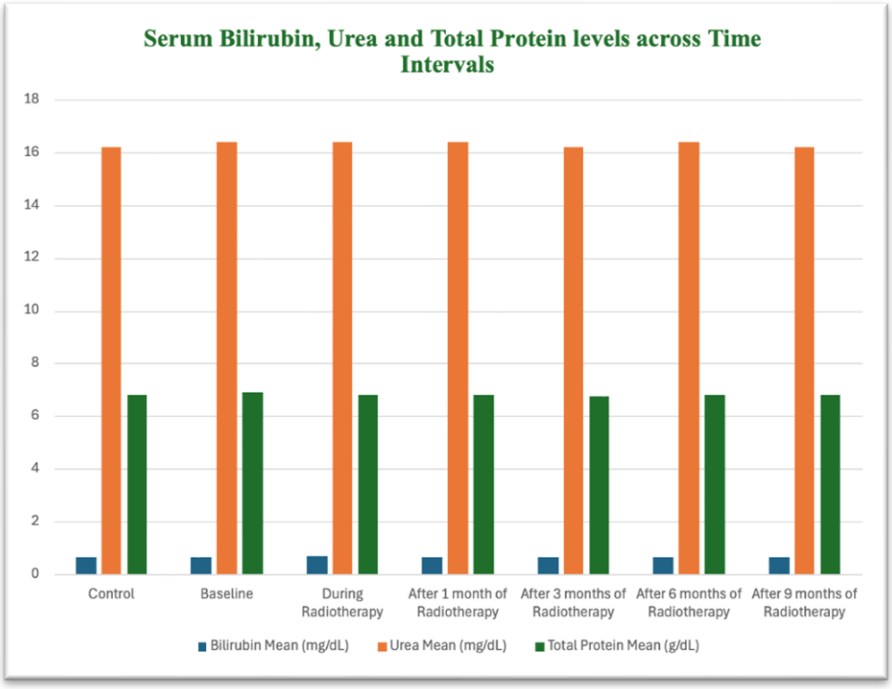

Fig 5. Mean values of bilirubin, urea, total protein levels in stage II cervical cancer patients

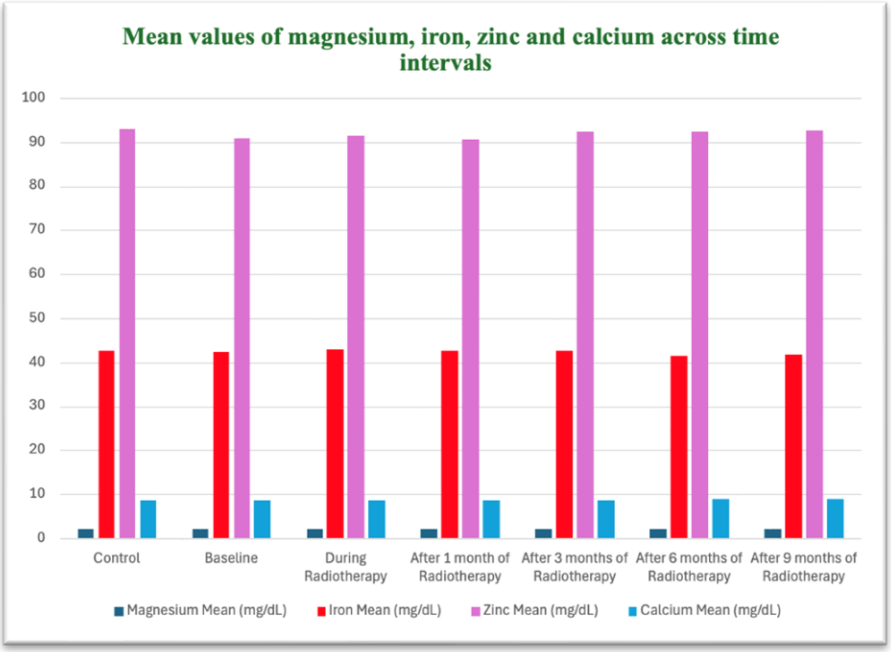

Fig 6. Mean values of magnesium, iron, zinc and calcium in stage II cervical cancer patients

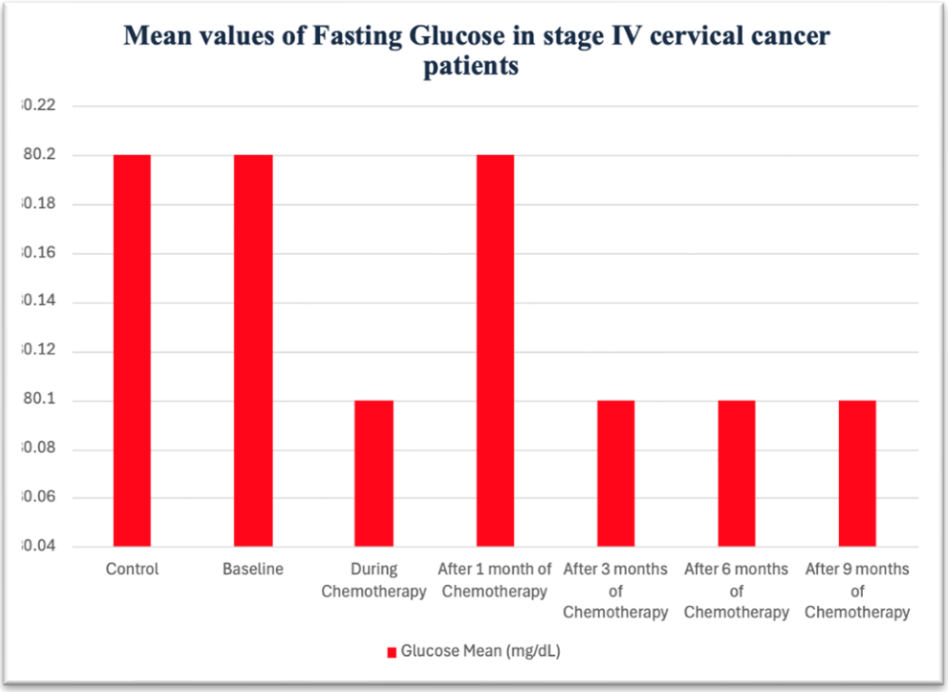

Fig 7. mean values of fasting glucose in stage IV cervical cancer patients

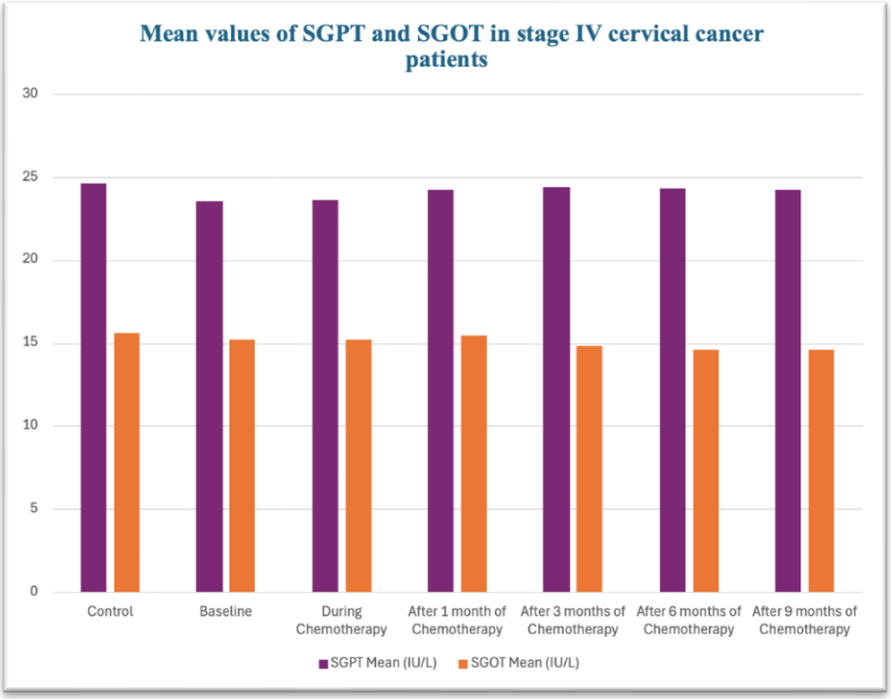

Fig 8. mean values of SGPT and SGOT in stage IV cervical cancer patients

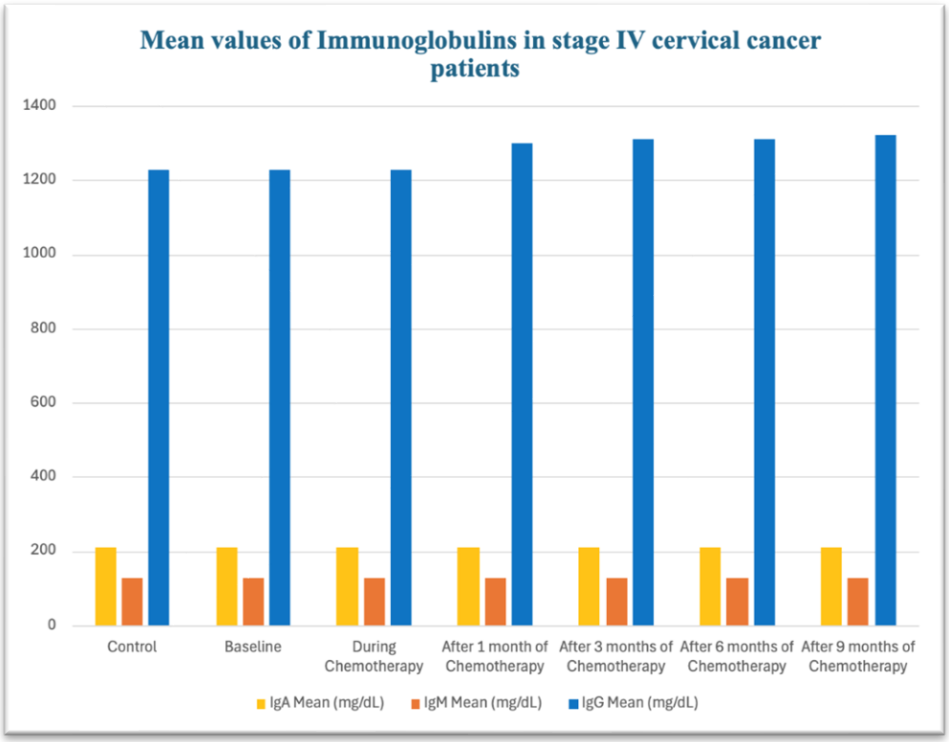

Fig 9. Mean values of immunoglobulins in stage IV cervical cancer patients

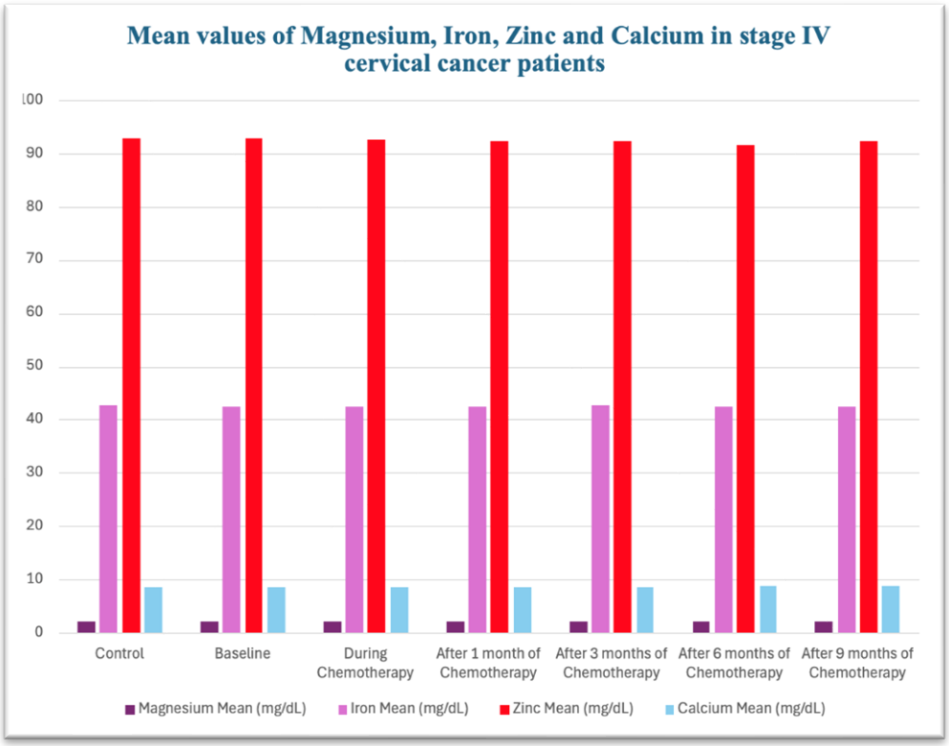

Fig 10. Mean values of magnesium, iron, zinc and calcium in stage IV cervical cancer patients

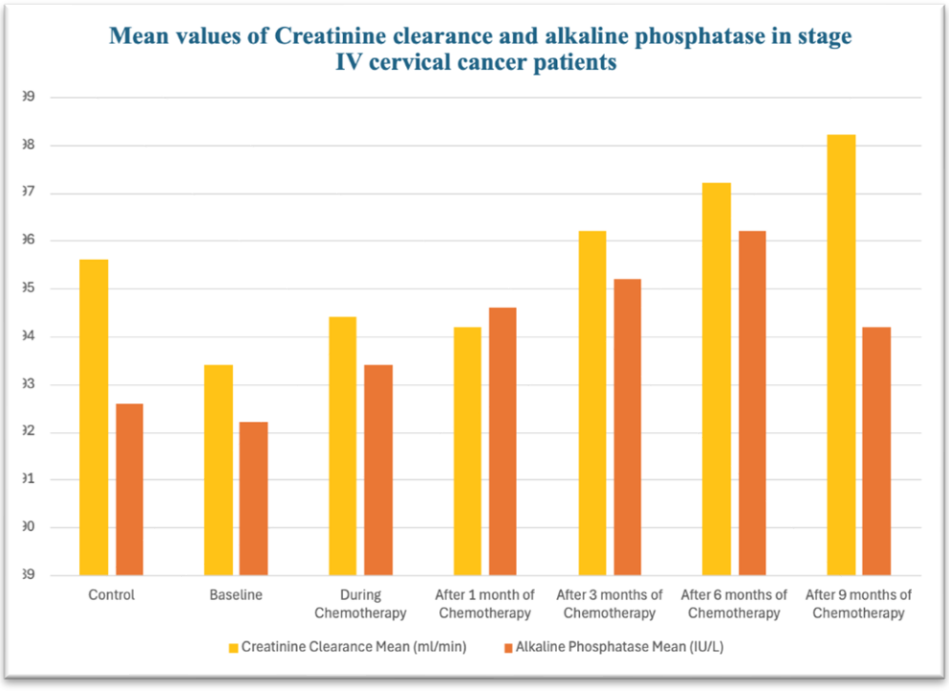

Fig 11. Mean values of creatinine clearance and alkaline phosphatase in stage IV cervical cancer patients

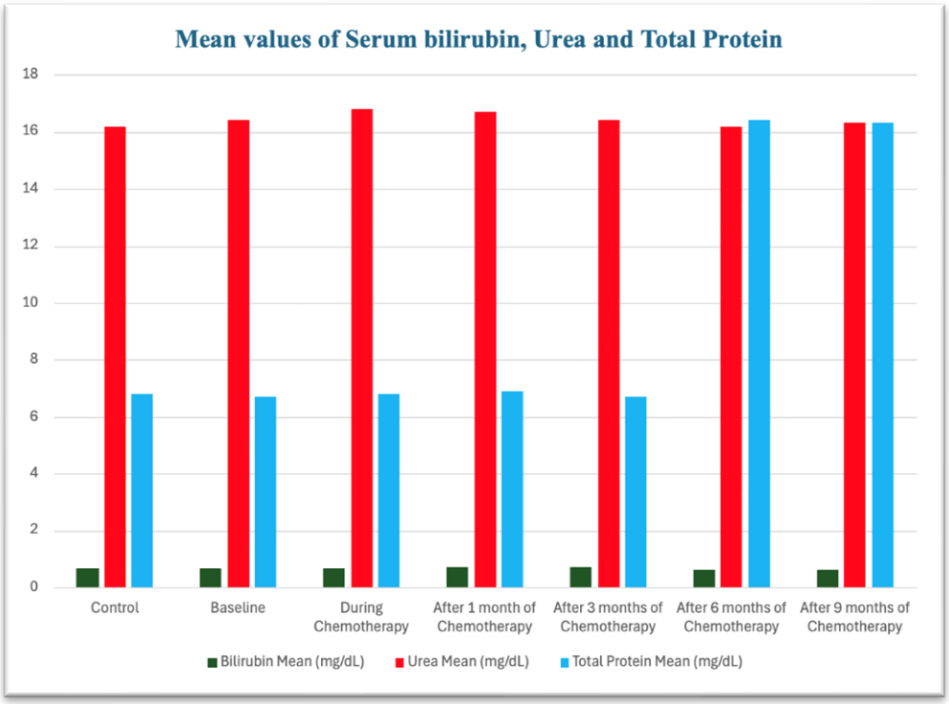

Fig 12. Mean values of serum bilirubin, urea and total protein in stage IV cervical cancer patients

The study identified key trends in the biochemical parameters of cervical cancer patients undergoing different treatment modalities, offering valuable insights into the physiological impact of chemotherapy and radiotherapy. The following summarizes the key findings -

Liver Function Enzymes (SGPT, SGOT)

1. SGPT: The levels showed minor fluctuations, but these changes were not clinically significant, indicating minimal hepatocellular stress during treatment.
2. SGOT: A slight downward trend was observed, suggesting possible liver adaptation over time.
3. Implication: These results suggest that liver function remains resilient under current treatment protocols, though long-term monitoring is advisable for detecting potential delayed hepatic effects.

Renal Function (Creatinine Clearance, Urea)

1. Creatinine Clearance: Remained stable within normal limits, showing no signs of renal impairment due to the treatment.
2. Urea: Slight fluctuations were noted, though these were not indicative of renal dysfunction.
3. Implication: The treatment protocols had a minimal short-term effect on renal function, although the cumulative effects over extended periods warrant further investigation.

Glucose Metabolism

1. Glucose Levels: Remained consistently stable across all patient groups and time points, suggesting that the treatments did not disrupt glucose homeostasis.
2. Implication: Routine glucose monitoring is likely unnecessary unless accompanied by other comorbidities.

Immune Markers (IgA, IgM, IgG)

1. IgA and IgM: Minor fluctuations were observed during treatment, with levels stabilizing post-therapy, indicating transient immune activation.
2. IgG: Levels remained stable throughout the study, demonstrating preserved humoral immunity.
3. Implication: These findings suggest that the immune system remains resilient to treatment, although more advanced immune profiling could uncover subtle effects.

Mineral Levels (Magnesium, Iron, Zinc, Calcium)

1. Minerals: Magnesium, iron, zinc, and calcium levels remained within normal ranges, with only minor fluctuations observed.

- **Implication**: No significant disruption of mineral metabolism was noted, indicating that routine supplementation may not be required unless specific deficiencies are detected.

Alkaline Phosphatase and Bilirubin

1. **Alkaline Phosphatase**: A slight increase was observed post-treatment, possibly linked to bone remodeling or mild liver stress.
2. **Bilirubin**: Minor increases were observed, remaining within normal physiological ranges, indicating no major liver dysfunction.
3. **Implication**: Although these changes are not of immediate concern, regular monitoring is recommended to detect any delayed adverse effects.

Implications Of Findings

1. Preservation of Organ Function: The minimal changes in liver and kidney markers (SGPT, SGOT, creatinine clearance, and urea) suggest that the treatment protocols do not induce significant organ damage, supporting their safety from an organ toxicity perspective.
2. Stable Immune Responses: The transient immune marker fluctuations (IgA and IgM) without long-term suppression imply that the therapies temporarily activate the immune system without compromising long-term immunity, crucial for patients' ability to fight infections.
3. Minimal Disruption of Metabolism: Stable glucose and mineral levels point to minimal metabolic disruptions, ensuring that patients can maintain energy balance and nutritional status, aiding in treatment tolerance.
4. Implications of Minor Increases: Slight increases in alkaline phosphatase and bilirubin may suggest minor liver or bone stress; however, as values remained within normal ranges, these changes likely pose minimal risk. Regular monitoring is recommended for early detection of potential delayed effects.
5. Quality of Life Maintenance: The overall biochemical stability observed in the study highlights the tolerance to treatment and underscores the preservation of quality of life for cervical cancer patients undergoing chemotherapy and radiotherapy.

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