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Role of nitric oxide in predicting radiotherapy-related side effects in patients with cervical cancer

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ABSTRACT

Objective: To assess whether serum nitric oxide (NO) levels can predict radiation-induced side effects in cervical cancer patients undergoing pelvic radiotherapy (RT).

Patients and Methods: Twenty participants diagnosed with locally advanced-stage cervical cancer were included. Weekly blood samples were analyzed for NO levels. Genitourinary (GU), lower gastrointestinal (LGI), and upper gastrointestinal (UGI) toxicities were graded weekly. Two separate analyses were conducted based on initial NO levels either categorized as NO-low and NO-high or the mean NO ratios (NOR) recorded before and after RT. Lastly, the mean clinical symptoms (grade < 2 versus grade ≥ 2) at the end of RT were correlated with the mean NO values.

Results: Serum NO levels increased significantly from baseline ($p = 0.001$). No significant differences in toxicity were found when comparing mean NOR values before and after RT. Symptomatic patients (grade ≥ 2) exhibited higher NO levels at week 5 for GU and LGI toxicities. Baseline NO levels did not consistently predict the severity of side effects.

Conclusion: Serum NO levels increased significantly during RT. No definitive correlation with toxicity severity and NO levels were observed. Further studies require to clarify the potential of NO as a biomarker for predicting RT-induced side effects.

Keywords: Cervical cancer, Nitric oxide, Predictive, Radiotherapy, Side effects

1. INTRODUCTION

Cervical cancer remains one of the most prevalent cancers among women [1]. While early-stage cases can often be effectively managed through surgery, the treatment of advanced-stage cases that involve the extension of cancer into pelvic tissues requires a combination of external and intracavitary radiotherapy (RT) [2]. However, RT can result in both early and late side effects due to toxicity to normal tissues [3]. Pelvic RT can cause issues such as vaginal dryness and stenosis, as well as urinary and gastrointestinal side effects, which can negatively impact patient compliance and overall quality of life [4,5]. Although, advancements in technology have helped reduce radiation exposure to surrounding organs, and various pharmacological and non-pharmacological interventions have been suggested to alleviate toxicity, identifying biochemical markers to predict radiation-induced side effects remains an ongoing challenge [6, 7].

Ionizing radiation causes damage to normal tissues mainly through the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) as a result of water radiolysis [8]. These free radicals initiate molecular changes that lead to oxidative damage in proteins, lipids, and DNA. Various enzymes, such as lipoxygenase, nitric oxide synthase (NOS), and cyclooxygenase, are involved in the regulatory pathways that mediate this type of damage. Under stress conditions, such as inflammation, inducible NOS (iNOS) becomes the primary source of nitric oxide (NO). NO produced by macrophages interacts with superoxide generated by mitochondria, contributing to DNA double-strand breaks. Furthermore, iNOS is implicated in radiation-induced injury by participating in post-translational modifications that are part of the DNA base excision repair pathway [9].

Several studies are investigating the relationship between NO levels and toxicity in patients undergoing RT [10]. Exhaled nitric oxide (eNO) levels may serve as a significant biomarker for predicting radiation pneumonitis. Researchers have found that baseline eNO levels in cancer patients are often higher than those in healthy individuals. An increase in eNO during

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or after RT has been associated with a greater risk of developing radiation pneumonitis. Additionally, NO produced by iNOS has been linked to tumor progression in various cancers [11-14].

Accurately estimating the treatment dose, considering the likelihood and severity of adverse effects, is crucial. Identifying reliable predictors of both early and late side effects is essential for improving therapeutic outcomes. Although, several studies have examined the normal tissue complication probability in RT, no biochemical markers have been validated for routine clinical use [15].

This prospective study evaluates whether serum NO levels can predict and reflect side effects related to pelvic RT in cervical cancer patients.

2. PATIENTS and METHODS

This prospective study was approved by the Ethics Committee of Kartal Dr. Lütfi Kırdar Hospital (the approval number: 23.02.2006/3). A total of 20 patients with cervical cancer were enrolled in the study and all of whom provided informed consent. The median age of the participants was 58 years, ranging from 44 to 68 years. All patients were diagnosed with locally advanced squamous cell carcinoma (stage IIB–IVA) according to the International Federation of Gynecology and Obstetrics (FIGO) Staging System [16]. Inclusion criteria for the study included a definitive indication for chemoradiotherapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 [17], postmenopausal status, and the absence of cardiovascular disease.

Before treatment, each patient underwent a physical examination, an assessment of their performance status, and a weight measurement. Weekly physical examinations were conducted during RT, and side effects were evaluated using the Common Toxicity Criteria (CTC) [18]. These weekly assessments specifically focus on toxicities related to genitourinary (GU), lower gastrointestinal (LGI), and upper gastrointestinal (UGI) systems.

Radiation therapy was delivered to the pelvic region using a four-field box technique with a linear accelerator, using photon energy of 15 MV. The total external dose administered was 50.4 gray (Gy), given in 1.8 Gy fractions. After the external RT, intravaginal brachytherapy was performed to all patients. Additionally, cisplatin was administered weekly at a dosage of 40 mg/m^2 as a radiosensitizer.

Routine laboratory tests were conducted to assess hemoglobin levels, liver and kidney function, and electrolyte balance. All tests were repeated weekly.

At the beginning of the study, the mean baseline serum NO levels were obtained from blood samples taken from healthy volunteers (n=10) of similar age to the patients to be studied for use in analyses. Following the start of the study, blood samples for NO analysis were collected from patients on days 1, 6, 11, 16, and 21 of RT, 15 minutes before the corresponding RT fraction. Samples were transported to the laboratory within two hours and centrifuged at 5,000 rpm for 10 minutes. From each serum sample, 0.5 mL was mixed with 1 mL of ethanol, thoroughly vortexed, and then incubated in an ice bath for 30 minutes. Subsequently, the samples were centrifuged at 14,000 rpm at 0 °C for 5 minutes. The resulting supernatant was collected into separate Eppendorf tubes. NO levels were measured using an analyzer, with five µL of each sample being analyzed. The results were multiplied by three to account for the dilution caused by ethanol, providing accurate serum NO concentrations.

Statistical Analysis

The mean ± standard deviation (SD) values, along with the 95% confidence intervals, were used to compare changes and differences between groups over the weeks. Due to the small sample size of the study (n = 20), the Shapiro-Wilk test was performed to assess the normality of the data. The p-value was found to be <0.05, leading to the decision to use nonparametric tests for analysis.

Three different analyses were conducted. First, patients were categorized based on their initial NO values at the start of RT. Two groups were defined: NO-low and NO-high, based on the mean NO value of healthy volunteers (53.22 ± 8 µL). The Wilcoxon rank sum test was utilized to compare weekly differences in NO values between these two groups. Given the sample sizes (11 patients with low NO and 9 patients with high NO), the statistical power was determined to be approximately 18.4% when assuming a medium effect size (Cohen's d = 0.5) and α level of 0.05 for this analysis.

Secondly, the mean NO ratios (NOR) before and after RT were calculated as previously described. The mean weekly toxicities were compared according to the mean NOR value (2.71 ± 2.14 µL) using the Mann-Whitney U test.

Finally, patients were classified into clinically asymptomatic (grade < 2) or symptomatic (grade ≥ 2) groups for each type of toxicity at the end of RT (week 5). The mean NO values were compared for each week of RT between the two groups using the Mann-Whitney U test. A statistical significance level of $p < 0.05$ was set for all analyses.

3. RESULTS

All patients completed chemoradiotherapy without interruption, and none experienced clinical disease progression. Weight changes and laboratory values during RT are summarized in Table I. By the end of RT, patients experienced significant weight loss compared to their baseline measurements (65 ± 9.06 kg vs. 62.6 ± 10.76 kg; $p < 0.006$). There were also significant changes in laboratory values: hemoglobin ($p = 0.008$), and magnesium ($p = 0.032$) levels significantly decreased. NO levels increased significantly by the end of chemoradiotherapy, rising from 50.74 ± 35.77 µL to 71.47 ± 45.14 µL ($p = 0.001$), as shown in Figure 1.

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Table I. *Side effects and laboratory results according to radiotherapy weeks for study population (n=20).*

	Week 1	Week 2	Week 3	Week 4	Week 5
GU grade*	11	19	11	16	14
LGI grade*	10	9	18	18	21
UGI grade*	21	11	13	18	22
Weight (kg)	65±9.06	-	-	-	62.6±10.76
NO (micro/L)	53.22±35.77	59.89±44.93	55.71±33.85	56.86±29.82	71.47±45.14
Hemoglobin (g/dL)	11.15±0.58	11.63±0.27	11.21±0.24	11.21±0.43	10.61±0.30
AST (U/L)	19.05±1.97	21.11±2.01	19.50±1.90	22.75±2.62	25.93±3.76
ALT (U/L)	13.65±1.65	17.39±2.80	15.35±2.0	17.13±3.0	17.33±2.85
LDH (U/L)	340.82±28.08	443.92±41.07	365.58±27.52	365.53±26.60	422.30±38.96
GGT (U/L)	24.61±6.28	23.94 ±5.52	21.21±5.0	21.44 ±4.33	23.77± 8.24
ALP (U/L)	230.22±19.29	216.19±23.06	202.31±19.56	223.50±16.17	214.42±37.66
Total bilirubin (mg/dL)	0.61±0.06	0.67±0.06	0.52±0.08	0.60±0.07	0.52±0.04
BUN (mg/dl)	32.15±1.86	37.11±5.13	34.78±3.88	38.47±3.99	32.50±3.04
Magnesium (mg/dL)	1.25±0.28	1.23±0.27	1.11±0.25	0.97±0.22	1.28±0.29
Sodium (mmol/L)	137.99±0.76	137.82±0.73	138.47±0.94	137.07±1.14	138.21±1.03
Chloride (mmol/L)	103.8±1.23	104.32±1.22	103.50±1.25	101.28±1.67	102.63±1.44
Calcium (mg/dl)	9.08±0.29	9.31±0.14	9.29 ±0.11	8.81±0.31	9.19±0.32
Potassium (mmol/L)	4.20±0.11	4.21±0.11	4.17±0.12	4.95±0.89	4.35±0.36

**Total scores of side effects according to RTOG scale; GU: Genitourinary. LGI: Lower gastrointestinal, UGI: Upper gastrointestinal, NO: Nitric oxide, AST: Aspartate transaminase, ALT:Alanine transaminase, LDH: Lactate dehydrogenase, BUN: Blood urine nitrogenase, GGT: Gamma-glutamyl transpeptidase, ALP: Alkaline phosphatase*

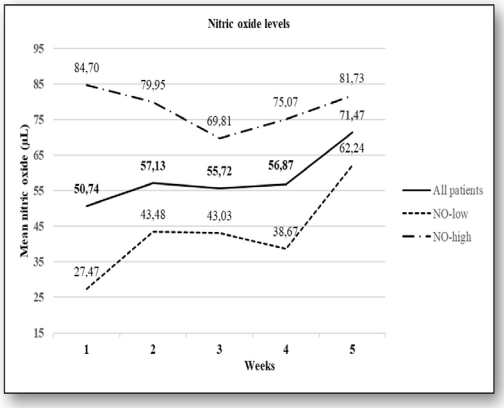

Figure 1. *Mean NO levels (µL) according to radiotherapy weeks. (The mean NO level of healthy volunteers 53.22 ± 8 µL). The difference was significant in the NO-low group between week 1 and week 5 (p= 0.037). NO: nitric oxide.*

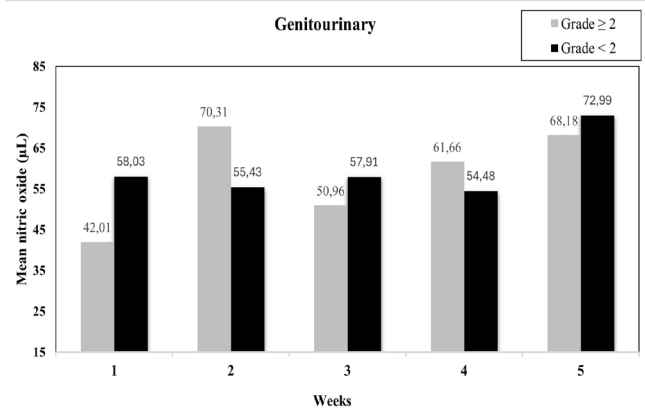

Figure 2. *Mean genitourinary toxicity scores in groups according to symptomatic toxicity grade. NO: nitric oxide*

Table II presents the differences in side effects for each week in the NO-low and NO-high groups. There was no significant difference between the groups, except for LGI toxicity in the fourth week in the NO-low group (p=0.026).

The comparative results of mean NOR before and after RT are summarized in Table III. There were no significant differences in toxicity between the two groups.

The mean levels of NO due to clinical side effects grading are illustrated in Figures 2-4. The NO levels were higher in week 5 compared to the first week of RT in the symptomatic group for GU and LGI toxicities. The increment was not as prominent in the asymptomatic group. For UGI toxicity, NO levels were higher in the symptomatic group than in the asymptomatic group, especially in the early weeks of therapy.

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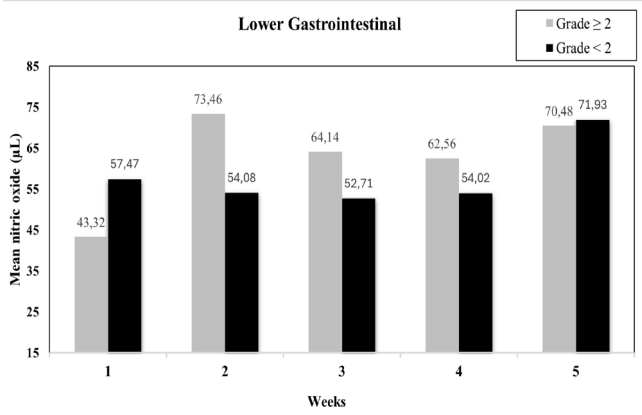

Figure 3. *Mean lower gastrointestinal toxicity scores in groups according to symptomatic toxicity grade. NO: nitric oxide*

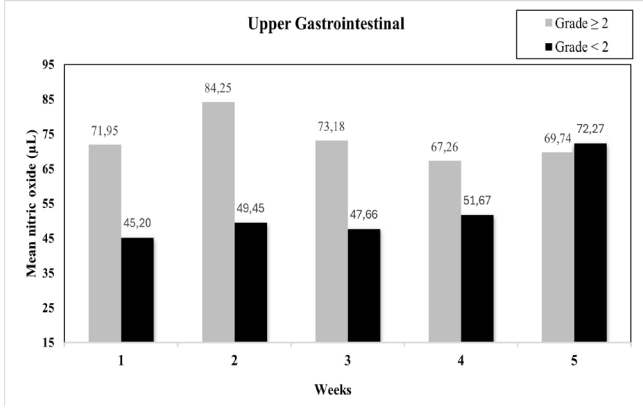

Figure 4. *Mean upper gastrointestinal toxicity scores in groups according to symptomatic toxicity grade. NO: nitric oxide*

Table II. *Comparison the study results according to the initial nitric oxide level of lowerα (n=11) or higherβ (n=9) according to the healthy volunteers (n=10).*

	Week 1	p	Week 2	p	Week 3	p	Week 4	p	Week 5	p	Total Score Mean	p
GUα	4		9		3		8		7		31	
GUβ	7	0.247	10	0.440	8	**0.042**	8	0.743	7	0.673	40	0.137
LGIα	5		3		10		6		11		35	
LGIβ	5	0.674	6	0.174	8	0.953	12	**0.022**	10	0.755	41	0.458
UGIα	11		6		6		7		11		41	
UGIβ	10	0.979	5	0.540	7	0.539	11	0.099	11	0.506	44	0.553

GU: Genitourinary, LGI: Lower gastrointestinal, UGI: Upper gastrointestinal, α: Nitric oxide low group (NO-low) (n=11); β: Nitric oxide high group (NO-high) (n=9).

Table III*. Comparison of the toxicity results according to the nitric oxide ratio (NOR)*

	Week 1	p	Week 2	p	Week 3	p	Week 4	p	Week 5	p
GUα	0.57±0.34	0.778	0.93±022	0.861	0.71±0.19	0.095	0.71±0.24	0.472	0.71±0.24	0.850
GUβ	0.50±0.20		1.0±0.36		0.17±0.16		1.0±0.36		0.67±0.42	
LGIα	0.57±0.13	0.342	0.43±0.17	0.667	0.93±0.30	0.787	0.86±0.36	0.725	1.07±0.19	0.859
LGIβ	0.33±0.121		0.50±0.22		0.83±0.19		1.00±0.20		1.0±0.36	
UGIα	1.07±0.19	0.859	0.50±0.22	0.526	0.64±0.22	0.891	1.00±0.21	0.379	1.14±0.25	0.653
UGIβ	1.00±0.36		0.67±0.33		0.67±0.33		0.67±0.33		1.00±0.20	

GU: Genitourinary, GI: Gastrointestinal, Nitric oxide ratio low (α) (n=6), high (β) (n=14) groups

4. DISCUSSION

This study examined the relationship between serum NO levels and side effects associated with RT. In the study, NO levels were observed to increase over the course of the weeks (Figure 1). Toxicity increased toward the end of the RT due to dose accumulation. However, there was an exception noted in the UGI tract, where an increase was recorded during the second week (Figure 4). This increase seemed to be caused by nausea and vomiting associated with the concurrent chemotherapy.

The first analysis was based on the initial NO values as predictors of toxicity during RT. It was observed that in patients with initially high NO values, these values remained elevated at the end of the treatment. Conversely, in patients with lower initial values, although NO levels increased by the end of the treatment, they remained lower compared to those in the high NO group (Figure 1).

Our second analysis compared the initial and final NO values to determine the NOR value using a similar method to that in literature [14]. McCurdy et al., stratified esophageal and lung cancer patients based on the clinical score as symptomatic (grade ≥2, 7 patients) or asymptomatic (grade 0 or 1, 43 patients) for radiation pneumonitis in their study [14]. They calculated the exhaled NO ratios with the comparing NO values of the

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end versus the beginning of RT. According to the NOR value, symptomatic patients had a higher NO level than asymptomatic patients had ($p < 0.006$). However, in our study, no significant differences were found in toxicities between the two groups, as indicated by the mean NOR value.

Another analysis shows that NO levels were higher in week 5 compared to the first week of RT, especially in the symptomatic group for GU and LGI toxicities. For UGI toxicity, NO levels were dramatically higher in the symptomatic group than in the asymptomatic group. Accordingly, serum NO values were observed to be similar or higher in the symptomatic and asymptomatic groups at the end of treatment. This elevation was more pronounced in the symptomatic group, but it was not statistically significant. A rise in NO by week 5 in the symptomatic groups in our study may reflect late or cumulative inflammatory damage. Meanwhile, in the UGI tract, a consistently higher NO in severe toxicity cases suggests a robust early inflammatory response, which may contribute to or signal the development of higher-grade toxicity. These results may suggest that the pattern of NO changes differs by organ system. Therefore, there may be organ-specific inflammatory dynamics in response to RT.

Tissue-based NO levels may be a toxicity biomarker for combined and sequential treatments in cancer patients. Gao et al., examined the correlation between alveolar NO concentration and checkpoint inhibitor pneumonia in lung cancer patients in their study [19]. They reported that alveolar NO concentration was significantly higher in patients suffering from pneumonia. In multivariate analysis, pre-existing RT was the most prominent risk factor for toxicity in those patients ($p < 0.001$).

In another study, authors investigated the level of NO in nasal mucosa (tissue) for predicting radiation-induced side effects in patients with nasopharyngeal cancer [20]. On the contrary, impaired mucociliary function presents with a low level of NO, and this result is related to more sinonasal-related symptom burdens in the post-irradiation period.

This is the first study to investigate the predictive role of NO in RT-related toxicity in patients who have a pelvic tumor like cervical cancer. Given its low cost and accessibility, serum NO testing may offer a practical tool for anticipating the severity and frequency of RT-related side effects.

Limitations

Our study is limited by its small sample size, single-center experience, and short follow-up duration. There may be potential confounders like diet, smoking status, active infection, medication, and comorbidities. Future research with larger participant groups and prospective designs is necessary to validate these findings. Incorporating quality-of-life and survival metrics could further highlight the clinical relevance of serum NO as a predictive biomarker. Another point is that a receiver operating characteristic (ROC) curve analysis for NO level would have been a more robust method for defining a clinically relevant threshold, rather than the cutoff we have chosen based on the results of healthy volunteers. However, the sample size of healthy volunteers was not adequate for a ROC curve analysis.

Conclusion

This may be a pilot study to examine the relationship between serum NO levels and the side effects of pelvic RT in patients with cervical cancer. RT elicits an inflammatory response that contributes to both tumor control and adverse effects. Although a clear and significant relationship between NO levels and the intensity of toxicities could not be established, this topic may be a subject for further investigation with a larger patient population. Understanding the potential role of NO level determination may help predict and manage RT-associated side effects.

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Compliance with Ethical Standards

Ethical approval: This study was approved by the Ethics Committee of Kartal Dr. Lütfi Kırdar Hospital (the approval number: 23.02.2006/3).

Conflict of interest: The authors declare that there are no conflicts of interest.

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Author contributions: DG: Conceptualization, investigation, methodology, formal analysis, writing, reviewing, and editing the manuscript, HO: Conceptualization, investigation, methodology, formal analysis, supervision, writing, and editing the manuscript, OGB: Methodology, formal analysis, validation, visualization, and manuscript editing, AM: Investigation, methodology, supervision, writing, and editing the manuscript. All authors had approved the final version of the manuscript.

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