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ORIGINAL ARTICLE/ORİJİNAL MAKALE

Investigation Of The Effect Of Nutrition In Gynecologic Malignancy On The Early Genitourinary And Gastrointestinal Side Effects Profile Of Patients Receiving Pelvic Radiotherapy

Jinekolojik Malignitelerde Beslenmenin Pelvik Radyoterapi Alan Hastaların Erken Genitoüriner ve Gastrointestinal Yan Etki Profiline Etkisinin Araştırılması

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ABSTRACT

Aim: The The role of therapeutic or adjuvant radiotherapy in gynecological cancers is crucial. Genitourinary and gastrointestinal symptoms can occur in these diseases due to the anatomical relationships in the pelvic region. To prevent these complications, enriching the intestinal flora and microbiota, as well as providing supplementation with trace elements, vitamins, and minerals, has been shown to reduce side effects. This study aimed to investigate the early gastrointestinal and genitourinary side effect profiles in patients receiving nutritional support (NS) and radiotherapy.

Material and Methods: Patients who presented to the Department of Obstetrics and Gynecology and Radiation Oncology Department at Selçuk University Faculty of Medicine between 2023 and 2024 and received pelvic radiotherapy for gynecological malignancy were evaluated. Nutritional support is routinely provided in the clinic, and the study was designed as a retrospective study. The Radiation Therapy Oncology Group's Radiation Toxicity Index was used for side effect scoring. A total of 120 patients were included in the study. Based on nutritional support, Group 1 (n=60) included those who received nutritional support, and Group 2 (n=60) included those who did not receive nutritional support.

Results: There was a difference in the distribution of genitourinary side effects among patients receiving radiotherapy according to their use of nutritional support ($p<0.05$). It was observed that the use of NS had the potential to reduce genitourinary side effects. There was a difference in the distribution of gastrointestinal side effects in patients receiving radiotherapy according to their NS use ($p<0.05$). Gastrointestinal side effects were less common in patients receiving NS.

Conclusion: Nutritional support is thought to reduce genitourinary and gastrointestinal side effects in gynecologic cancer patients undergoing pelvic radiotherapy. Individualized approaches are essential, regardless of nutritional index.

Keywords: Radiotherapy, Hysterectomy, Side effect, Nutrition, Malignancy

ÖZET

Amaç: Jinekolojik kanserlerde radyoterapinin rolü çok önemlidir. Pelvik bölgedeki anatomik ilişkiler nedeniyle bu hastalıklarda genitoüriner ve gastrointestinal semptomlar ortaya çıkabilir. Bu çalışmada beslenme desteği (ND) alan hastalarda erken gastrointestinal ve genitoüriner yan etki profillerinin araştırılması amaçlanmıştır.

Materyal ve Metod: Selçuk Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı ve Radyasyon Onkolojisi Anabilim Dalı'nda 2023-2024 yılları arasında başvuran ve jinekolojik malignite tanısıyla pelvik radyoterapi alan hastalar değerlendirildi. Klinikte rutin olarak beslenme desteği verilmekte olup, çalışma retrospektif olarak tasarlandı. Yan etki skorlaması için Radyasyon Terapisi Onkoloji Grubu'nun Radyasyon Toksisite İndeksi kullanıldı. Çalışmaya toplam 120 hasta dahil edildi. Beslenme desteğine göre Grup 1 (n=60) beslenme desteği alanlar, Grup 2 (n=60) ise beslenme desteği almayan hastalardan oluşturuldu.

Bulgular: Radyoterapi alan hastalarda beslenme desteği kullanımına göre genitoüriner yan etkilerin dağılımında farklılık görüldü ($p<0,05$). ND kullanımının genitoüriner yan etkileri azaltma potansiyeline sahip olduğu görüldü. Radyoterapi alan hastalarda ND kullanımına göre gastrointestinal yan etkilerin dağılımında farklılık görüldü ($p<0,05$). ND alan hastalarda gastrointestinal yan etkiler daha az yaygın olarak raporlandı.

Sonuç: Pelvik radyoterapi uygulanan jinekolojik kanser hastalarında beslenme desteğinin genitoüriner ve gastrointestinal yan etkileri azalttığı düşünülmektedir. Beslenme indeksi ve ek hastalıklara göre kişiye özel yaklaşımlar esastır.

Anahtar Sözcükler: Radyoterapi, Histerektomi, Yan etki, Beslenme, Malignite

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INTRODUCTION

Gynecologic malignancies are a heterogeneous group of tumors that pose a significant burden of morbidity and mortality worldwide in terms of both incidence and mortality rates (1). This group includes malignancies originating from the cervix, endometrium, ovary, vagina, and vulva, each characterized by unique pathophysiological mechanisms, clinical course, and treatment algorithms (2). Current oncological treatment approaches utilize surgery, chemotherapy, and radiotherapy, either alone or in multimodal combinations. Pelvic radiotherapy, in particular, is a highly preferred treatment modality with demonstrated evidence-based efficacy in the treatment of locally advanced disease and adjuvant treatment strategies (3). However, the ionizing radiation effect of pelvic radiotherapy on healthy pelvic tissues outside the target volume poses a significant clinical problem in terms of its early (acute) toxicity profile. Symptoms such as dysuria, pollakiuria, urinary retention, and hematuria in the genitourinary system, and diarrhea, rectal bleeding, abdominal cramping, and mucositis in the gastrointestinal system are frequently observed during or within the first 90 days following treatment (4,5). These adverse effects not only negatively impact quality of life but can also indirectly limit treatment effectiveness by reducing treatment compliance (6). In recent years, increasing scientific evidence has been reported that nutritional status and dietary modifications may be determining variables in the toxicity profile associated with pelvic radiotherapy (7,8). In particular, the effects of diet on the composition of the gut microbiota, mucosal barrier integrity, inflammatory response, and hydration balance have the potential to modulate the incidence and severity of gastrointestinal and genitourinary toxicities (9). Randomized controlled trials and prospective cohort analyses report that modification of fiber intake, lactose restriction, low-FODMAP diet practices, probiotic and prebiotic supplementation, and optimal fluid intake provide clinically significant reductions in the severity of symptoms such as diarrhea, abdominal discomfort, and urinary tract irritation (10,11). This study aimed to investigate the early gastrointestinal and genitourinary side effect profiles in patients receiving nutritional support (NS).

MATERIALS AND METHODS

This is a retrospective study conducted at the Department of Obstetrics and Gynecology and Radiation Oncology, Selcuk University Faculty of Medicine. Patients aged 46-79 who received pelvic radiotherapy for gynecological malignancy between 2023 and 2024 were evaluated.

A total of 120 patients were evaluated in the study, and two randomized groups were formed with 60 patients in each group.

Group 1: Pelvic radiotherapy, nutritional support (n=60)

Group 2: Pelvic radiotherapy, nutritional support (n=60)

Groups were classified according to age, parity, comorbidities, previous surgery, the type of cancer and the treatment modalities they received laboratory parameters (WBC, Hemoglobin, Platelet count), medication, pathology results, radiotherapy duration and dose, surgery type, grading of genitourinary (GU) and gastrointestinal (GI) side effect profiles on the seventh day after pelvic radiotherapy, and nutritional support status. The Radiation Therapy Oncology Group/ European Organization for Research and

Treatment of Cancer (RTOG/EORTC) Radiation Toxicity Grading System guide was used for grading.

The RTOG/EORTC acute radiation toxicity assessment system was developed to standardize the classification of adverse events occurring during radiotherapy or within 90 days following its completion. This assessment examines changes in various organ and tissue groups, including the skin, mucosa, gastrointestinal system, genitourinary system, lungs, blood counts, nervous system, and heart. Skin erythema, edema, peeling, or ulcers; mucosal redness, ulceration, or bleeding; gastrointestinal diarrhea, abdominal pain, or bleeding; urinary frequency, burning sensation, or hematuria; lung cough and shortness of breath; blood counts of leukocytes, platelets, and hemoglobin; nervous system headache, neurological deficits, and seizures; and cardiac ECG changes, arrhythmias, or signs of heart failure.

Check-ups are performed weekly throughout treatment and every 2–4 weeks for 90 days after the end of treatment. Scoring is performed separately for each organ system and ranges from Grade 0 (no toxicity) to Grade 4 (life-threatening toxicity). Grade 1 represents mild symptoms that do not require treatment; Grade 2 represents significant symptoms and the need for medical treatment; Grade 3 represents severe symptoms that interfere with daily life and often require hospitalization; and Grade 4 represents life-threatening complications that require urgent intervention (12). This form is routinely used in wards to report the side effect scale. Protein and energy, containing arginine, omega-3 fatty acids, RNA (dietary nucleotides) and soluble fiber (Nestlé Impact Oral, Novartis, Switzerland) the nutritional supplement routinely used in the clinic, is three suspension per day (237 ml/sus) for 5-7 days. It is a food formula for medical purposes containing 341 kcal, arginine, omega-3 fatty acids, RNA (dietary nucleotides), and soluble fiber. Each 237 ml serving contains approximately 18 g protein (21% energy), 44.8 g carbohydrate (53% energy), 9.2 g fat (24% energy), and 3.3 g fiber (2% energy); it also provides 4.3 g arginine, 1.4 g omega-3 fatty acids, and 0.43 g RNA. Its osmolarity is 680 mOsm/L. Mineral content includes (mg/100 ml) Na 150, Zn 2.1, Ca 114, P 101, Cl 169, Mg 32, Fe 1.7, and K 190.

All patients in this study were treated using advanced Intensity-Modulated Radiation Therapy (IMRT). In a total of 120 cases, radiotherapy was administered to the pelvic region in the range of 45–50.4 Gy, according to international guidelines and our clinic's standard treatment protocols. The treatment schedule was planned at 1.8 Gy per fraction, which represents the standard dose range widely accepted in the literature for oncological efficacy in irradiating the pelvic lymphatic spaces.

Exclude Criteria

Patients with inflammatory bowel disease, irritable bowel syndrome, interstitial cystitis, and chronic painful bladder syndrome were excluded from the study.

Statistics

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) 26.0 Statistics package program. Categorical data for female patients receiving radiotherapy are presented as numbers and percentages, and numerical variables are presented as mean, standard deviation, minimum, and maximum. The conformity of the female patients' age, WBC,

Hb, and PLT values to a normal distribution was determined by examining the skewness and kurtosis values. Except for WBC values, age, Hb, and PLT values were observed to conform to the rules of normal distribution. The reference value taken for a normal distribution is between ±1.96 (12). The Chi-Square test was used to compare comorbidities, surgical history, pathology results, surgery types, side effects, and gastrointestinal monitoring results of female patients receiving radiotherapy according to their formula use status. The Independent Samples T Test was used to compare age, Hb, and PLT values, and the Mann-Whitney U Test was used to compare WBC values. Significance levels throughout the study were calculated using values of 0.05 and 0.01 (13).

RESULTS

The mean age of patients who did not use Formula was 63.75 years, while the mean age of patients who used Formula was 63.47 years. According to these findings, no difference was observed between the mean ages of female patients receiving radiotherapy based on their formula use status (p>0.05).

Whole blood cell counts were measured at an average of 10.19 in the non-formula group and 10.91 in the formula-using group. Hemoglobin levels were measured at an average of 11.95 in non-formula patients and 12.26 in formula-using patients. Platelet counts were measured at an average of 260.37 in the non-formula group and 281.20 in the formula-using group.

Table 1: Comparison of Descriptive Characteristics of Female Patients Receiving Radiotherapy According to Formula Use Status

Parameter		Not using Formula (n: 60)		Using Formula (n: 60)		p
		Sayı	%	Sayı	%	
Medical State	No	27	45,0	37	61,7	0,100
	Yes	33	55,0	23	38,3	
Prior Operation	No	40	66,7	48	80,0	0,148
	Yes	20	33,3	12	20,0	
Patology	Endometrium cancer	42	70,0	43	71,7	0,452
	Cervical cancer	13	21,7	8	13,3	
	Serous Carcinoma	2	3,3	5	8,3	
	Others	3	5,0	4	6,7	
Surgery Type	Debulking	13	21,7	14	23,3	0,103
	Hys+Bso+Rplnd	18	30,0	18	30,0	
	Wertheım	8	13,3	8	13,3	
	Hys+Oop+LND+Omen	9	15,0	10	16,7	
	LS hys+Bso+Rplnd	1	1,7	7	11,7	
	Others	11	18,3	3	5,0	
		Mean.±S.D(Min.-Max.)		Mean .±SD (Min.Max.)		
Age		63,75±12,02 (30-86)		63,47±10,29 (28-85)		0,890

*p<0,05, **p<0,01, x^2: Chi-square test (Categorical data), t: Independent Sample T Test

Table 2: Comparison of Laboratory Findings of Female Patients Receiving Radiotherapy According to Formula Use Status

Laboratory findings	Not using Formula (n: 60) Mean.±S.D (Min.-Max.)	Using Formula (n: 60) Meant.±S.D (Min.-Max.)	
WBC (White Blood Cells) z	10,19±3,57 (2,5-21,1)	10,91±4,68 (3,77-31,8)	0,530
HB (Hemoglobin)t	11,95±1,66 (8,5-15,3)	12,26±1,49 (9,6-16,4)	0,286
PLT (Platelet)t	260,37±67,11 (151-452)	281,20±76,95 (111-460)	0,117

*p<0,05, **p<0,01, x^2: Chi-square test (Categorical data), t: Independent Sample T Test; z: Mann-Whitney U Test

These findings suggest that there was no significant effect on WBC, HB, or PLT levels in patients receiving radiotherapy (p>0.05).

In the non-formulated group, there were 42 patients with endometrial cancer, 13 with cervical cancer, 2 with ovarian serous carcinoma, and 3 with rare malignancies. In the formula-treated group, there were 43 patients with endothelial cancer, 8 with cervical cancer, 5 with ovarian serous carcinoma, and 4 with rare malignancies. A total of 27 patients underwent debulking, and 72 patients underwent Wertheim's disease, total hysterectomy, bilateral salpingo-oophorectomy ± omentectomy, and lymph node dissection.

Table 3: Comparison of Side Effects and Gastrointestinal Monitoring Results of Female Patients Receiving Radiotherapy According to Formula Use Status

Parameter		Not using Formula (n: 60)		Not using Formula (n: 60)		p
		No	%	No	%	
Genitourinary side effects	Grade 0	20	33,3	22	36,7	**0,000****
	Grade1	12	20,0	34	56,7	
	Grade 2	27	45,0	4	6,7	
	Grade 3	1	1,7	0	0,0	
Gastrointestinal side effects	Grade 0	22	36,7	23	38,3	**0,001****
	Grade 1	17	28,3	33	55,0	
	Grade 2	20	33,3	3	5,0	
	Grade 3	1	1,7	1	1,7	
Gastrointestinal transit	Grade 0	42	70,0	50	83,3	0,117
	Grade 1	15	25,0	10	16,7	
	Grade 2	3	5,0	0	0,0	
Transition during the day	Grade 0	36	60,0	44	73,3	0,217
	Grade 1	21	35,0	12	20,0	
	Grade 2	3	5,0	4	6,7	

*p<0,05, **p<0,01, x^2: Chi-square test (Categorical data)

The distributions of comorbidities, parity, surgical status, pathology results, and surgery types were similar in patients who received and did not receive radiotherapy (p>0.05).

A difference was observed in the distribution of genitourinary side effects among female patients receiving radiotherapy according to their formula use status (p<0.05). While 33.3% of non-formula patients experienced Grade 0 side effects, this rate was 36.7% in the formula-using group. The Grade 1 side effect rate increased to 56.7% in formula-using patients, while this rate was 20.0% in the non-formula-using group. Grade 2 side effects occurred in 45.0% of non-formula-using patients and only 6.7% in formula-using patients. Furthermore, Grade 3 side effects were observed in 1.7% of non-formula-using patients, while none were observed in the formula-using group. These findings suggest that formula use has the potential to reduce genitourinary side effects.

There was a difference in the distribution of gastrointestinal side effects among female patients receiving radiotherapy based on their formula use status (p<0.05). While 36.7% of non-formulated patients experienced Grade 0 side effects, this rate was 38.3% in the formula-using group. Grade 1 side effects were 55.0% in the formula-using group, compared to 28.3% in the non-formulated group. Grade 2 side effects were 33.3% in the non-formulated group and only 5.0% in the formula-using group. These findings suggest that formula use has the potential to reduce gastrointestinal side effects.

There was no difference in the distribution of gastrointestinal transit effects among female patients receiving radiotherapy based on their formula use status (p>0.05). Seventy percent of non-formula users experienced Grade 0 transit, compared to 83.3% in the formula-using group.

There was no difference in the distribution of daily transit effects among female patients receiving radiotherapy based on formula use status (p>0.05). Sixty percent of non-formula users experienced Grade 0 transit, compared to 73.3% in the formula-using group.

DISCUSSION

This study demonstrated that NS use reduced in gynecologic cancer the gastrointestinal and genitourinary side effect profiles of radiotherapy. This reflects the importance of nutritional support for the quality of life of oncology patients. The use of arginine and immunonutritional products in this study was motivated by the fact that short-term oral nutritional support enriched with immunomodulatory ingredients (arginine, omega-3, nucleotides, and soluble fiber) in patients with gynecological malignancies undergoing pelvic radiotherapy reduces early-stage genitourinary and gastrointestinal toxicity and is an integral component of nutrition in oncology. Medical nutritional support is recommended early and in a controlled manner to improve cancer care (14). Pathophysiologically, epithelial damage, microvascular dysfunction, immune system aggression, and gut microbiota dysbiosis all play a role in the pathogenesis of radiation enteropathy; this is a multifaceted condition that, in addition to short-term symptoms such as acute diarrhea, cramping, and bleeding, also paves the way for late effects such as progressive fibrosis and dysmotility (15). Therefore, concurrent NS formula feeding not only affects the acute phase but also has additional preventative effects in the late phase. On the toxicity side of GU, acute cystitis is characterized by mucosal inflammation and scarring, and in the late stage, by an obliterative process; this process can lead to short-term findings such as pollakiuria, dysuria, and

macroscopic hematuria, and over time, serious problems such as decreased bladder capacity, strictures, and fistulas can develop. Therefore, any intervention that reduces toxicity in the early stage has the potential to reduce the risk of late-term complications (16) indirectly. Metabolites of the gut microbiota, such as short-chain fatty acids (SCFAs; for example, butyrate), exert protective effects on epithelial integrity, mucus layer, occlusive junctions, and immune response. The association of pelvic radiotherapy with dysbiosis and SCFA reduction forms the basis for dietary and probiotic/prebiotic adjustments (17). The Formula used in this study did not contain probiotics, but it did contain prebiotic properties. Failure to provide probiotics appropriately leads to bacterial overgrowth, making this selection strategy potentially more effective. At the clinical level, randomized studies evaluating the effect of probiotics on radiotherapy-induced diarrhea—for example, studies with Lactobacillus-containing formulas showing a reduction in the incidence of diarrhea in pelvic radiotherapy (18) also support the superiority of probiotics over placebo in preventing radiotherapy-associated enteropathy in patients undergoing chemoradiotherapy (19). This association underscores the importance of supplementation.

Meta-analyses supporting these findings have reported that probiotics may be beneficial, particularly in reducing Grade ≥2 diarrhea, and have a favorable safety profile; however, standardization of strains, doses, and treatment duration remains necessary (20). Evidence suggests that immunonutrition formulas (arginine, omega-3, and nucleotide enrichment) of the type used in this study may reduce toxicity across the mucositis-enteritis spectrum by modulating epithelial repair, collagen synthesis, eicosanoid profile, and inflammatory signaling pathways, primarily in head and neck oncology and perioperative surgical populations. Although high-quality randomized controlled trials in pelvic radiotherapy patient groups are scarce, the findings are significant due to the biological rationale and similar mucosal targets (21,22). This is also believed to be the mechanism of action in this study.

Regarding dietary patterns, there are pilot randomized clinical trials and observational data suggesting that a low-FODMAP approach may help reduce intestinal gas and symptoms during pelvic radiotherapy (23,24). However, the ESMO (European Society for Medical Oncology) supportive care guideline emphasizes that an evidence-based standard for these diets has not yet been established and that they should be implemented on a personalized basis, with the guidance of a dietitian, and for short periods (25). An individualized approach goes beyond standard protocols. Formulas should be tailored to comorbidities.

Behavioral-dietary measures, such as maintaining hydration, avoiding bladder irritants such as caffeine, alcohol, and green tea, and symptom-based pharmacological support (e.g., alpha-blockers, alkalizing agents), are early steps recommended in clinical literature for GU toxicity and are not contradictory to nutritional support; instead, they complement it (26).

In this context, the lower incidence of Grade 2–3 GU/GU toxicity in our patients receiving NS may be explained by microbiota-mucosal barrier interactions. It may be more clinically significant, particularly in patients receiving concurrent chemotherapy, those at high risk for sarcopenia or cachexia, or those with marginal nutritional status at baseline (14,17,19,21).

However, to clarify the most effective composition of NS, timing of initiation (including neoadjuvant/induction), dose-duration, and target population, powered, multicenter randomized controlled trials blinded to RTOG/EORTC or CTCAE (Common Terminology Criteria for Adverse Events) are needed (15,19,25,26). In conclusion, individualized medical nutrition support, probiotic and prebiotic strategies, short-term dietary changes and programs, if necessary, combined with lifestyle recommendations including hydration and avoidance of irritants and modern radiotherapy techniques, have the potential to reduce early GI and GU toxicity associated with pelvic radiotherapy in gynecologic cancers. These strategies aim to maintain and improve treatment continuity and quality of life.

CONCLUSION

Appropriate nutritional support is believed to play a crucial role in the treatment process of gynecological cancer patients receiving pelvic radiotherapy. Research indicates that dietary modification may reduce side effects that may occur in the genitourinary and gastrointestinal systems. This is important for maintaining patients' quality of life and improving treatment compliance. The effectiveness of nutritional support is not solely dependent on a specific dietary index; each patient's needs, health status, and response to treatment may vary. Therefore, implementing personalized, individualized nutritional approaches is of great value. Comprehensive, multicenter studies encompassing larger patient groups are planned for the future, and the resulting data are expected to guide clinical practice.

Ethical Statement

Ethical approval was obtained from the Ethics Committee of Selçuk University Faculty of Medicine (Approval No: E-70632468-05004-905549). This study complies with the principles of the Declaration of Helsinki.

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