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ORIGINAL ARTICLE

Does Diabetes Mellitus Increase Radiotherapy/ Chemoradiotherapy Acute Toxicities?

Eda ERDİŞ, Birsen YÜCEL

Department of Radiation Oncology, Sivas Cumhuriyet University, Sivas-*Türkiye*

OBJECTIVE

The effect of DM on the acute toxicities of RT/CRT was investigated.

METHODS

1892 patients were evaluated retrospectively. Acute toxicities were evaluated weekly during Radiotherapy (RT)/Cardiac resynchronization therapy (CRT) and follow ups were performed after 1 and 3 months according to Radiation Therapy Oncology Group criteria. The patients were divided into those without diabetes mellitus (DM) (Group 1, n=1557 82%) and patients with DM (Group 2, n=335 18%).

RESULTS

There was a difference between the groups in terms of gender (p<0.001), median age (p<0.001), diagnosis (p=0.023), adjuvant (p=0.023), and concurrent (p=0.047) chemotherapy. Grade 3–4 skin (p=0.001), Grade 1–2 lower gis (lower gastrointestinal system [GIS], p<0.001), and Grade 1–2 gus toxicities (GUS, p=0.012) were all observed more in Group 2; the time for which skin toxicity occurred was earlier in Group 2 (p=0.002). Grade 1–2 white blood cells (p=0.027) and Grade 1–2 hemoglobin toxicities (p=0.033) were observed more in Group 1. Hypertension coexisted in 206 patients (61% of the DM group), and blood glucose was not regulated in 256 patients (76%). In DM patients, the toxicity of grade 3–4 skin (p<0.001) and grade 1–2 lower GIS (<0.001) was higher if hypertension coexisted, while grade 1–2 lower GIS (p=0.029) was higher in DM patients whose blood glucose was not regulated.

CONCLUSION

In this study, it was observed that DM negatively affected acute toxicity of RT/CRT, and having hypertension and lack of regulation of blood glucose contributed to this negativity.

Keywords: Acute toxicity; diabetes mellitus; radiotherapy.

INTRODUCTION

Radiotherapy (RT) is a treatment method that aims to destroy cancer cells using ionizing radiation. However, normal tissue around the tumor is also exposed to some side effects, depending on the type of tissue. The toxicity of RT is affected not just by factors of treatment (such as radiation dose, fraction scheme, and duration of treatment) but also patient factors (such as age and presence of comorbidity), and the incidence or duration of occurrence varies from patient to patient.[1] Completing the RT course without interruption is important in terms of providing local control of the disease. For this reason, it is important to isolate the factors that can potentialize the side effects of RT. [1]

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Dr. Eda ERDİŞ
Sivas Cumhuriyet Universitesi,
Radyasyon Onkolojisi Anabilim Dalı,
Sivas-Türkiye
E-mail: dr.erdiseda@hotmail.com

Diabetes mellitus (DM) is a systemic metabolic disease that causes impairment in glucose metabolism and has the potential to affect multiple organ systems. [2] DM can cause retinopathy, nephropathy, neuropathy, and cardiovascular disease as well as problems with platelet aggregation, leukocyte function, protein metabolism, and disorders in microvascular circulation. [3,4] DM patients have an increased susceptibility to infection as a result of weak macrophage activity, decreased chemotaxis and phagocytic activity, decreased cell proliferation and collagen production, decreased fibroblast and growth factors, increased apoptosis in cells in the scar tissue, angiogenesis, and granulation tissue formation.[2,4,5] Post-operative studies have also highlighted delayed wound healing in patients with DM compared to the general population.[2–6] Tissue damage due to RT may, therefore, be slow to heal because of overall impaired wound healing, and so acute RT toxicity may increase in patients with DM. A number of researchers have investigated this issue, but most of the studies investigating the toxicity of RT in DM patients have tended to investigate late-RT toxicity.[7–9]

In this study, the effects of DM on acute toxicities of treatment in cancer patients receiving RT or cardiac resynchronization therapy (CRT) were investigated.

MATERIALS AND METHODS

This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the local ethical committee (Sivas Cumhuriyet University Ethical Committee).

The data of 1892 cancer patients who were treated at the Department of Radiation Oncology at Cumhuriyet University Medical Faculty Hospital between January 2010 and December 2018 were retrospectively evaluated. Patients without distant metastases who received curative/definitive RT or CRT were included in the study. Patients receiving palliative RT were excluded from the study. The patients were divided into two groups: Group 1 comprised patients without a DM diagnosis, and Group 2 included patients with DM.

DM

- Hypertension
- Heart disease
- Chronic renal failure.

The performance status of the patients was assessed according to the Eastern Cooperative Oncology Group performance scale. Weight loss has been defined as the loss of more than 5% of the patient's weight. HbA1c patients were measured on the 1st day they started RT. The upper limit of HbA1c is considered to be 6.5.

Acute toxicities were observed within 90 days from the start of RT/CRT. Treatment toxicities were evaluated weekly during treatment and after 1 and 3 months following the end of treatment according to the acute radiation morbidity measurement criteria of Radiation Therapy Oncology Group (RTOG). According to these criteria, both hematological and non-hematological toxicities are graded between 0 and 5,[10] where grade 5 toxicity is associated with death from direct radiation. Here, hematological aspects include the assessment of white blood cells (WBC), neutrophils, platelets, hemoglobin, and hematocrit, while non-hematological areas include skin, mucous membrane, eye, ear, salivary gland, pharynx/esophagus, larynx, lung, upper gastrointestinal system, lower gastrointestinal system (GIS), genitourinary system (GUS), and central nervous system. Patients were actively questioned for each of the 10 symptoms during each interview. To minimize observer bias, the assessment forms themselves detailed the specifics of each grade of toxicity, so that the assessor could directly compare and choose the most appropriate grade of toxicity for the patient in front of them.

Statistical Evaluation

In this study, descriptive tests using the Statistical Package for the Social Sciences for Windows (v23.0) were used, along with the Chi-square test, the Student's t test (for those data with a near-normal distribution), and the Mann-Whitney U test (for those without a near-normal distribution) to compare the means of the groups. In addition, the mean, standard deviation, mean deviation, and median of the data were calculated using descriptive statistical methods. The results obtained from these tests were assessed according to a 5% level of significance, $p \leq 0.05$.

RESULTS

In Table 1, demographic characteristics and treatment schemes between Group 1 and Group 2 are compared. Among the groups, gender ($p=0.001$), median age ($p<0.001$), diagnosis ($p=0.023$), hypertension ($p<0.001$), heart disease ($p<0.001$), chronic renal failure ($p=0.005$), adjuvant ($p=0.023$), and concurrent chemotherapy administration ($p=0.047$) were found to be statistically significant predictors.

In Table 2, the groups were compared for the rate and time of acute non-hematological toxicities of RT/

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Table 1 Patients, cancers, and treatment characteristics

	All patients n=1892 (100%)		Group 1 n=1557 (82%)		Group 2 n=335 (18%)		p
	n	%	n	%	n	%	
Gender							
Male	979	52	830	53	148	44	0.001
Female	913	48	726	47	187	56	
Age (median years, range)	59 (7–90)		57 (7–90)		64 (23–85)		<0.001
Co-morbidity							
Hypertension	520	27	314	20	206	62	<0.001
Heart disease	196	10	130	8	66	20	<0.001
COPD1	94	5	72	5	22	7	0.092
Chronic kidney disease	17	1	9	1	8	2	0.005
Cancer							
Breast	526	29	435	28	91	27	0.023
GIS2	379	20	313	20	66	20	
Lung	252	13	205	13	47	14	
Head and Neck	201	11	169	11	32	9	
CNS3	149	8	126	8	23	7	
GUS4	163	9	127	8	36	11	
Gynecologic	101	5	72	5	29	9	
Hematologic	53	3	50	3	3	1	
Sarcom	36	2	33	2	3	1	
Skin	32	7	27	2	5	1	
Stage							
I	211	11	172	11	39	12	0.688
II	496	26	417	27	79	24	
III	851	45	690	44	161	48	
IV (non-metastatic)	87	5	73	5	14	4	
Non-stage	247	13	205	13	42	12	
Treatments							
Surgery							
No	710	38	574	37	136	41	0.115
Yes	1180	62	981	63	199	59	
Adjuvant chemotherapy							
No	758	40	607	39	151	45	0.023
Yes	1134	60	850	61	184	55	
Concurrent CRT5							
No	1078	57	873	56	205	61	0.047
Yes	817	43	684	44	130	39	
Dose of RT[6] (median Gy, range)	55.4 (18–80)		59.4 (18–80)		50.4 (18–80)		0.872
RT field							
CNS	149	8	127	8	22	6	0.161
Head and neck	244	13	207	13	37	11	
Breast	526	29	435	28	91	27	
Thorax	295	15	242	16	53	16	
Abdomen	206	11	173	11	33	10	
Pelvis	446	23	349	22	97	29	
Extremite	26	1	24	2	2	1	

Group 1: Patients without DM; Group 2: Patients with DM; COPD1: Chronic obstructive pulmonary disease; GIS: Gastrointestinal system; CNS: Central nervous system; GUS4: Genitourinary system; CRT5: Chemoradiotherapy, RT: Radiotherapy

Table 2 Incidence and time of acute non-hematological side effects

Non-hematological side effects	Frequency of side effects							Mean time to occurrence of side effects (weeks)			
	All patients		Group I		Group II		p	All	Group I patients	Group II	p
	n	%	n	%	n	%					
Skin											
None	1145	61	963	62	182	54	–	3 (1–7)	4 (1–7)	3 (1–7)	**0.002**
Grade 1–2	704	37	568	36	136	41	0.085				
Grade 3–4	43	2	26	2	17	5	**0.001**				
Mucous membrane											
None	1709	90	1402	90	307	91	–	3 (1–7)	3 (1–7)	2.5 (1–7)	0.821
Grade 1–2	150	8	124	8	26	8	0.051				
Grade 3–4	33	2	31	2	2	1	0.503				
Eye											
None	1873	99	1543	99	330	99	–	3 (1–6)	3.5 (1–6)	3 (1–6)	0.823
Grade 1–2	16	1	12	1	4	1	0.443				
Grade 3–4	3	0.3	2	0.1	1	0.3	0.310				
Ear											
None	1874	99	1543	99	331	99	–	3 (2–7)	3 (2–7)	2.5 (2–3)	0.327
Grade 1–2	18	1	14	1	4	1	0.398				
Pharynx & Esophagus											
None	1323	70	1087	70	236	70	–	3 (1–7)	3 (1–7)	3 (1–7)	0.844
Grade 1–2	558	29	459	29	99	30	0.496				
Grade 3–4	11	1	11	1	–		0.116				
Salivary gland											
None	1787	95	1470	95	317	95	–	3 (1–7)	2 (1–6)	3 (2–7)	0.055
Grade 1–2	101	5	84	5	17	5	0.474				
Grade 3–4	3	0.2	3	0.2	–		0.558				
Larynx											
None	1804	96	1484	96	320	96	–	3 (1–7)	3 (1–7)	2 (1–5)	0.212
Grade 1–2	81	4	68	4	13	4	0.416				
Lung											
None	1732	92	1421	91	311	93	–	3 (1–7)	3 (1–7)	2 (1–6)	0.355
Grade 1–2	154	8	133	9	21	6	0.102				
Grade 3–4	5	0.3	3	0.2	2	1	0.216				
Upper GIS[1]											
None	1398	74	1150	74	248	74	–	2 (1–7)	2 (1–7)	2 (1–7)	0.635
Grade 1–2	489	26	402	26	87	26	0.502				
Grade 3–4	5	0.3	5	0.3	–		0.377				
Lower GIS[1]											
None	1579	84	1323	85	256	76	–	3 (1–7)	3 (1–7)	3 (1–7)	0.678
Grade 1–2	307	16	228	15	79	24	**<0.001**				
Grade 3–4	5	0.3	5	0.3	–		0.377				
GUS[2]											
None	1666	88	1383	89	283	84	–	2 (1–7)	2 (1–6)	2 (1–7)	0.811
Grade 1–2	221	12	169	11	52	16	**0.012**				
Grade 3–4	5	0.3	5	0.3	–		0.377				
CNS[3]											
None	1835	97	1508	97	327	98	–	2 (1–7)	2 (1–7)	2 (1–5)	0.761
Grade 1–2	53	3	45	3	8	2	0.387				
Grade 3–4	4	0.2	4	0.3	–		0.458				

GIS: Gastrointestinal system; GUS: Genitourinary; CNS: Central nervous system

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Table 3 Incidence and time of acute hematological side effects

Hematological side effects	Frequency of side effects							Mean time to occurrence of side effects (week/median, range)			
	All patients		Group I		Group II		p	All patients	Group I	Group II	p
	n	%	n	%	n	%					
WBC[1]											
None	1320	70	1072	69	248	74	–	3 (1–7)	3 (1–7)	2 (1–7)	0.497
Grade 1–2	470	25	401	26	69	21	**0.027**				
Grade 3–4	102	5	84	5	18	5	0.557				
Neutrophils											
None	1608	85	1321	85	287	86	–	3 (1–7)	3 (1–7)	3 (1–7)	0.471
Grade 1–2	204	11	165	11	39	12	0.320				
Grade 3–4	78	4	69	4	9	3	0.091				
Platelets											
None	1737	92	1427	92	310	93	–	3 (1–7)	3 (1–7)	3 (2–6)	0.796
Grade 1–2	127	7	109	7	18	5	0.169				
Grade 3–4	28	1	21	1	7	2	0.214				
Hemoglobin											
None	1617	86	1319	85	298	89	–	3 (1–7)	2 (1–7)	3 (1–7)	0.321
Grade 1–2	271	14	234	15	37	11	**0.033**				
Grade 3–4	3	0.2	3	0.2	–		0.557				
Hematocrit											
None	1767	94	1454	94	313	93	–	3 (1–7)	3 (1–7)	2 (1–7)	0.579
Grade 1–2	119	6	99	6	20	6	0.452				
Grade 3–4	4	0.2	2	0.1	2	1	0.147				

WBC1: White blood cell

CRT. According to the table, grade 3–4 skin toxicity (p=0.001), grade 1–2 lower GIS toxicity (p<0.001), and grade 1–2 GUS toxicity (p=0.012) were observed more in Group 2 patients. In terms of time of appearance, only skin toxicity appeared earlier in Group 2 patients (3 weeks vs. 4 weeks, p=0.002).

In Table 3, a comparison of the groups was made for the rate and time of the RT/CRT acute hematological toxicities. Grade 1–2 WBC toxicity (p=0.027) and grade 1–2 hemoglobin toxicity (p=0.033) were observed more in Group 1.

In 273 patients (14% of the total sample), RT/CRT had to be suspended due to the side effects of the treatment. Of these patients, 231 were in Group 1 (15% of that group), and 42 were in Group 2 (13% of that group) (p=0.158). During the treatment, weight loss was detected in 266 patients (14% of the total sample), of which 220 were in Group 1 (14% of that group), and 46 were in Group 2 (14% of that group) (p=0.464). Performance deterioration during RT/CRT was observed in 334 patients (18% of the total sample); 271 of these patients were from Group 1 (17% of Group 1), and 63 were from Group 2 (19% of Group 2).

Hypertension accompanied diabetes in 206 of the 335 patients with DM (61%). Toxicities at a level of grade 3–4 skin (p<0.001) and grade 1–2 lower GIS system (p<0.001) were found to be significantly higher in patients with DM and hypertension compared to DM patients without hypertension (Table 4).

In 256 of the 335 DM patients (76%), the HbA1c level was ≥6.5, meaning that glucose regulation was not under control in these patients. In the comparison of side effects observed in patients whose blood glucose regulation was/was not under control, only grade 1–2 lower GIS toxicity was found to differ (Table 4).

DISCUSSION

Acute toxicities of RT are usually reversible effects that occur in rapidly dividing cells. They are one of the most important issues in the treatment of cancer patients because they have the potential to prevent continuity

Table 4 Comparison of DM and hypertension association and early side effects of RT according to HbA1c values

	Diabetes mellitus n=129 (48%)		Diabetes mellitus+ hypertension n=206 (62%)		p
	n	%	n	%	
Skin					
Grade 3–4	27	2	16	8	<0.001
Lower Gastrointestinal system					
Grade 1–2	255	15	52	25	<0.001
	HbA1c <6.5 n=79 (24%)		HbA1c ≥6.5 n=256 (76%)		p
	n	%	n	%	
Lower Gastrointestinal system					
Grade 1–2	12	15	67	26	0.029

RT: Radiotherapy

of treatment. Adding simultaneous chemotherapy to RT naturally increases the side effects observed during treatment. The presence, in addition to cancer, of a disease such as DM having systemic effects may further increase the side effects of treatment. In this study, we investigated how DM affected treatment toxicities in cancer patients receiving RT/CRT. As a result of our research, we determined that certain non-hematological toxicities (grade 3–4 skin, grade 1–2 lower GIS, and grade 1–2 GUS) were observed more in patients with DM. We also observed that skin toxicity appeared earlier in patients with DM. The situation was slightly different in hematological toxicities. In patients without DM (who received more adjuvant and simultaneous chemotherapy compared to patients with DM), grade 1–2 WBC and hemoglobin toxicities were observed more. In patients with hypertension as well as DM, grade 3–4 skin and grade 1–2 lower GIS were observed more, whereas in patients without DM, grade 1–2 lower GIS toxicities were more prevalent.

Radiation dermatitis is known to be one of the most common acute toxicities, at a historical rate above 90%.[11,12] However, of these, most of the observed toxicities are grade 1–2, and only 15–25% are grade 3–4 toxicities.[13–15] The radiation sensitivity of the skin is related to rapidly growing cells. Basal keratinocytes, hair follicle stem cells, and melanocytes are the most sensitive.[16] Tissue damage occurs through the formation of short-lived free radicals from the beginning of RT. Eventually, irreversible breaks and inflammation begins in cellular DNA. This inflammatory response is mediated by pro-inflammatory cytokines (IL-1, IL-3, IL-5, IL-6, and TNF-a) and chemokines (IL-8, eotaxin, CCR receptor). These factors attract eosinophils and neutrophils to the site of local inflammation. This leads to tissue damage and the loss of the protective barrier.[17] Radiation destruction of basal keratinocytes further impairs wound healing, so each additional exposure to RT results in more direct tissue damage, inflammation, and impaired epithelial regeneration.[18]

In patients with DM, prolongation of the inflammatory phase, increased susceptibility to infection, and delayed wound healing have been shown as a result of decreased phagocytic activity, poor macrophage activation, and increases in cytokines and chemokines.[19–21] In chronic diabetic patients, atherosclerosis develops as a result of microvascular occlusive changes (capillary hyalinization, arteriolar obliteration, and decreased tissue perfusion).[22] In diabetic patients, microvascular flow is disrupted by long-term exposure of blood cells to hyperglycemia, hardening of the spectrum (a red blood cell membrane protein), and platelet aggregation.[23] As a result, there is a delay in wound healing.[23]

In diabetic patients receiving RT, the presence of conditions that can potentiate each other may increase the possible complications. Furthermore, because DM has a pathophysiological process that can compromise tissue oxygenation, it can potentially hinder or delay the repair of radiation damage. Studies have shown that, compared with the general population, diabetics are at a higher risk for the development of complica-

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tions associated with perioperative or post-operative wound healing.[23–27] In the same way, the relationship between RT complications and DM has been the subject of research in the 1990s. Kucera et al. investigating the relationship between radiation toxicity and DM in patients receiving RT, they found no difference in skin side effects between diabetics and non-diabetics.[28,29] Porock investigated the predictive factors that increased the severity of skin reactions in breast cancer patients; they identified smoking, chemotherapy, history of skin cancer, skin reaction to UV radiation, lymphocele aspiration, condition of lumpectomy scar at the beginning of treatment, weight, and breast size as factors that predicted the severity of skin toxicity. However, it is acknowledged that the scarcity of published research means there is insufficient evidence to conclude about the role of DM on radiation reactions.[30] In our study, the rate of grade 3–4 toxicity was found to be higher in diabetics treated with external RT compared to non-diabetic patients. It has also been found that skin toxicity occurs earlier in patients with DM.

It is a known fact that radiation causes significant damage to rapidly proliferating tissues such as gastrointestinal and genitourinary system mucosa. However, the vascular configuration that plays a key role in repairing radiation damage deteriorates in the presence of DM. Accordingly, an activated coagulation system and decreased blood flow disrupt the mucosal barrier in the gastrointestinal and genitourinary system.[31–33] DM disrupts vascular endothelial function and causes dysfunctional tissue repair.[31] Several studies have identified an association between DM and late-lower GIS and GUS toxicity; however, the results are generally mixed.[31–35]

Özkan et al. investigated the factors affecting gynecologic malignancies and treatment toxicity of 129 patients who received RT/CRT for cervical carcinoma, assessing toxicity according to the RTOG mortality criteria.[8] In the study, a relationship was found between lower GIS toxicity and DM, but not with upper GIS and GUS. In the study published by Alashkham et al., higher rates of late-grade 3–4 lower GIS toxicity (especially proctitis-like complaints) were reported in prostate cancer patients (n=716) receiving RT compared to non-diabetic patients.[36] This suggested that DM increased the risk of radiation toxicity and drove the onset of symptoms to an earlier time. Herold et al. investigated the effects of diabetes on radiation toxicity in 944 prostate cancer patients (13% of whom were diabetic).[22] Acute lower GIS and GUS toxicities could not be demonstrated in connection with diabetes in this study. However, grade 2–4 late-lower GIS and GUS toxicities were shown to be significantly higher in diabetics. In the Herold's study, radiation dose for lower GIS toxicity, rectal blocking, and a history of DM were seen as predictors of having a history of DM in GUS toxicity. Kalakota and Liauw investigated the factors affecting RT toxicity in 626 prostate cancer patients (16% of whom were diabetic).[37] In this study was pointed that late grade 2 and 3 GUS toxicity was negatively affected by DM, but that this effect could not be demonstrated for lower GIS. In the PORTEC study,[38] the factors affecting the acute toxicity of pelvic RT in patients with post-operative endometrial cancer were examined. It was reported that DM, hypertension, age, and RT technique did not affect acute toxicity. As can be seen from examining these studies, DM is often associated with late-lower GIS and GUS toxicity rather than acute toxicity. However, in our study, it was found that grade 1–2 acute lower GIS and GUS toxicity were observed more frequently in patients with DM.

DM is known to affect bone marrow maturation as well as impairing neutrophil function and an increased apoptosis of leukocytes.[39] In addition, in cases such as nephropathy that develops due to the microvascular complications of DM, anemia can result from the decrease in erythropoietin.[39] Due to the effects of both chemo/RT and DM on the bone marrow and other complications of diabetes, hematologic. Due to the effects of both chemo/RT and diabetes on the bone marrow and other complications of diabetes, it seems plausible that hematological side effects increase during treatment. However, contrary to this proposition, in our study, more grade1–2 WBC and hemoglobin toxicity was observed in patients without DM compared to those with DM. This contrast may be attributed to the fact that patients without DM received more adjuvant or concurrent chemotherapy in the study.

Hypertension is one of the most common comorbid diseases in patients with malignancies.[40] It causes a number of systemic complications in hypertension such as DM. In addition, there is no negligible association of DM and hypertension in the society. As a matter of fact, in our study, 62% of diabetic patients were associated with DM and hypertension. It should not be overlooked that the combination of DM and hypertension may increase the side effects of cancer treatments. Studies of some researchers related to this subject are also included in the literature.[30,41–43] Van Nagell et al. examined late side effects in 271 patients who received definitive RT for locally advanced cervical cancer (mean follow-up 5 years). Researchers detected

rectovaginal fistula in 11 cases and they observed that DM and hypertension coexisted in 6 of these cases.[41] Maruyama et al. reported late side effects of the treatments of 270 cervical cancer patients after 60 months of follow-up. This study documented that 9 of the ileus cases not associated with tumor progression were associated with DM and hypertension. As a result, they concluded that the risk of late toxicity was higher in patients with DM and hypertension.[42] Harwood and Tierie. studied about 204 localized glottic cancer patients treated with RT. They stated that DM and/or hypertension significantly contributed to the risk of subsequent major complications (severe edema requiring tracheotomy, laryngeal necrosis, or laryngeal stenosis).[43] Porock and Kristjanson investigated the effect of advanced age on radiation dermatitis, they found that coexisting diseases such as hypertension, DM or malnutrition affect the severity and occurrence of radiation dermatitis in elderly patients. They associated this situation with the coexistence of hypertension and diabetes with impaired epidermal cycle and regeneration ability.[30] In this study, in which we examined early side effects in cancer patients receiving RT/CRT, we observed that grade 3–4 skin and grade 1–2 lower GIS toxicities were statistically significantly higher in patients with DM and hypertension compared to diabetic patients without hypertension.

In patients with DM, it is possible to show blood sugar regulation for the last 3 months with HbA1c. Failure to regulate blood sugar may result in increased complications of the disease. It has been shown in some studies that after the diagnosis of cancer, patients adapt less to diabetic drugs, discontinue drug use or reduce the use of drugs.[44,45] Does RT/CRT toxicity increase in patients whose blood glucose is not regulated? Moonkyoo Kong et al. evaluated the effects of DM and DM-related serological factors (HbA1c and fasting glucose) on the development of radiation pneumonia in patients with lung cancer. They considered DM, HbA1c, and fasting glucose level as important predictive factors for the development of grade 3 radiation pneumonia in patients with lung cancer. They emphasized that patients with DM, patients with HbA1c > 6.15, and patients with fasting glucose >121 mg/dL should be treated with care.[46] In our study, it was observed that 76% of 335 patients with DM had HbA1c level 6.5 and glucose regulation of these patients was not under control. Grade 1–2 lower GIS toxicity was found to be higher in patients without blood glucose regulation compared to patients with regulation. However, in our study, the number of patients whose blood glucose was not regulated was not balanced with the number of those who were regulated. If the number of patients in the study were balanced, perhaps we could see this difference in more side effects.

As a result; in this study was pointed that DM negatively affected acute toxicity of RT/CRT, and having hypertension and lack of regulation of blood glucose contributed to this negativity.

Limitations

The main limiting factors of our study are the retrospective nature of the data and that they come from a single center. In addition, the following information was lacking: the accompanying metabolic syndrome parameters (which may affect the RT toxicities of the patients), information on the use of metformin and other antidiabetic agents, and data on fasting insulin levels.

CONCLUSION

According to this study, it was found that DM patients generally tolerated RT very well. The incidence rates of lower gastrointestinal and genitourinary side effects have been found to increase. In addition, acute side effects have started to appear at the same time as in patients without DM.

Peer-review: Externally peer-reviewed.

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Ethics Committee Approval: The study was approved by the Sivas Cumhuriyet University Non-interventional Clinical Research Ethics Committee (no: 2021-04/28, date: 14/04/2021).

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