Original Article

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Effect of Diabetes Mellitus and Metformin Usage on Treatment Outcomes and Side Effects on Prostate Cancer Treated with Radical Radiotherapy

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Abstract

Objective: Diabetes mellitus (DM) is a common comorbidity in patients with prostate cancer. Radiotherapy was reported to induce acute and late side effects in patients with DM due to vascular damage. Moreover, some studies have shown that metformin, an oral antidiabetic drug, can reduce biochemical and disease recurrence in patients with prostate cancer. This study aimed to evaluate retrospectively the effect of metformin on biochemical disease control and to observe the acute and late side effects of prostate cancer treated with radiotherapy.

Materials and Methods: This study enrolled 94 patients who received radical radiotherapy between 2010 and 2017. However, out of 22 patients with DM, 17 received metformin and five received metformin plus insulin treatment. Biochemical recurrence-free survival (bRFS), overall survival, and side effects were assessed between patients with and without DM.

Results: The median follow-up time was 57 (15-128) months. The 5-year bRFS rate in patients with and without DM were 100% and 89.2%, respectively (p=0.10). Acute grade 1-2 side effects were observed in all patients with DM, while 56 (78%) patients without DM had acute side effects, and the difference is significant (p=0.02). Acute grade 3 genitourinary and gastrointestinal toxicity was found in one patient without DM, whereas late grade 3 gastrointestinal toxicity was observed in one patient with DM.

Conclusion: Although patients with DM were found to have better bRFS than patients without DM, we could not show the benefit of metformin, and the difference was not significant. By contrast, acute side effects were significantly higher in patients with DM.

Keywords: Prostate cancer, diabetes mellitus, metformin, radiotherapy, side effects

Introduction

Prostate cancer is the most common cancer in men, the second leading cause of cancer-related death, and usually observed in older men (1). Diabetes mellitus (DM) is a common chronic endocrine disease developed by either genetically or acquired deficiency. Type 1 and type 2 are the common forms of DM, and more than 90% of patients have type 2 DM (2). Type 2 DM is mainly caused by insulin resistance, particularly common in the older population, and the prevalence of DM in individuals aged >65 years is 26.9% (3). Therefore, coexisting diagnoses of prostate cancer and DM increased because of aging. Metformin is an orally administered and frequently used as a insulin sensitizer drug that belongs to the biguanide antidiabetic family. Recently, the antineoplastic activity of this compound shown in some in vitro models is gaining interest (4). Several retrospective studies have demonstrated that metformin treatment can reduce the incidence of prostate cancer, prostate-specific antigen (PSA) levels, and disease recurrence (5,6).

Especially, breast, colorectal, endometrium, liver, and pancreatic cancers occur more commonly in individuals with DM, and the prevalence of DM in patients newly diagnosed with cancer is even higher, ranging from 8% to 18% (7). DM can cause long-term complications, such as cardiovascular disease, retinopathy, and neuropathy. Patients with both cancer and DM have an increased risk of long-term mortality in comparison with patients without DM (8).

Radiotherapy is one of the main treatment modalities for locally advanced prostate cancer. Management and side effects of prostate cancer treatment are particularly affected by comorbidities. Some studies have reported that patients with DM experienced more radiation-induced genitourinary and gastrointestinal system side effects than patients without DM after prostate cancer radiotherapy (9).

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This single-center retrospective study aimed to evaluate the effect of metformin on biochemical disease control and to observe the acute and late side effects of prostate cancer treated with definitive radiotherapy.

Materials and Methods

Study Population

This study included 94 consecutive patients with prostate cancer treated by definitive radiotherapy between 2010 and 2017. Moreover, 22 (23%) patients had DM and received metformin treatment (1.000 mg/day), while five patients received insulin treatment in addition to metformin treatment. Metformin therapy had varied duration. Patients had T1-T2 (79%) and T3-T4 (21%) disease. At presentation, 16 (17%) patients had high-grade tumors (Gleason score 8≤) and 43 (46%) had high-risk disease. The cohort comprised of 26% low, 28% medium, and 46% high-risk groups according to the National Comprehensive Cancer Network risk category (10). Luteinizing hormone-releasing hormone agonists were used for 6 months in 16 and for 24 months in 43 patients as androgen deprivation therapy. Characteristics of the patients are listed in Table 1.

Treatment Preparation and Planning

Patient preparation was performed before radiotherapy planning computer tomography (CT) and every treatment fraction as reported previously (11). The patients were asked to avoid eating gas-producing food and to consume a low-fiber diet before simulation and during treatment. Organs at risk and target volumes were contoured according to Radiation Therapy Oncology Group guidelines in planning CT.

Table 1. Patient characteristics

Patient characteristics	n (%)
T-stage	
T1	4 (4%)
T2	70 (75%)
T3	17 (18%)
T4	3 (3%)
N-stage	
N1	5 (5%)
Risk groups	
Low	24 (26%)
Intermediate	27 (28%)
High	43 (46%)
Androgen deprivation therapy	
Short-term	16 (17%)
Long-term	43 (46%)
Diabetic patients	22 (23%)
DM treatments	
Metformin	17 (18%)
Metformin + insulin	5 (5%)

DM: Diabetes mellitus

Treatment

Intensity-modulated radiotherapy plans were generated for each patient using the Eclipse version 8.6 treatment planning system by using 6 MV photon beams. The median dose of radiation therapy was 78 Gy (range, 70-80 Gy) in 39 (range, 28-40) fractions. Only prostate volume is irradiated in 78 patients, whereas pelvic lymphatics were added to the treatment volumes in 16 patients. Field verification for image-guided radiation therapy was carried out with cone-beam CT every day.

Follow-up

During radiotherapy, all patients were examined once a week for urinary symptoms such as dysuria, urinary incontinence, and hematuria, gastrointestinal symptoms such as the number of daily defecation and stool density, and complaints about abdominal pain and gas. After the radiotherapy, patients were followed up every 3 months for the first 2 years, every 6 months between 2 and 5 years, and annually after 5 years. PSA was evaluated at each follow-up, and additional examinations were postulated according to the PSA result. All patients were examined at each visit and assessed for late toxicity.

Statistical Analysis

This study was conducted retrospectively. Biochemical recurrence-free survival (bRFS) was defined as the time from the end of radiotherapy to PSA recurrence. Kaplan-Meier survival analysis was performed for medicine use (i.e., antidiabetic drugs) with the endpoint of bRFS. Univariate and multivariate analyses performed by Cox-regression method were adjusted for the baseline characteristics, including age, stage, Gleason score, PSA, treatment field, radiotherapy doses, androgen deprivation therapy, doses of organs at risk, other comorbidities (hypertension and coronary artery disease), and DM. Common Terminology Criteria for Adverse Events v5.0 was used for the evaluation of acute and late gastrointestinal and genitourinary side effects. Comparisons of acute and chronic side effects for patients with and without DM were made by the chi-square test. The retrospective study protocol was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine and the study was conducted in accordance with the tenets of the Helsinki Declaration. SPSS version 21 for Windows (IBM Corp., Armonk, NY) was used for all statistical analyses, and $p<0.05$ was considered for significance.

Results

The median follow-up time was 57 (15-128) months, and the median age was 69 (53-88) years. Thirteen patients died; however, only three of them died from prostate cancer. PSA relapse was observed in eight patients without DM. The 5-year and 8-year overall survival (OS) for the total study population were 91.4% and 75.4%, respectively (Figure 1). Patients aged ≥70 years were significantly associated with a higher risk of mortality [p=0.023, confidence interval (CI) =0.22 (0.06-0.81)] than patients aged <70 years in the univariate analyses. Results of the univariate and multivariate analyses are listed in Table 2.

In this study, the 5-year and 8-year bRFS rates were 91.6% and 89.5%, respectively. In the multivariate analyses, Gleason score

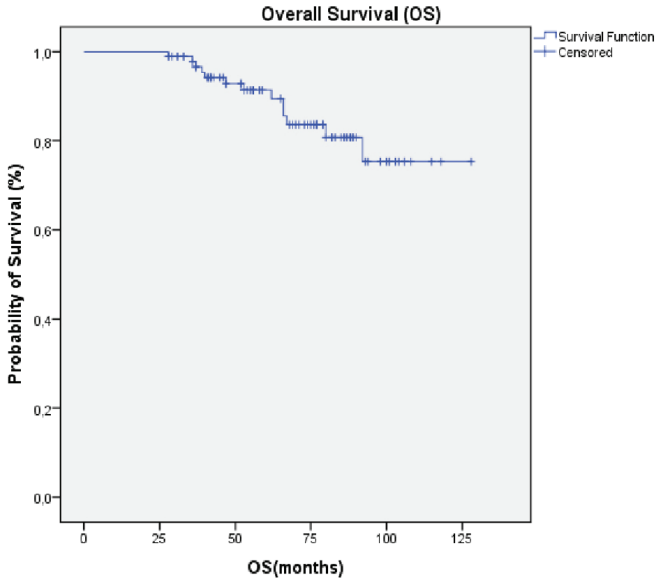

Figure 1. Overall survival for patients

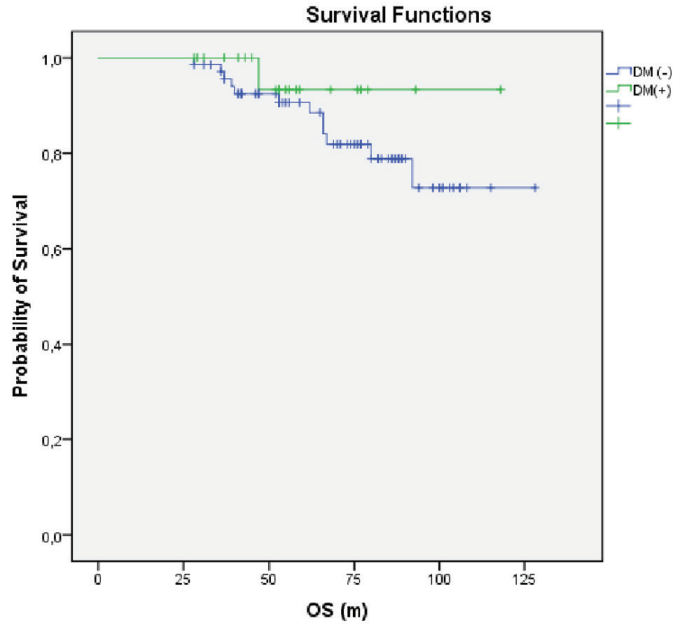

Figure 2. Overall survival for diabetic and non-diabetic patients

Table 2. Univariate and multivariate Cox-regression analyses of overall survival

Characteristic	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Risk category				
Intermediate	0.78 (0.17-3.54)	0.73	NS	
High	0.70 (0.19-2.53)	0.59		
Older age	4.53 (1.24-16.59)	0.02	4.87 (1.30-18.24)	0.019
PSA level	0.99 (0.33-2.99)	0.94	NS	
TNM stage	1.03 (0.28-3.76)	0.96	NS	
ADT				
Short-term	2.49 (0.55-11.18)	0.23	NS	
Long-term	1.22 (0.30-4.93)	0.78		
Pelvic nodal RT	1.42 (0.31-6.55)	0.65	NS	
DM status	2.6 (0.33-20.1)	0.30	1.36 (0.16-11.29)	0.775
Recurrence	4.64 (1.43-15.11)	0.01	5.12 (1.51-17.34)	0.009

ADT: Androgen deprivation therapy, DM: Diabetes mellitus, CI: Confidence interval, RT: Radiation therapy, HR: Hazard ratio, PSA: Prostate-specific antigen

≥8 (p=0.003; CI=0.11 (0.03-0.49) and age <60 years (p=0.019; CI=0.19 (0.05-0.76) were found to be negative factors for bRFS.

Subgroup analyses showed similar OS and bRFS rates. The 5-year OS rates in patients with and without DM were 93% and 91%, respectively (p=0.30) (Figure 2). The 5-year bRFS rates in patients with and without DM were 100% and 89.2%, respectively (p=0.10) (Figure 3). A comparison of the survival results of patients with and without DM are listed in Table 3.

As regards side effects, acute grade 1-2 side effects were observed in all patients with DM, whereas 78% of patients without DM had acute side effects, and the difference is significant (p=0.02)

Table 3. Comparison of diabetic and non-diabetic patients

	DM (-)		DM (+)		p
	n	%	n	%	
Risk category					
Low	18	25	6	27.3	0.557
Medium	19	26.4	8	36.4	
High	35	48.6	8	36.4	
PSA					0.199
<10	33	45.8	13	59.1	
≥10	39	54.2	9	40.9	
TNM					0.138
Stage 1-2	53	73.6	19	86.4	
Stage 3-4	19	26.4	3	13.6	
Age					0.313
<70	37	51.4	14	63.6	
≥70	35	48.6	8	36.4	
ADT					0.213
None	26	36.1	9	40.9	
Short-term	10	13.9	6	27.3	
Long-term	36	50	7	31.8	
Pelvic nodal RT					0.315
Absent	59	81.9	20	90.9	
Present	13	18.1	2	9.1	

DM: Diabetes mellitus, ADT: Androgen deprivation therapy, RT: Radiation therapy, PSA: Prostate-specific antigen

(Table 4). Urinary side effects were more common in all patients. Side effects such as dysuria, nocturia, urinary incontinence, pollakiuria, and hematuria were observed in 95.5%, 45.5%, 22.5%, 18.1%, and 4.5% of the patients, respectively. Six

patients experienced diarrhea as an acute gastrointestinal side effect. Late side effects especially dysuria and nocturia were found in 23% and 13% of the patients, respectively (p=0.26) (Table 5). Acute grade 3 genitourinary and gastrointestinal toxicity was observed in one patient without DM, whereas late grade 3 gastrointestinal toxicity was seen in one patient with DM.

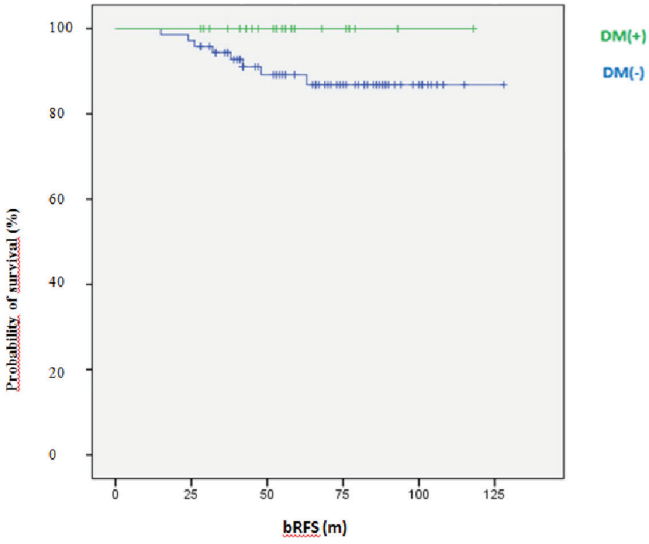

Figure 3. Biochemical recurrence free survival (bRFS) for diabetic and non-diabetic patients

Table 4. Acute side-effects of patients

DM	Acute gastrointestinal side effects				Total
	Absent	Grade 1	Grade 2	Grade 3	
Diabetic	16 (73%)	4 (18%)	2 (9%)	0 (0%)	22 (100%)
Non-diabetic	54 (75%)	9 (12%)	7 (10%)	2 (3%)	72 (100%)
	Acute genitourinary side effects				
	Absent	Grade 1	Grade 2	Grade 3	
Diabetic	2 (9%)	18 (82%)	2 (9%)	0 (0%)	22 (100%)
Non-diabetic	18 (25%)	34 (47%)	19 (26%)	1 (2%)	72 (100%)

DM: Diabetes mellitus

Table 5. Late side-effects of patients

DM	Late gastrointestinal side effects				Total
	Absent	Grade 1	Grade 2	Grade 3	
Diabetic	19 (85%)	1 (5%)	1 (5%)	1 (5%)	22 (100%)
Non-diabetic	69 (96%)	1 (1%)	2 (3%)	0 (0%)	72 (100%)
	Late genitourinary side effects				
	Absent	Grade 1	Grade 2	Grade 3	
Diabetic	18 (82%)	3 (14%)	1 (4%)	0 (0%)	22 (100%)
Non-diabetic	63 (88%)	8 (10%)	1 (2%)	0 (0%)	72 (100%)

DM: Diabetes mellitus

Discussion

Prostate cancer is the most common male cancer and the second leading cause of death among other malignancies. The incidence rates of prostate cancer and DM are increasing in the last decades. At present, treatment guidelines recommend metformin as the first-line therapy for DM (12). Metformin is an insulin sensitizer and a potent adenosine monophosphate-activated protein kinase activator. It inhibits the mammalian target of rapamycin complex-1 pathway in carcinogenesis (13). In the last decades, many studies have investigated the effect of DM and metformin on cancer incidence and mortality (11). It is believed that metformin may have a greater effect on cancer survival by modulating cellular energy rather than the transformation of benign cells to malignant cells.

Studies examining the influence of metformin on prostate cancer have inconsistent results. In addition to cancer incidence, several studies have investigated the role of metformin on prostate cancer-specific mortality as well as recurrence. However, data are limited about the positive effect of metformin on treatment results with radiotherapy. Spratt et al. (8) conducted a retrospective study and revealed that metformin may improve bRFS, distant metastases-free survival, prostate cancer-specific mortality, and OS and reduce the development of castration-resistant prostate cancer. A previous large database study about the effect of DM and metformin in prostate cancer demonstrated that metformin users have reduced recurrence rates when compared with non-metformin users (14). Moreover, patients with DM had a worse OS than those without SM. In a surgical series, metformin was not associated with bRFS in patients who underwent radical prostatectomy (15). Kaushik et al. (16) found that metformin use was not associated with bRFS or OS in their retrospective cohort study (16). Coyle et al. (17) conducted a systematic review and reported that patients receiving prostate cancer radiotherapy had better OS, bRFS, and CSS, which might be related to metformin usage, although no any significant benefit was found for patients who underwent surgery. In the present study, metformin caused a 10% increase in bRFS rate; however, it was not significant, and results of the present study were similar to those of previous investigations.

In the present study, we also evaluated acute and late side effects and observed that patient with DM were more likely to have acute gastrointestinal and genitourinary side effects. Several previous studies have indicated that DM increases treatment-related toxicity in many cancers such as breast, colorectal, and lung cancer (18,19,20). Several theses were put forward about this association. DM might negatively affect leukocyte functions, including chemotaxis, phagocytosis, and insufficient bacterial killing; therefore, it negatively affects host immunity. More tissue damage occurs especially in fast proliferating cells such as the epithelium of the gastrointestinal and genitourinary tract and endothelial tissues after radiotherapy. Consequently, because of endothelial tissue damage, the coagulation system is also activated, resulting in diminished blood flow, thrombosis, and capillary necrosis (21). In patients with DM, endothelial dysfunction is a common reason for morbidity and mortality. Therefore, those with DM would have increased impairment in tissue repair after radiotherapy.

Gastrointestinal disorders are one of the common complications of DM and include gastroparesis, nonalcoholic fatty liver disease, gastroesophageal reflux disease, and chronic diarrhea (22). Moreover, metformin has some gastrointestinal side effects such as diarrhea. Although patients were asked to report the symptoms that occurred or increased after the start of radiotherapy, it may be sometimes difficult for the patient to tell the difference and distinguish gastrointestinal symptoms related with DM, metformin treatment, or radiotherapy. Some other factors such as androgen deprivation therapy and pelvic field radiotherapy may induce the occurrence and severity of side effects.

Study Limitations

This study has several limitations. The small sample size, heterogeneous patient characteristics, and retrospective nature of the analysis are the main limitations of this study. Metformin was used in different durations and may influence independently the outcomes of metformin-dependent factors. Moreover, the study did not include a group with DM not treated with metformin. In addition, no analysis was performed on patients with DM who received metformin and did not receive metformin. Furthermore, glycemic control data and hemoglobin A1c levels were not available in this study, which might have some effects on toxicity. Finally, the study had a relatively short follow-up time for observing late side effects and recurrence.

Conclusion

In this retrospective study, patients with DM and prostate cancer who used metformin and underwent radical radiotherapy have a better bRFS, but significance was not reached. Patients with DM experienced significantly more grade 1-2 acute side effects, whereas a trend toward increased low grades of late side effects was found. Vascular damage in DM may cause impairment in tissue repair after radiotherapy and increase radiotherapy-related toxicities. Controlled trials in patients with both DM and prostate cancer should be performed to evaluate the effect of DM and metformin usage on outcomes of radiotherapy.

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Contribution: There is not any contributors who may not be listed as authors.

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Financial Disclosure: The authors declared that this study received no financial support.

Ethics

Ethics Committee Approval: The retrospective study protocol was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine and the study was conducted in accordance with the tenets of the Helsinki Declaration (approved no: 150113, date: 02.10.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Supervision: S.Ç.K., Concept: M.D., H.F.Ö.D., Design: H.F.Ö.D., Data Collection or Processing: C.B., Analysis or Interpretation: C.Y., Literature Search: C.Y., Writing: M.D.

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