

Research Article

Impact of Diabetes on Clinical Outcomes of Prostate Cancer

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Abstract

Objectives: Diabetes is both a risk factor associated with increased incidence and a prognostic determinant for various cancer types. This study aimed to evaluate the impact of diabetes on prostate cancer outcomes.

Methods: The study included patients diagnosed with prostate cancer either at non metastatic stage at diagnosis and later developed metastasis or at metastatic stage at diagnosis. The characteristics of disease including patient age, date of diagnosis, gleason score (GS), stage, PSA level, time-to-distant metastasis for non-metastatic disease at diagnosis and time-to-castration resistance for metastatic disease, presence of diabetes, last date of control were reviewed retrospectively.

Results: A total of 149 patients were included in the study. Median overall survival of patients with diabetes was 32 months whereas it was 66 months for those without diabetes (HR=2; 95% CI:1.33–3; p=0.001). For non-metastatic disease at diagnosis, median time-to-distant metastasis was 48 months for those with diabetes, and 63 months for those without (p=0.13). Median time-to-castration resistance was 12 months vs. 27 months for patients with diabetes and without diabetes (HR=3.66; 95% CI:2.46–5.45; p=0.000).

Conclusion: Presence of diabetes is a robust and reliable prognostic marker for predicting poor survival outcomes including time-to-distant metastasis, time-to-castration resistance and overall survival in prostate cancer.

Keywords: Castration resistance, diabetes mellitus, overall survival, prostate cancer

Cite This Article: Özçelik M, Yaprak G, Gemici C, Oyman A, Çil İ, Özçelik S. Impact of Diabetes on Clinical Outcomes of Prostate Cancer. EJMA 2022;2(3):100–104.

Worldwide incidence of prostate cancer is ahead of numerous cancer types. Prostate carcinoma is the second most commonly encountered cancer in men following lung cancer and constitutes about 7-15% of newly diagnosed malignancies in men.^[1] Age, race, family history and inherited changes in some genes are among the risk factors for prostate cancer.^[2] On the other hand, advanced disease stage, high level of prostate specific antigen (PSA) at clinical presentation, high Gleason score, lymphovascular invasion, perineural invasion, high proliferation index and positive resection margins are unfavorable features for prostate cancer-specific outcomes.^[3-6]

Diabetes is an other entity affecting millions of people globally. Results from epidemiological research, have shown that this metabolic disease is correlated with increased risk of certain types of cancer. Malignant neoplasms of breast, colon, rectum, endometrium, liver, pancreas and bladder are among these cancers.^[7] Conversely, existing literature suggest that men with diagnosis of diabetes have reduced risk of prostate cancer. However, there is some evidence supporting the association of diabetes with increased risk of aggressive disease in prostate cancer.^[8,9] Elevated insulin to promote tumor proliferation, increased gene expression of androgen receptor and its substrates in the pathway, high-

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Submitted Date: May 06, 2022 **Accepted Date:** October 01, 2022 **Available Online Date:** October 10, 2022

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er insulin receptor A/B ratio leading to production of mitogenic variants and decreased amount of estrogen receptor ligands which inhibit androgen signalling, are considered to be the underlying factors.^[10,11]

While some data support the positive relation between the presence of diabetes and increased death from prostate cancer, some do not.^[12] In this research studying diabetic and non-diabetic patients both at metastatic and non-metastatic stage, we aimed to evaluate the impact of diabetes on prostate cancer outcomes including time-to-castration resistance, time-to-distant metastasis and overall survival.

Methods

Data Collection

The medical records of patients diagnosed with prostate cancer and treated at Departments of Medical and Radiation Oncology in Kartal Dr. Lutfi Kirdar Training and Research Hospital, between 2010-2020, were retrospectively reviewed. The characteristics of disease and participants including patient age, date of diagnosis, gleason score (GS), stage, PSA level, time-to-distant metastasis for non-metastatic disease at baseline and time-to-castration resistance for metastatic disease, presence and duration of diabetes, antidiabetic drugs used, last date of control and final status. The research was guided by the principles of Declaration of Helsinki and Ethics Committee of Kartal Dr. Lutfi Kirdar Training and Research Hospital, hospital has approved the study.

Treatment Characteristics

In total, 149 patients were included in the study. Thirty-five out of 149 patients had non-metastatic disease at diagnosis and the other 114 patients were at metastatic stage at diagnosis (Fig. 1). Amongst 35 patients who had non-metastatic disease at diagnosis, active surveillance, definitive radio-

therapy and radical prostatectomy were performed in 13, 8 and 14 patients, respectively. Entire study population of 149 patients underwent androgen deprivation therapy at metastatic stage. From these, castration resistance developed in 121 patients of which 85 cases received systemic chemotherapy. Thirty-four patients who failed first-line chemotherapy went on to receive second-line systemic treatment. Diabetes was diagnosed in 47 of patients based on the plasma glucose and HbA1c criterias.

Definition of Castration Resistance

Time-to-castration resistance was defined as the time between the onset of androgen deprivation treatment (ADT) and the development of either: a) At least 2 new bone lesions on bone scintigraphy or radiological progression according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, b) Three consecutive PSA increase with PSA above 2ng/ml, reported at least 1 week apart, while the serum testosterone level <50 ng/dl, whichever comes first.

Statistical Analyses

Time-to-distant metastasis in non-metastatic disease at baseline, time-to-castration resistance in metastatic disease and overall survival were the co-primary end points. The following parameters were compared between patients with and without diabetes: Time-to-distant metastasis in non-metastatic disease at baseline, time-to-castration resistance on androgen deprivation therapy, progression-free interval on chemotherapy, progression-free interval on second-line systemic treatment and overall survival, using Kaplan–Meier survival plots and Cox proportional hazard ratios.

Results

Median follow-up time was 73.97 months (range, 22.68–186.38). Characteristics of patients according to presence of diabetes was listed in Table 1. Median overall survival of patients with diabetes was 32 months whereas it was 66 months for those without diabetes (HR=2; 95%CI:1.33–3; p=0.001) (Fig. 2). Five-year survival rate was 55% for those without diabetes and 38% for diabetes. Median overall survival was 86 months and 36 months for GS:0-7 (n=67) versus GS:8-10 (n=82), respectively (HR=2.77; 95% CI: 1.78–4.32; p=0.000). Median overall survival was found to be improved most in patients without diabetes and with GS:0-7 tumors (130 months) compared to GS:0-7 with diabetes (40 months), GS:8-10 without diabetes (37 months) and GS:8-10 with diabetes (24 months) (p=0.000) (Fig. 3).

For non-metastatic disease at diagnosis, median time-to-

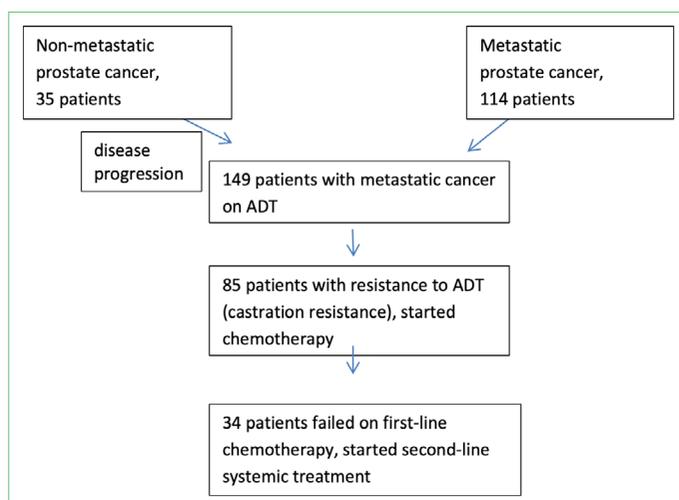


Figure 1. Treatment characteristics of study population.

Table 1. Characteristics of patients according to presence of diabetes

Characteristic	Without Diabetes n=102	With Diabetes n=47	p
Age (median)	67 (42-88)	69 (54-86)	0.430
Gleason score (%)			0.690
≤7	47 (46)	20 (43)	
8-10	55 (54)	27 (57)	
Stage at diagnosis (%)			0.390
Non-metastatic	23 (23)	12 (26)	
Metastatic	79 (77)	35 (74)	
Metastatic stage	73 (55-98)	80 (62-110)	0.420
PSA level (median)			

distant metastasis was 48 months for those with diabetes, and 63 months for those without (p=0.13) (Fig. 4). Castration resistance developed in 45 of 47 diabetes patients and 77 out of 102 non-diabetic patients. Median time-to-castration resistance was 12 months vs. 27 months for patients with diabetes and without diabetes (HR=3.66; 95% CI:2.46–5.45; p=0.000). Median time-to-castration resistance was 19 months and 24 months for GS:0-7 and GS:8-10, respectively (HR=1.62; 95% CI:1.12–2.34; p=0.007) (Fig. 5).

For chemotherapy employed patients after castration resistance, median progression free survival was 8 months and 12 months in those with diabetes and without diabetes, respectively (p=0.15). For second line systemic treatments,

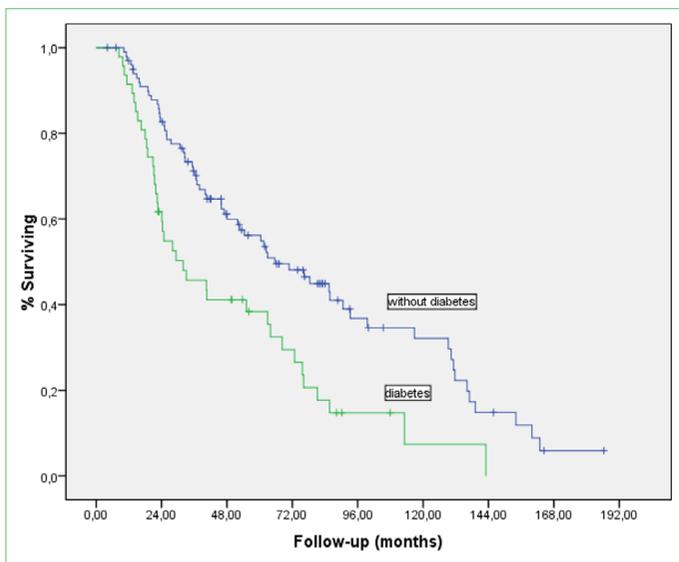


Figure 2. Overall survival curves according to presence of diabetes.

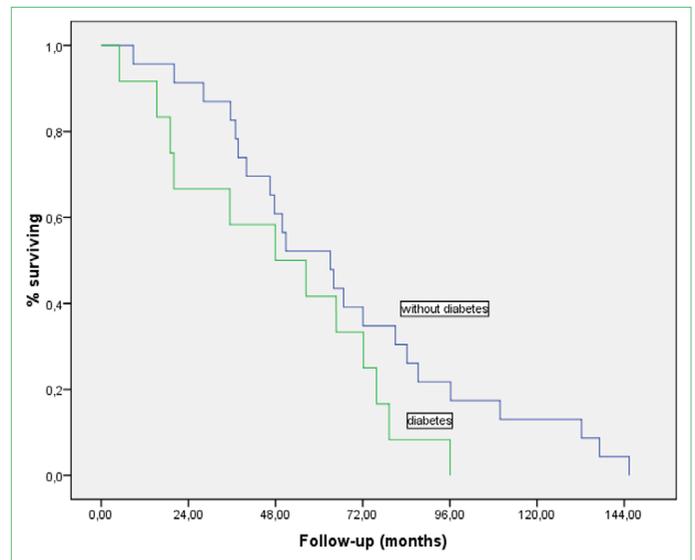


Figure 4. Time-to-distant metastasis in patients with non-metastatic disease at diagnosis, according to presence of diabetes.

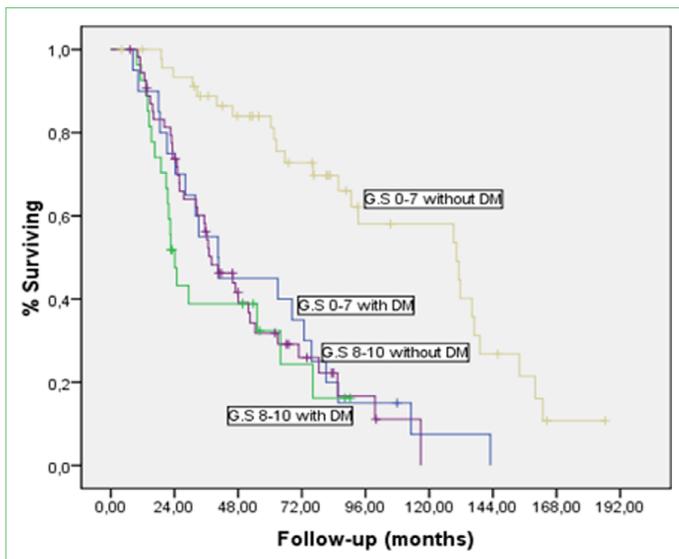


Figure 3. Overall survival curves according to Gleason score and presence of diabetes.

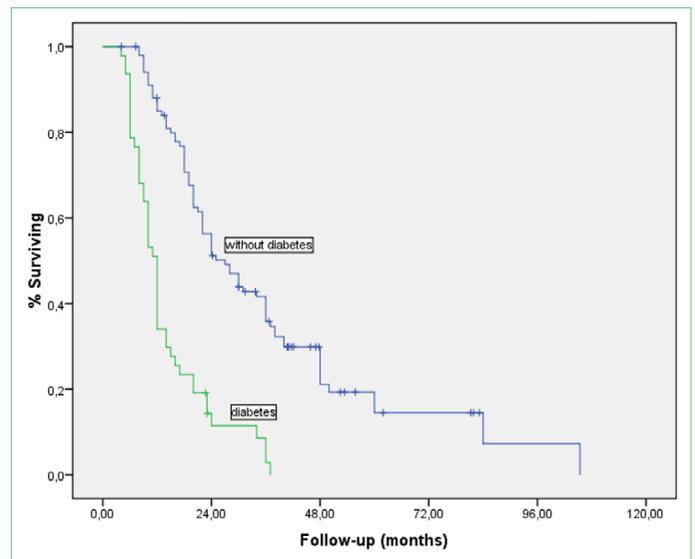


Figure 5. Time-to-castration resistance according to presence of diabetes.

median progression free survival was 12 months and 20 months in those with diabetes and without diabetes, respectively ($p=0.34$).

In multivariate analysis to evaluate whether or not the clinicopathological features are independently associated with time-to-castration resistance; GS:8-10 ($p=0.04$, HR:1.47) and presence of diabetes ($p=0.000$ HR: 3.49) were found as unfavorable variables related to shorter time-to-castration resistance compared to GS:0-7 or absence of diabetes. Similarly in multivariate analysis performed to identify independent prognostic characteristics for overall survival; G.S:8-10 (HR=2.71, $p=0.000$) and presence of diabetes (HR=1.94, $p=0.002$) were the variables associated with poor overall survival.

Discussion

A complex pattern of relation exists between diabetes and prostate cancer. Some of the literature suggest that diabetes is inversely proportional to the incidence, on the other hand, directly proportional to an aggressive phenotype of prostate cancer, if occurs. By the present work, we provide data in favor of the association of diabetes with aggressive disease course in prostate cancer.

A quite high incidence to lethality ratio of prostate cancer likely elucidate that the determinants of mortality can differ from the risk factors for incidence. Whether diabetic patients tend to have a decreased incidence of prostate cancer is open for discussion. Results of a recent study revealed that diabetic men has a high threshold to get a prostate biopsy after an elevated level of PSA,^[13] which is contradicting with the hypothesis that some protecting effects of antidiabetic medications exist. Similar to the incidence, whether diabetic patients tend to have an aggressive disease biology is an area that a consensus hasn't been reached. Asking for collection of the existing data concerning the impact of diabetes mellitus on prostate cancer outcome, a meta analysis involving 11 cohort studies was conducted.^[14] Although the biological process underlying this association could not be clarified by the authors, summed up results revealed that presence of diabetes was associated with 50% increase in the all-cause mortality among patients with prostate cancer. Parallel to the all-cause mortality, prostate cancer specific-mortality was also higher in diabetics vs. non-diabetics.

Lutz et al. studied 624 patients with local prostate cancer who underwent radical prostatectomy.^[10] Of these, they compared diabetic and non-diabetic patients in terms of T-stage, N-stage, Gleason score and PSA level. Although, they found out no significant difference in T-stage, Gleason score and PSA levels between diabetic and non-diabetic

groups, N-stage was more advanced in patients with diabetes compared to those without. We, in the present study compared the Gleason score and PSA levels at metastatic stage, between the diabetic and non-diabetic groups. Gleason score ≤ 7 vs 8-10 groups did not differ significantly among diabetic and non-diabetic patients. Similarly, PSA levels at metastatic stage were not statistically significantly different.

In a large study of prospective cohort design, amongst the metabolic risk factors including body mass index, plasma cholesterol, diabetes, diastolic/systolic blood pressure, alcohol, smoking, to predict prostate cancer mortality, diabetes was not found to be an independent variable,^[15] while high levels of cholesterol proposed to be related with increased mortality. In their research Shevach et al., evaluated 148 advanced stage prostate cancer patients on androgen deprivation treatment, of whom 35 were diagnosed with diabetes.^[16] The authors concluded that time-to-castration resistance did not differ between patients with and without diabetes. Similarly overall survival was not found to be different between two groups. Contrary to these findings, both the time-to-castration resistance and overall survival were statistically and clinically worse in diabetic patients in the present work.

In a systematic review investigating whether the pre-existing diabetes affect the prognosis of prostate cancer, only one of the included studies showed that diabetes was not associated with the mortality of prostate cancer.^[17] Remaining ten studies in the review with various end-points including overall long-term mortality, prostate cancer-specific mortality, non-prostate cancer mortality and 30-day mortality concluded that diabetes was an unfavorable risk factor for both prostate cancer-specific mortality and all-cause mortality. We preferred to address all-cause mortality rather than cancer-specific mortality in the current study given that the drawback related to incorrect identification of the reason of death in retrospective analysis.

Retrospective study model and relatively small sample size are among several limitations related to this study. Additionally, lack of adequate information on antidiabetic medications may have had an effect on outcomes. Extent of metformin exposure is considered to have protective effect on prostate cancer mortality according to the majority of data in the literature. Also other environmental and intrinsic potential confounders highlighted in previous studies are missing.

Our study evaluated the effect of diabetes on clinical outcomes of prostate cancer involving patients at both early-stage and metastatic stage. The present results suggest that, although initial PSA levels and gleason scores did not

significantly differ between diabetic and non-diabetic patients, the presence of diabetes has a detrimental effect on overall survival and also on time-to-castration resistance and time-to-distant metastasis, which are considered to be the surrogate endpoints for overall survival. Thus, it would be appropriate to manage the patients with both prostate cancer and diabetes proactively perhaps with commencing the effective treatments earlier in these population than in those with average risk.

Disclosures

Ethics Committee Approval: This study was approved by the institutional review board of Kartal Dr. Lutfi Kirdar City Hospital, Istanbul Hospital (No: 2017/514/109/3, Date: 20.06.2017).

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Authorship Contributions: Concept – M.O., G.Y., A.O., S.O.; Design – M. O., G.Y., C.G., I.C.; Supervision – M.O., G.Y., C.G., I.C.; Materials – G.Y., C.G.; Data collection & processing – M.O., G.Y., A.O., S.O.; Analysis and interpretation – M.O., G.Y., A.O., S.O.; Literature search – M.O., G.Y., A.O., I.C., S.O.; Writing – M.O., G.Y., A.O., I.C., S.O.; Critical review – M.O., G.Y., C.G.

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