Impact of diabetes and metformin use on prostate cancer outcome of patients treated with radiation therapy: results from a large institutional database

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Introduction: *Conflicting data exists on the influence of metformin on prostate cancer. We investigated the importance of metformin in patients treated with radiotherapy or brachytherapy.*

Materials and methods: *All patients from a large institutionalized database, treated for primary localized prostate cancer with either brachytherapy or external-beam radiotherapy ± androgen deprivation therapy were identified. Groups were compared by Kaplan–Meier analyses and Cox regression models. Multivariate analysis was adjusted for CAPRA-Score, type of treatment and age.*

Results: *A total of 2441 patients with complete data was identified. Among the 382 patients (16% of total) were diabetic. Two-hundred and eighty-one of the 382 diabetics (74%) were treated with metformin and 101 were treated with other anti-diabetic medication. Median follow up was 48 months (interquartile range [IQR] 24-84). Two-hundred eighteen patients (9%) died and 150 (6%) experienced biochemical recurrence (BCR). On unadjusted univariate analysis for BCR-free survival, metformin users showed a 50% reduction in BCR compared to non-metformin users. The results remained significant on multivariate analysis comparing diabetic metformin users to non-metformin users (diabetics and non-diabetics combined) (hazard ratio [HR] 0.5-0.6, p = 0.03-0.04) but lost its significance when adjusting for cancer aggressiveness. On multivariate analysis, diabetics had worse overall survival (OS) than non-diabetics (HR 1.5, 95% confidence interval [CI] 1.08-2.06, p = 0.01), but diabetics on metformin fared better than diabetics not taking metformin (HR 0.5, 95% CI 0.26-0.86, p = 0.01).*

Conclusion: *Metformin use in this analysis appears to be associated with better BCR and OS. Larger datasets and prospective trials are warranted to validate these results.*

Key Words: prostate cancer, metformin, radiotherapy, overall-survival, biochemical recurrence

Accepted for publication August 2018

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Introduction

The role of glucose metabolism in prostate cancer is not fully elucidated.[1] Metformin is a widely-used first-line treatment for type 2 diabetes in Canada. The influence of metformin on prostate cancer has been investigated

in several epidemiological studies, and it has even been proposed as a form of prostate cancer treatment. The literature on whether diabetics with prostate cancer have a higher risk of prostate cancer-specific and all-cause mortality is not uniform.[2] There is contradictory data on whether metformin has an influence on prostate cancer. Metformin is an ideal agent for use in prostate cancer because of its well-known metabolic effect, its good tolerance and its low cost.[3] The rationale for using metformin in prostate cancer also stems from its ability to act on insulin-independent and dependent pathways and interact with the androgen receptor.[4] In a clinical phase 2 study, metformin has been shown to stabilize prostate-specific antigen (PSA) progression in patients with castration-resistant prostate cancer (CRPC).[5]

The effect or lack of effect of metformin on prostate cancer could be due to the different populations studied, the different dosages used and the different times of exposure to the drug. In a Canadian population-based retrospective cohort, the cumulative duration of metformin treatment after prostate cancer diagnosis was associated with a significant decreased risk of prostate cancer-specific mortality in a dose-dependent fashion.[6] In addition, the STAMPEDE trial is studying whether metformin in non-diabetic patients with prostate cancer can improve overall survival (OS).[7]

The role of metformin in prostate radiotherapy for localized disease is less studied. In a recent single-center retrospective study of 2901 consecutive patients, metformin use was associated with less biochemical recurrence (BCR), less distant metastasis, and better prostate cancer-specific survival compared with diabetic patients not taking metformin.[8] Since the study included patients who had various exposures to metformin and included the use of metformin at diagnosis of prostate cancer or at any time after radiotherapy, the results were criticized for an immortal time bias.[9]

In this present study, we analyzed the influence of diabetes and metformin in our own institutional database with patients treated with radiotherapy, diagnosed with diabetes, and treated with metformin or other anti-diabetic drugs before starting radiation treatment.

Materials and methods

All patients from our institutionalized database were treated for primary localized prostate cancer who had complete information on follow up and data for calculation of the Cancer of the Prostate Risk Assessment (CAPRA) score. Our database included 2756 patients with primary localized prostate cancer of which 2441 patients (89%) had complete data available for the *CAPRA* score and follow up in this study. The CAPRA score measures prostate cancer aggressiveness from 0-10 and can predict outcome post-treatment.[10] It has been validated in our database as well as in a large Canadian collaborative database.[11] CAPRA scores are grouped as low (0-2 points), intermediate (3-5 points) and high-risk (6-10 points). Diagnosis with diabetes was defined as being treated with medication and excluded patients who were only on a diet.

Included patients were treated from September 2001 to September 2017 with either low-dose rate prostate brachytherapy (LDR-PB), high-dose rate (HDR) brachytherapy as monotherapy, HDR brachytherapy as a boost in combination with external-beam radiotherapy (EBRT), or with EBRT alone. Patients treated with neoadjuvant or adjuvant androgen deprivation therapy (ADT) were also included. Approval from the institutional ethical review board was obtained.

Diagnosis, age and type of treatment for diabetes were recorded at the time of radiotherapy treatment. No data on new diagnosis or medication use was recorded following radiotherapy treatment.

Descriptive statistics included frequencies and proportions for categorical variables. Means, medians, and ranges were reported for continuously coded variables. The Chi-square test determined the statistical significance in proportion differences. The Student's t-test examined the statistical significance in mean differences.

Kaplan-Meier analyses were used to graphically depict recurrence-free survival and OS. Finally, univariable and multivariable Cox regression models tested the effect of diabetes mellitus and metformin on the recurrence-free and OS. Adjustments were made for CAPRA-Score, type of treatment and age.

Results

Sixteen percent (382/2441) of patients were diagnosed with diabetes before radiation treatment. Of these patients, 281 (74%) were treated with metformin combined or not with other anti-diabetic medication, and 101 were treated with medication other than metformin. Among the other drugs for diabetes were insulin (n = 32) and secretagogues such as glyburide (n = 84), gliclazide (n = 26) and glitazone (n = 52). Thirteen patients were on insulin and metformin at the same time.

Median follow up was 48 months (interquartile range [IQR] 24-84). Median follow up to recurrence was 52 months (IQR 26.8-68.8) and median follow up to death was 52 months (IQR 24-78). Two hundred eighteen patients (9%) died, of which 18 (8%) died from prostate cancer and 150 (6%) experienced a BCR.

Table 1 lists the patient characteristics. At the time of treatment, diabetics were less than 1 year older (p = 0.04) than non-diabetics. Diabetics were also more frequently associated with intermediate and high-risk cancers than non-diabetics (p = 0.02). Seventy-two percent of patients had hypertension (76% of patients taking metformin versus 60% of patients not taking metformin, p = 0.002) and 66% were treated for dyslipidemia (69% of patients taking metformin versus 56% of patients not taking metformin, p = 0.034). ADT was given in 18% of patients (15% of patients taking metformin versus 24% of patients not taking metformin (p = 0.058).

Table 2 lists the effect of diabetes and metformin on BCR and OS. In general, diabetics taking metformin had a 50% reduced risk of BCR in univariate analysis when compared to diabetics not taking metformin and non-diabetics grouped together (hazard ratio [HR] 0.5, 95% confidence interval [CI] 0.3-0.99, p = 0.047). This result was lost when comparing only diabetics taking metformin versus non-diabetics (p = 0.6). Figure 1 illustrates the difference between patients taking metformin versus patients not taking metformin, including diabetics and non-diabetics. When adjusting for clinical factors and comorbidity, Table 3a and 3b, metformin lost its influence on BCR but retained its significance on overall survival on univariate and multivariate Cox-regression analysis.

Diabetic patients had worse OS than non-diabetic patients in multivariate analysis (HR 1.5, 95% CI 1.1-2.1, p = 0.01). However, using metformin eliminated that difference and resulted in the same OS as non-diabetics

TABLE 1. **Prostate cancer aggressiveness according to patients with diabetes or patients treated with metformin**

Factor	**Non-diab n = 2060**	**Diab -/+ metf n = 382**	**Non-diab vs. diab p value[a]**	**Diab -metf n = 101**	**Diab +metf n = 279**	**Diab -metf vs. diab +metf p value[a]**
Mean age (y)	66.8	67.5	**0.04**	68.2	67.3	0.057[b]*
(SD)	(6.8)	(5.9)		(5.1)	(6.2)	
≥ 70	34%	31%	0.2	34%	30%	0.39
CAPRA score			**0.02**			**0.035**
1-2 (low-risk)	41	33		28	35	
3-5 (intermediate	46	53		55	52	
6-10 (high)	13	14		18	13	
PSA (ng/mL)			0.5			0.2
0-6	45	40		34	43	
6-10	35	40		42	39	
10-20	15	15		15	15	
20-30	3	3		5	2	
> 30	2	2		5	1	
Gleason score			0.3			0.1
3+3	46	42		45	41	
3+4	35	36		28	39	
4+3	20	23		28	21	
Mean % of pos. cores	43%	43%	0.9	45%	43%	0.7[b]
(SD)	(26%)	(25%)		(26%)	(24%)	
> 33% pos. cores	52%	50%	0.7	50%	51%	0.9
Treatment			0.08			**< 0.001**
Exclusive brachy	48	43		26	49	
Exclusive EBRT	37	43		60	37	
Combination	15	14		14	14	

non-diab = non-diabetic; diab = diabetic; +metf = taking metformin; -metf = not taking metformin; SD = standard deviation; PSA = prostate-specific antigen; % of pos. cores = percentage of positive cores on prostate biopsy; brachy = brachytherapy; EBRT = external beam radiotherapy.
[a]chi-square test if not stated otherwise; [b]student's t-test

TABLE 2. **Cox regression analysis on the effect of diabetes and metformin on biochemical recurrence and overall survival**

	Biochemical recurrence						Overall survival					
	Univariate			Multivariate*			Univariate			Multivariate*		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Diabetes vs. no diabetes	**0.6**	**0.4-1.1**	**0.09**	**0.6**	**0.3-0.9**	**0.03**	**1.6**	**1.1-2.1**	**0.007**	**1.5**	**1.1-2.1**	**0.01**
Diabetics only +metf vs. -metf	0.5	0.3-1.0	0.047	0.7	0.3-2.0	0.6	0.4	0.2-0.7	0.003	0.5	**0.3-0.9**	**0.01**
All patients +metf vs. -metf	**0.5**	**0.3-1.0**	**0.047**	**0.5**	**0.3-1.0**	**0.04**	1.0	0.7-1.6	0.9	1.0	0.7-1.6	0.8
Diabetes +metf vs. no diabetes	**0.5**	**0.3-1.0**	**0.047**	**0.5**	**0.2-1.0**	**0.04**	1.1	0.7-1.7	0.7	1.1	0.7-1.7	0.6
Diabetes -metf vs. no diabetes	0.97	0.5-2.1	0.9	0.7	0.3-1.5	0.4	2.6	1.7-4.0	**< 0.001**	**2.2**	**1.4-3.4**	**0.0003**

HR = hazard ratio; 95% CI = 95% confidence interval; +metf = taking metformin; -metf = not taking metformin
*adjusted for CAPRA score, type of treatment, age

(HR 1.1, 95% CI 0.7-1.7, p = 0.6) while diabetics not taking metformin had worse OS (HR 2.2, 95% CI 1.4-3.4, p = 0.0003). Figure 2 illustrates the difference in OS between diabetics not taking metformin versus diabetics taking metformin and non-diabetics.

Discussion

In summary, we showed on unadjusted univariate analysis for BCR that metformin use was associated with a 50% reduction in BCR compared to non-metformin use. The results remained significant with multivariate analysis comparing diabetic metformin users to non-metformin users (diabetics and non-diabetics combined). But when adjusted for clinical factors such as cancer aggressiveness and comorbidity, metformin lost its significance.

By multivariate analysis, diabetics had worse OS than non-diabetics, but diabetics on metformin fared better than diabetics not taking metformin, even when adjusted for cancer aggressiveness and comorbidity. When comparing diabetics only, the difference between metformin-users and non-users was not significant, and was likely due to the relatively small number of

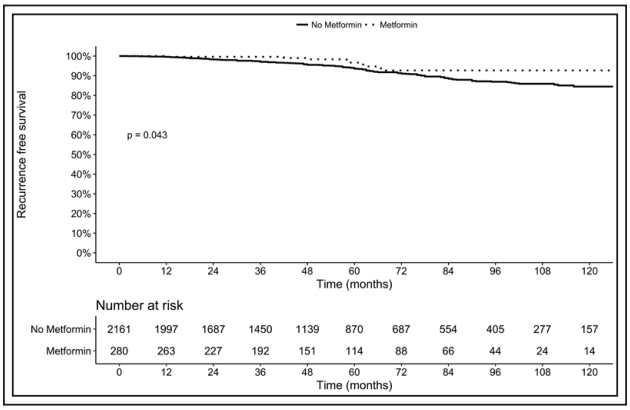

Figure 1. Recurrence free survival.

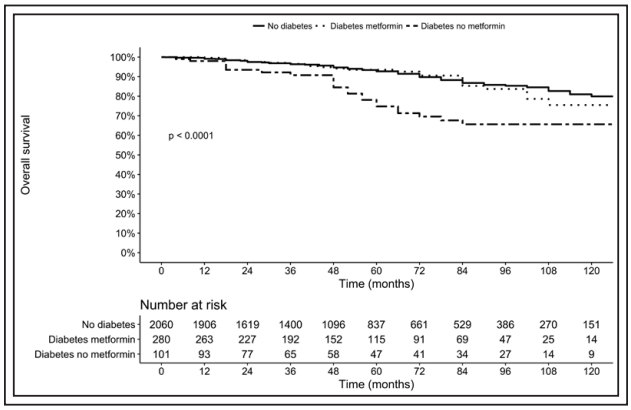

Figure 2. Overall survival.

TABLE 3a. **Univariate and multivariate analysis on the effect of clinical factors on biochemical recurrence**

Factor	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Metformin	0.55	0.20-1.47	0.2	0.92	0.33-2.60	0.9
CAPRA	1.34	1.09-1.64	0.005	1.40	1.04-1.90	0.02
Age	1.04	0.96-1.13	0.3	1.03	0.93-1.14	0.6
ADT	2.07	0.72-5.96	0.2	0.29	0.05-1.16	0.1
Hypertension	1.22	0.39-3.80	0.7	0.56	0.46-5.24	0.5
Dyslipidemia	0.43	0.16-1.15	0.09	0.55	0.19-1.58	0.3
Year of treatment	0.68	0.56-0.83	< 0.001	0.66	0.51-0.86	0.001

HR = hazard ratio; 95% CI = 95% confidence interval; CAPRA = cancer of the prostate risk assessment; ADT = androgen deprivation therapy

TABLE 3b. **Univariate and multivariate analysis on the effect of clinical factors on overall survival**

Factor	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Metformin	0.48	0.28-0.85	0.01	0.53	0.29-0.95	0.03
CAPRA	1.09	0.95-1.25	0.2	1.09	0.91-1.31	0.4
Age	1.07	0.102-1.13	0.008	1.07	1.01-1.23	0.02
ADT	1.35	0.69-2.64	0.4	0.65	0.26-1.64	0.4
Hypertension	1.13	0.60-2.14	0.7	1.34	0.68-2.64	0.4
Dyslipidemia	0.76	0.42-1.37	0.4	0.92	0.50-1.70	0.8
Year of treatment	0.84	0.76-0.93	< 0.001	0.86	0.76-0.97	0.01

HR = hazard ratio; 95% CI = 95% confidence interval; CAPRA = cancer of the prostate risk assessment; ADT = androgen deprivation therapy

diabetic patients who experienced BCR. This may also explain why the differences between metformin users and the combined group of diabetics not taking metformin and non-diabetics remained significant.

Diabetics had worse OS in univariate and multivariate analyses. Indeed, diabetics will likely die from other causes such as cardiovascular complications than from prostate cancer. Diabetics taking metformin had better OS than diabetics not taking metformin. There was no difference in OS between diabetics taking metformin compared to non-diabetics. Since metformin is given to patients early in the disease, these patients are in better general health than diabetics not taking metformin. Because of the relatively short follow up of 48 months, diabetics taking metformin had probably not yet developed complications from their diabetes.

We found that diabetic patients did have a higher frequency of being diagnosed with more advanced prostate cancer compared to non-diabetics. Diabetics were significantly older at time of radiation treatment, this difference was less than 1 year and, therefore, of no clinical significance or due to chance. Diabetics were also less frequently associated with low risk cancer than non-diabetics; however, this could represent a bias in a selected population as nearly half of the patients were treated with LDR-PB alone.

It is not clear why diabetes plays a role in prostate cancer and can have an influence on treatment outcomes; results from well-designed studies are not conclusive. In a Swedish nationwide population-based case-control study, men with type 2 diabetes had a 20% reduced risk of being diagnosed with prostate cancer.[12] Interestingly, patients treated with insulin had the lowest rate of prostate cancer. This effect of insulin was less for high-risk or metastatic cancer. In another study from Northern Europe, from Finland, men using anti-diabetic drugs had a lower overall prostate cancer risk, and metformin decreased the prostate cancer

risk in a dose-dependent manner.[13] A further study of these patients investigated whether single-nucleotide polymorphisms (SNPs) of genes involved in energy metabolic pathways were associated with prostate cancer-risk and prognosis. A genetic risk score was calculated from each significant SNP, and this score was associated with prostate cancer-specific survival. This genetic risk score was a significant predictor only in men who had not used anti-diabetic drugs.[14] A Danish study[15] found that the use of metformin and insulin decreased the incidence of prostate cancer, but for patients who had a previous PSA testing, insulin-use was no longer a significant factor.

One of the most cited articles reporting an influence of metformin use on prostate cancer is by Margel et al.[6] Published in 2013, diabetic patients over 66 years old were identified from the Ontario health care databases, of which 33% were receiving metformin before diagnosis of prostate cancer. Margel et al found that OS was better in patients taking metformin, although this effect declined the longer metformin was taken. More importantly, they showed that cumulative metformin use was associated with less prostate cancer-specific mortality. Although diabetics were older with a mean age of 66.9 years in our present study, we were able to confirm a survival advantage for diabetics taking metformin over those patients not taking metformin. We found that diabetics had more frequently intermediate and high-risk cancers than non-diabetics. One of the reasons explaining this finding may be that diabetics often weigh more than non-diabetics and increased bodyweight is associated with more aggressive cancer.[2] The mechanism is not known, but interestingly diabetes may decrease the rate of low-grade cancers, therefore increasing the relative rate of intermediate or high risk cancers.[16]

Diabetics in our study often had other factors of the metabolic syndrome (MetS), 72% had hypertension and 66% dyslipidemia. Whether the MetS and whether the treatment of metformin in patients with MetS was beyond the scope of this study with a limited number of patients with diabetes. In general, in a recent meta-analysis, the MetS was not significantly associated with prostate cancer risk.[17] Another study showed that the presence of at least 3 components of the MetS was associated with a reduced risk of prostate cancer and was not associated with higher-grade cancer.[18]

The effect of metformin on radiotherapy was first analyzed by Spratt et al[8] in a large database in the United States, including 2901 patients treated with radiotherapy in a single center. They identified 319 diabetics (11%) compared to our cohort with 382/2756 patients who were identified as diabetic (16%). Metformin use was more prevalent in our study with 281 patients (74% of diabetics) compared to their 157 patients (49% of diabetics), even though Spratt et al included patients who were diabetic or received medication at the time of prostate cancer diagnosis and treatment as well as at any time after completing their radiation therapy.

Metformin is more commonly used in Canada than in the United States as first-line treatment for type 2 diabetes, and could explain the larger percentage of metformin-users in our cohort. Spratt et al reported that 11% were diabetics. They found that diabetics taking metformin had OS that was very similar to non-diabetics (HR 1.38, 95% CI 0.9-2.1, p = 0.14), which is similar to our results (HR of 1.1, 95% CI 0.7-1.7, p = 0.6). Also comparable to our results, Spratt et al reported that diabetics taking metformin had better OS than diabetics not taking metformin (HR 2.25, 95% CI 1.4-3.7, p = 0.001). Unfortunately, they did not report on the influence of diabetes and metformin on BCR.

In their single-center database of 2298 patients treated with brachytherapy, either as monotherapy or boost, Taira et al[19] found that metformin use did not influence BCR (defined as PSA > 0.40 ng/mL) or prostate cancer-specific mortality. For OS, they found that diabetic men not taking metformin had higher overall mortality than non-diabetic men. Similar to our study as well as Spratt et al, Taira et al found that OS was the same between non-diabetics and diabetics taking metformin. They also reported that OS was better in non-diabetics than in diabetic patients not taking metformin.

When examining patients treated with prostatectomy, the influence of diabetes and metformin is not as clear. For example, in a recent single-center publication of 12,052 patients, Kaushik et al.[20] found that only 7% were diabetic, of which 36% were taking metformin. They found that metformin use was not associated with any difference in outcome (e.g., BCR, OS) or cancer aggressiveness in the specimen.

A possible radiobiological explanation for the better recurrence-free survival in diabetic patients, particularly metformin users, is that metformin has been shown to inhibit insulin-like growth factor 1 receptor (IGF-1R).[21] Increased cytoplasmic IGF-1R has been shown to be associated with an increased risk of BCR after radiotherapy. Furthermore, the over-expression of IGF-1R has been shown to be associated with primary Gleason grade 4-5 cancer.[22] Among other possible pathways to explain decreased BCR in diabetics are the effects on 5'-AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR) and NF-kappa B.[2]

Limitations of our study include the lack of information on dosage and time of exposure to metformin as well as medication use after treatment. Because of the relatively small number of diabetic patients on metformin in our study, it is not possible to rule out that other medication given in combination with metformin may have influenced the results. There may also be a population-bias because of the large group of patients treated exclusively with LDR-PB (47%) and, therefore, were with low-risk prostate cancer or with a lower-tiered intermediate-risk prostate cancer. However, this is similar to the 50% of patients treated exclusively with brachytherapy in the study by Taira et al and the 67% of patients with low or intermediate risk cancers in the study by Spratt et al where patients only received EBRT.

Conclusion

We found that metformin was associated with a lower incidence of BCR in diabetic patients with prostate cancer who were treated with metformin in unadjusted analysis. OS also improved in diabetics using metformin in comparison to diabetics who were not on metformin. When adjusting for clinical factors and comorbidity, metformin lost its influence on BCR but retained its significance on OS. Although these results are encouraging, prospective randomized trials or analysis of larger databases are necessary to determine the benefit of metformin use in prostate cancer patients undergoing radiotherapy. □

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