Original Study

Prostate Cancer Patients With Unmanaged Diabetes or Receiving Insulin Experience Inferior Outcomes and Toxicities After Treatment With Radiation Therapy

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Abstract

We evaluated the effect of type 2 diabetes, and medications used in its management, on prostate cancer patients receiving radiation therapy. Men who were receiving insulin and those not receiving any medication had increased risk of death and toxicity than those without diabetes.

Background: The purpose of the study was to determine the effect of type 2 diabetes mellitus (T2DM) on outcomes and toxicities among men with localized prostate cancer receiving definitive radiation therapy. **Patients and Methods:** We performed a retrospective review of 3217 patients, from 1998 to 2013, subdivided into 5 subgroups: (I) no T2DM; (II) T2DM receiving oral antihyperglycemic agent that contains metformin, no insulin; (III) T2DM receiving nonmetformin oral agent alone, no insulin; (IV) T2DM receiving any insulin; and (V) T2DM not receiving medication. Outcome measures were overall survival, freedom from biochemical failure (BF), freedom from distant metastasis, cancer-specific survival, and toxicities. Kaplan–Meier analysis, log rank tests, Fine and Gray competing risk regression (to adjust for patient and lifestyle factors), Cox models, and subdistribution hazard ratios (sHRs) were used. **Results:** Of the 3217 patients, 1295 (40%) were low-risk, 1192 (37%) were intermediate-risk, and 652 (20%) were high risk. The group I to V distribution was 81%, 8%, 5%, 3%, and 4%. The median dose was 78 Gy, and the median follow-up time was 50 (range, 1-190) months. Group V had increased mortality (sHR, 2.1; 95% confidence interval [CI], 0.66-1.54), BF (sHR, 2.14; 0.88-1.83), and cause-specific mortality (sHR, 3.87; 95% CI, 1.31-11). Acute toxicities were higher in group IV versus group I (genitourinary: 38% vs. 26%; $P = .01$; gastrointestinal: 21% vs. 5%; $P = 001$). Late toxicities were higher in groups IV and V versus group I (12%-14% vs. 2%-6%; $P < .01$). **Conclusion:** Men with T2DM not receiving medication and men with T2DM receiving insulin had worse outcomes and toxicities compared to other patients.

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Introduction

Prostate cancer is the second most prevalent solid tumor diagnosed in men of the United States and Western Europe.[1] The etiology and biological mechanisms for the development of prostate cancer are complex.[2] A consensus statement from the American Cancer Society and the American Diabetes Association emphasized a link between type 2 diabetes mellitus (T2DM) and prostate cancer.[3] This association is believed to be rooted on biological evidence of insulin and insulin-like growth factors (IGFs) potentiating cancer cell growth and cell cycle progression[4-7] and the clinical findings of increased all-cause mortality among diabetic patients compared with their nondiabetic counterparts.[8,9]

Among prostate cancer patients, hyperinsulinemia is associated with increased cancer-specific mortality.[10] Moreover, studies suggest that metformin use is associated with improved rates of overall survival (OS), freedom from biochemical failure (FFBF), freedom from distant metastasis (FFDM), cancer-specific survival (CSS), and

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the transformation of prostate cancer from androgen-sensitive to castrate-resistant disease.[11,12] However, the type of antihyperglycemic medication (eg, metformin, insulin) best used for these patients is unknown.

We evaluated the effect of T2DM, oral antihyperglycemic agents (subdivided into those containing metformin or not), and insulin, on the outcomes and toxicities among men who underwent definitive radiation therapy (RT) for localized prostate cancer. We hypothesized that men without T2DM would have the best outcomes and toxicities compared with other diabetic patients (specifically those receiving insulin or those not receiving medication).

Patients and Methods

Study Design

After institutional review board approval, we reviewed our prospectively collected institutional database of men who underwent RT for localized prostate adenocarcinoma, clinical stage T1 to T4, N0/X, M0. Men were staged using National Comprehensive Cancer Network (NCCN) criteria.[13,14]

Patient evaluation details are listed in the *Materials and Methods* section of the Supplemental Material (available in online). Using our drug database, we were able to parse out the medications in combination pills (eg, Actoplus MET: metformin and pioglitazone; Takeda Pharmaceuticals U.S.A., Inc. [TPUSA], Deerfield, IL) to create diabetes groups (Supplemental Table 1, available in online). Men were subdivided into 5 subgroups, depending on use of T2DM medication: (I) no T2DM; (II) T2DM receiving an oral antihyperglycemic agent that contains metformin, but not receiving insulin; (III) T2DM receiving nonmetformin oral antihyperglycemic agent alone (eg, glyburide; sitagliptin; pioglitazone), but not receiving insulin; (IV) T2DM receiving any insulin, with or without oral antihyperglycemic agent; and (V) T2DM not receiving medication. We created this distinction to parse out patients receiving metformin, who were hypothesized to have improved outcomes compared with those not receiving metformin[11,15,16]; and to separate men who have an advanced stage of T2DM requiring insulin, which is typically started only after oral antihyperglycemic agents have failed[17,18] and is associated with increased cancer-related death.[10] The techniques used for 3-dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT) have been previously reported[19-21] and are further described in the *Materials and Methods* section of the Supplemental Material (available in online).

Outcome Measures and Statistical Analysis

Patients were followed with clinical examination (including rectal examination) every 6 months for the first year; then yearly with prostate-specific antigen (PSA) levels drawn every 6 months. For FFBF, time to event was determined from date of initial RT to date of biochemical event (either date of nadir and 2 PSA, in ng/mL,[22-24] or date that salvage hormone treatments were started), or to date of last PSA measurement recorded in the database for those censored. For FFDM, CSS, and OS, censoring was determined as time from date of start of RT to either date of event or status date. The time component was from start of RT.

We used Kaplan–Meier methods to generate survival curves for OS, FFBF, FFDM, and CSS, and compared groups II to V versus group I using log rank tests. To adjust for patient and lifestyle factors, we used competing risk regression models (variables in models are listed in the *Materials and Methods* section of the Supplemental Material, available in online). For FFBF and FFDM, subdistribution hazard ratios (sHRs) were estimated using Fine and Gray competing risk regression.[25] We evaluated genitourinary (GU) and gastrointestinal (GI) toxicities using the Radiation Therapy Oncology Group (RTOG) definitions (Supplemental Table 2, available in online). We used competing risk regression to estimate sHRs for late toxicities (occurring $>$ 3 months after RT). Competing risk regression analyses and survival plots were done using Stata version 12 (Stata Corp, College Station, TX); additional analyses were performed with SAS 9.2 (SAS Institute Inc, Cary, NC), and a P value $< .05$ was considered significant.

Results

Patient characteristics are listed in Table 1. From 1998 to 2013, 3217 men were treated with RT, with a median dose of 78 (range, 76-80) Gy. The median follow-up was 4.9 years (range, 1-190 months). Of these men, 40% were low-, 37% intermediate-, and 20% high-risk, on the basis of NCCN criteria. Of the 3217 men, 80.9% were in group I, 7.8% in group II, 4.6% in group III, 2.8% in group IV, and 3.9% in group V. There was no statistically significant difference in distribution of the patients among risk groups; or among Gleason score groups, PSA groups, or T stage groups. Men in groups II to V were more likely to have hypertension and heart disease than those in group I ($P < .0001$). The average age among the groups was similar at 67 years. Men in group V were more frequently treated with 3D-CRT than with IMRT, compared with other groups ($P < .0001$) because most of these men were treated before 2002, when our institution acquired IMRT, which was controlled for in multivariate analysis.

Patient outcomes are shown in Table 2 and Figure 1. The 5-year OS rates for low-, intermediate-, and high-risk men were 94%, 91% ($P = .01$), and 88% ($P < .0001$), respectively (Table 1, upper portion). The 5-year OS rates for men in groups III, IV, and V were significantly worse compared with men in group I: 92% for group I (reference), 94% for group II ($P = .97$), 89% for group III ($P = .03$), 83% for group IV ($P = .01$), and 88% for group IV ($P = .002$), as shown in Table 1, middle portion and Figure 1, upper left panel. After adjusting for competing risk factors (Table 2, lower portion), men in groups IV and V were twice as likely to experience noncancer-related death as those in group I. Men in group II (ie, those taking metformin) had no difference in OS compared with men in group I.

The 5-year FFBF rates for low-, intermediate-, and high-risk men were 96%, 87% ($P = .12$), and 79% ($P < .0001$), respectively (Table 1, upper portion). The 5-year FFBF rates for men in group V were significantly worse compared with men in group I: 90% for group I (reference), 88% for group II ($P = .48$), 94% for group III ($P = .04$), 92% for group IV ($P = .43$), and 75% for group IV ($P < .0001$), as shown in Table 1, middle portion and Figure 1, upper right panel. After adjusting for competing risk factors (Table 2, lower portion), men in group V were twice as likely to experience biochemical failure (BF) than those in group I. Men in group II (ie, those taking metformin) had no difference in BF compared with men in group I.

The 5-year FFDM rates for low-, intermediate-, and high-risk men were 99%, 97% ($P < .0001$), and 91% ($P < .0001$),

Table 1 Patient Characteristics

Characteristic	All (n = 3217; 100%)		Diabetes Groups										
			I: No T2DM (n = 2603; 80.9%)		II: Metformin (n = 251; 7.8%)		III: Nonmetformin Oral Antihyperglycemic (n = 148; 4.6%)		IV: Any Insulin (n = 89; 2.8%)		V: T2DM, No Medication (n = 126; 3.9%)		
	n	%	n	%	n	%	n	%	n	%	n	%	χ^2 *P*
NCCN Risk Group													.43
Low	1295	40.3	1067	41	94	38	56	38	30	34	48	38	
Intermediate	1192	37.1	964	37	97	39	55	37	35	39	41	33	
High	652	20.3	515	20	54	22	33	22	20	23	30	24	
Unknown	78	2.4	57	2	6	2	4	3	4	5	7	6	
GS													.083
6	1706	53	1411	54	115	46	75	51	38	43	67	53	
7	1075	33.4	854	33	93	37	54	37	37	42	37	29	
8 to 10	436	13.6	338	13	43	17	19	13	14	16	22	18	
PSA, ng/mL													.59
<10	2472	76.8	1990	77	204	81	110	74	68	76	100	79	
10 to 20	523	16.3	427	16	38	15	26	18	15	17	17	14	
>20	222	6.9	186	7	9	4	12	8	6	7	9	7	
Mean (SD)			9.7 (17.3)		8.4 (9.8)		9.1 (10)		8.9 (10)		11 (20)		
T Stage													.35
T1 to T2a	2455	76.3	1990	77	195	78	119	80	67	75	84	67	
T2b to T2c	438	13.6	360	14	30	12	16	11	9	10	23	18	
T3 to T4	188	5.8	149	6	15	6	7	5	8	9	9	7	
TX	136	4.2	104	4	11	4	6	4	5	6	10	8	
Initial ADT Use	833	25.9	643	25	80	32	46	31	27	30	37	29	**.034**
Hypertension	1763	54.8	1337	51	173	69	108	73	67	75	78	62	**<.0001**
Heart Disease	727	22.6	541	21	67	27	52	35	23	26	44	35	**<.0001**
Time of Medication Start													
Before RT					155	62	116	78	47	53			
After RT					96	38	32	22	42	47			
Age at Initiation, Years													.059
36 to 55	246	7.6	204	8	19	8	9	6	6	7	8	6	
56 to 65	992	30.8	793	31	91	36	45	30	35	39	28	22	
66 to 75	1518	47.2	1224	47	116	46	69	47	33	37	76	60	
76 to 89	461	14.3	382	15	25	10	25	17	15	17	14	11	
Mean (SD)	67 (7.8)		67 (7.7)		66 (7.1)		68 (8.0)		67 (8.3)		68 (7.4)		

Table 1 Continued

Characteristic	All (n = 3217; 100%)		Diabetes Groups									
			I: No T2DM (n = 2603; 80.9%)		II: Metformin (n = 251; 7.8%)		III: Nonmetformin Oral Antihyperglycemic (n = 148; 4.6%)		IV: Any Insulin (n = 89; 2.8%)		V: T2DM, No Medication (n = 126; 3.9%)		χ^2 *P*
	n	%	n	%	n	%	n	%	n	%	n	%	<.0001
RT Technique													
3D-CRT	902	28	758	29	38	15	31	21	10	11	65	52	
IMRT	2315	72	1845	71	213	85	117	79	79	89	61	48	
Mean Follow-Up (SD), Months	58 (34)		63 (35)		62 (37)		63 (33)		51 (33)		49 (30)		.36
Minimum	1.1		1.1		4.7		5.5		5.8		1.7		
Maximum	212.1		197.5		212.1		162.8		167.7		167.9		

All staging information (eg, risk group, PSA, T stage, GS) is before RT. Comorbidities (eg, hypertension) were typically present before RT; some patients were diagnosed with these conditions during or after RT, but detailed information on exact date of diagnosis is unavailable. There was no statistically significant difference in the distribution of RT doses (3 levels: 76 Gy, 78 Gy, 79-80 Gy) among the patient subgroups.
Bold denotes *P* values < .05.
Abbreviations: ADT = androgen deprivation therapy; 3D-CRT = 3-D conformal radiation therapy; GS = Gleason score; IMRT = intensity modulated radiation therapy; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; RT = radiation therapy; T2DM = type 2 diabetes mellitus.

respectively (Table 1, upper portion). The FFDM rates were similar among all groups (Table 1, middle portion; Figure 1, lower left panel). After adjusting for competing risk factors (Table 2, lower portion), the FFDM rates remained similar among all of the groups. Men in group II (ie, those taking metformin) had no difference in FFDM compared with men in group I.

The 5-year CSS rates for low-, intermediate-, and high-risk men were 100%, 99% ($P = .12$), and 97% ($P < .0001$), respectively (Table 1, upper portion). The CSS rates for group V were significantly worse than those in group I: 98% versus 99% ($P = .01$); there was no difference in any other group compared with group I (Table 1, middle portion; Figure 1, lower right panel). After adjusting for competing risk factors (Table 2, lower portion), the cancer-specific mortality was 3.87 times higher in men in group V than in group I ($P = .01$); it was 2.32 times higher in group II than in group I (borderline significant at $P = .05$).

Early toxicity analysis is shown in Table 3, upper portion; late toxicity analysis is shown in Table 3, lower portion and Figure 2. Early RTOG Grade 2 to 4 GU toxicity was significantly higher in group IV versus group I (38% vs. 26%; $P = .01$). Early RTOG Grade 2 to 4 GI toxicity was significantly higher in group IV versus I (12% vs. 5%; $P = .01$). Late RTOG Grade 2 to 4 GU toxicity was significantly higher in group IV (11%; $P = .001$) and group V (12%; $P = .001$) than in group I (2.5%). Similarly, late RTOG Grade 2 to 4 GI toxicity was significantly higher in group IV (14%; $P = .01$) and group V (14%; $P = .001$) than in group I (6%).

Discussion

In this study, we analyzed the effect of metformin-containing oral antihyperglycemic agents, nonmetformin oral antihyperglycemic agents, insulin, and nonmedication controlled T2DM on the outcomes and toxicities of men with prostate cancer treated with definitive RT. We found that men with T2DM receiving insulin and those not receiving medication are twice as likely to die of noncancer causes than are those without T2DM; moreover, men with nonmedication controlled T2DM are twice as likely to experience BF than those without T2DM, and they are almost 4 times as likely to experience death from prostate cancer than men without T2DM. With respect to toxicity, men receiving insulin have approximately a twofold higher incidence of acute GU and GI toxicity; men receiving insulin and those with nonmedication controlled T2DM have an eightfold increase in late GU complications, and a twofold increase in late GI complications. Men with T2DM not receiving medication and men with T2DM receiving insulin have worse outcomes and toxicities than those without T2DM or those receiving oral antihyperglycemic agents. The type of oral antihyperglycemic agent (ie, presence or absence of metformin) used for control of T2DM might be minimally important for prostate cancer; rather, the development of hyperinsulinemia should be avoided.

These findings have several implications: (1) physicians caring for men with T2DM who are receiving RT for prostate cancer should counsel the patients and refer them to appropriate specialists (eg, endocrinologists) who might help them with T2DM management (including proper diet and exercise); (2) these physicians should also try to select a treatment modality with minimal toxicity effect by T2DM (eg, avoid brachytherapy with IMRT, because the

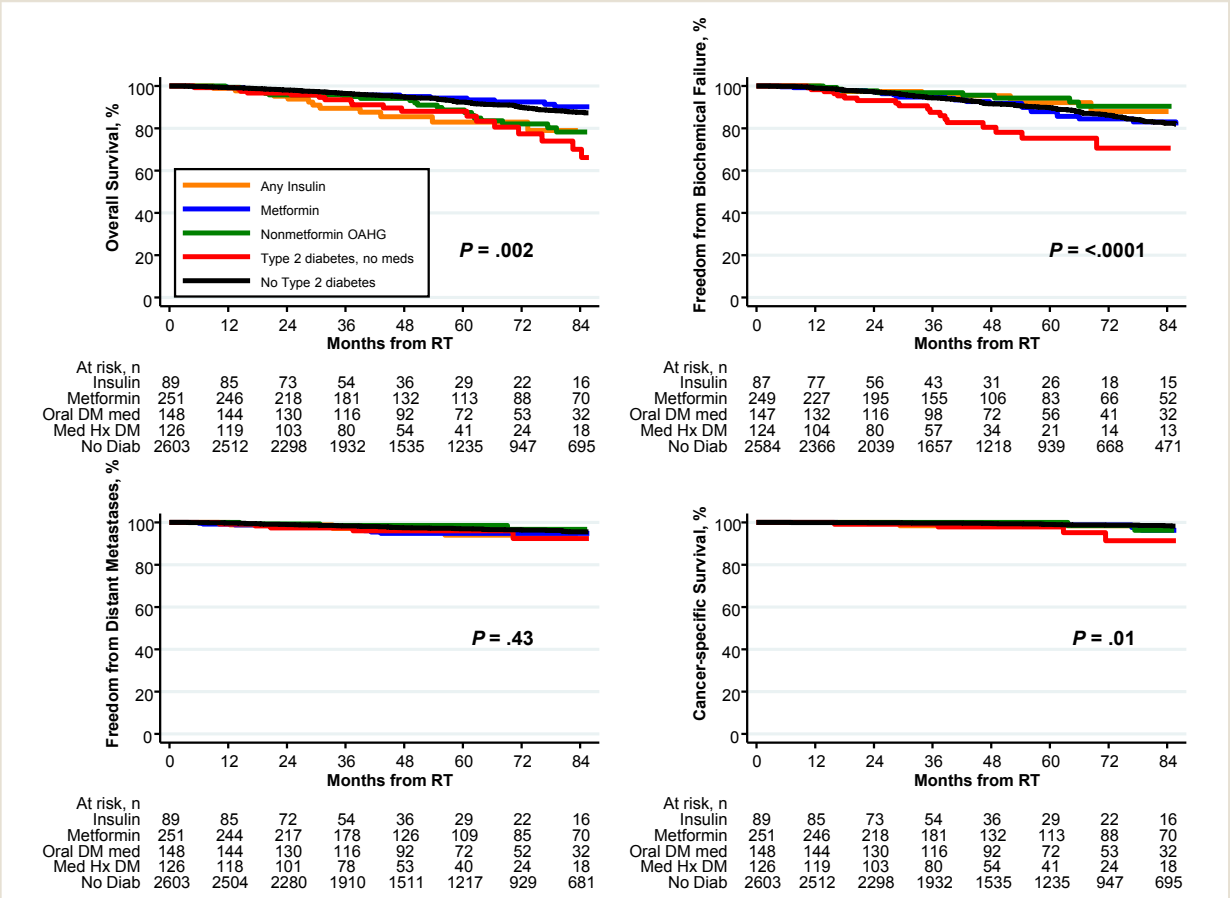
Table 2 Patient Outcomes, Stratified According to T2DM Group

	n	%	OS	95% CI	*P*	FFBF	95% CI	*P*	FFDM	95% CI	*P*	CSS	95% CI	*P*
Five-Year KM														
NCCN risk group														
Low	1295	41.3	94.3	92.6-95.6	Ref	96.4	94.7-97.5	Ref	99.4	98.5-99.7	Ref	99.9	99.1-100	Ref
Intermediate	1192	38.0	91.0	88.8-92.8	**.01**	87.3	84.7-89.6	.12	96.9	95.4-97.9	**<.0001**	99.2	98.0-99.6	.12
High	652	20.8	88.4	85.2-90.9	**<.0001**	79.1	74.8-82.7	**<.0001**	90.8	87.8-93.1	**<.0001**	96.8	94.7-98.0	**<.0001**
T2DM group														
I. No T2DM	2603	81	92.3	91.0-93.5	Ref	89.7	88.2-91.1	Ref	96.9	96.1-97.6	Ref	99	98.4-99.4	Ref
II. Metformin	251	7.8	94.3	89.9-96.8	.97	87.8	81.1-92.3	.48	94.8	90.5-97.2	.15	98.8	94.9-99.7	.07
III. Nonmetformin oral antihyperglycemic	148	4.6	**88.7**	**81.0-93.4**	**.03**	**94.3**	**87.4-97.4**	**.04**	98.5	94.2-99.6	.43	100		.90
IV. Any insulin	89	2.8	**82.9**	**70.6-90.4**	**.01**	92.1	78.8-97.2	.43	94	80.9-98.2	.64	98.4	89.1-99.8	.88
V. T2DM, no meds	126	3.9	**88.0**	**79.0-93.3**	**.002**	**75.3**	**62.0-84.5**	**<.0001**	96	89.6-98.5	.28	**97.8**	**94.5-99.5**	**.01**
sHR			**OM**			**BF**			**DM**			**CSM**		
T2DM group														
I. No T2DM	2603	81	1.00		Ref	1.00		Ref	1.00		Ref	1.00		Ref
II. Metformin	251	7.8	0.99	0.65-1.52	.98	1.22	0.84-1.77	.29	1.49	0.78-2.85	.22	2.13	0.90-5.08	.09
III. Nonmetformin oral antihyperglycemic	148	4.6	1.48	0.96-2.28	.07	0.54	0.27-1.06	.074	0.67	0.20-2.26	.52	1.11	0.25-5.01	.89
IV. Any insulin	89	2.8	**2.06**	**1.17-3.63**	**.012**	0.60	0.27-1.33	.21	1.24	0.38-4.04	.73	1.20	0.17-8.54	.86
V. T2DM, no meds	126	3.9	**2.01**	**1.24-3.26**	**.005**	**2.22**	**1.46-3.39**	**<.001**	1.94	0.76-4.86	.17	**3.91**	**1.33-11.46**	**.013**

All *P* values are pairwise comparisons with reference group (no T2DM). Bold denotes *P* values < .05. For OM, Cox proportional hazards models were used. For all sHRs, covariates included Gleason score, T stage, prostate-specific antigen group, initial hormone therapy (yes vs. no), RT type (2 levels), RT dose (3 levels), treatment year, and age at start of treatment. Additionally, for OM, a history of hypertension was included.

Abbreviations: BF = biochemical failure; CSM = cancer-specific mortality; CSS = cancer-specific survival; DM = distant metastasis; FFBF = freedom from biochemical failure; FFDM = freedom from distant metastasis; KM = Kaplan–Meier; NCCN = National Comprehensive Cancer Network; OM = overall mortality; OS = overall survival; Ref = reference; RT = radiation therapy; sHR = subhazard ratio; T2DM = type 2 diabetes mellitus.

Figure 1 Kaplan–Meier Curves for All Patients of Freedom From Biochemical Failure (FFBF) (Top Right), Freedom From Distant Metastasis (Lower Left), Cancer-Specific Survival (CSS; (Lower Right), and Overall Survival (OS; Top Left). The X-Axis on Each Plot Is Follow-Up Time (in Months); the Y-Axis Is Percent. Patients With Unmanaged Diabetes (i.e. Taking No Medication) or on Insulin Had Worse Outcomes Than Other Groups



Abbreviations: Diab = diabetes; Hx = history; Med = medication; OAHG = oral antihyperglycemic; RT = radiation therapy.

complication rates are higher for men with T2DM)[26-28]; subsequently, physicians should have a lower threshold to suspect toxicity in men with poorly managed T2DM; (3) clinical trialists evaluating toxicity as an end point should be mindful of patient comorbidities (including T2DM), which might predispose certain patients to worse outcomes and toxicities[29]; (4) men who are having their prostate cancer treated should be mindful of their comorbidities, they should not put these on the "back burner," but instead continue to see physicians who will manage these conditions appropriately; and (5) further research is necessary to explore the interplay among diabetes, antidiabetes medications, and cancer.

Men in groups II to IV (Table 1) did not have more aggressive cancers than those without T2DM, as suggested by the relatively equal distribution of patients among NCCN risk groups, Gleason score groups, PSA groups, or T stage groups. Our findings are consistent with data from Germany and the United Kingdom, which revealed no evidence of metformin or sulfonylureas having a protective effect among multiple lung cancers,[30,31] with data from Canada that revealed no association between metformin use and prostate cancer aggressiveness,[32] and with the patient characteristics from Memorial Sloan Kettering Cancer Center (MSKCC).[11] Additionally, our findings are consistent with a meta-analysis of studies showing no link between insulin use and incidence of prostate cancer.[33] The results do not suggest that T2DM is a protective factor for prostate cancer.[34]

Men in group V were more likely to be treated with 3D-CRT than with IMRT, most likely because more of the patients in group V were treated from 1998 to 2001 when IMRT was not implemented at our institution. Although the outcomes with these 2 technologies are considered to be equivalent, toxicity is typically more frequently observed with 3D-CRT than with IMRT[20,35,36]; thus, we controlled for this covariate when performing the toxicity analysis. It is difficult to fully adjust for the difference in planning technique and reduce it to a single universal coefficient; thus, some of the toxicity might be because of treatment technique. Nonetheless, on the basis of clinical trials[36] and data from MSKCC[35] that

Table 3 Patient Toxicity, Stratified According to T2DM Group

T2DM Group	n	%	RTOG Toxicity, Grade 2 to 4					
			GU			GI		
			%	n	*P*	%	n	*P*
Early, Incidence								
I. No T2DM	2603	81	26	688	Ref	5	146	Ref
II. Metformin	251	7.8	28	76	.19	7	18	.31
III. Nonmetformin oral antihyperglycemic	148	4.6	21	32	.20	4	6	.42
IV. Any insulin	89	2.8	38	34	.01	12	11	.01
V. T2DM, no meds	126	3.9	22	28	.29	9	11	.14
Late, KM at 3 Years				**95% CI**			**95% CI**	
I. No T2DM	2603	81	2.5	1.9-3.3	Ref	5.9	5.0-7.0	Ref
II. Metformin	251	7.8	2.1	0.8-5.6	.25	6.1	3.5-10.5	.42
III. Nonmetformin oral antihyperglycemic	148	4.6	4.8	2.2-10.4	.18	7.8	4.2-14.0	.49
IV. Any insulin	89	2.8	**11.4**	**5.5-22.6**	**.001**	**13.7**	**7.6-24.1**	**.01**
V. T2DM, no meds	126	3.9	**11.9**	**6.3-21.9**	**.001**	**13.9**	**8.4-22.5**	**.001**

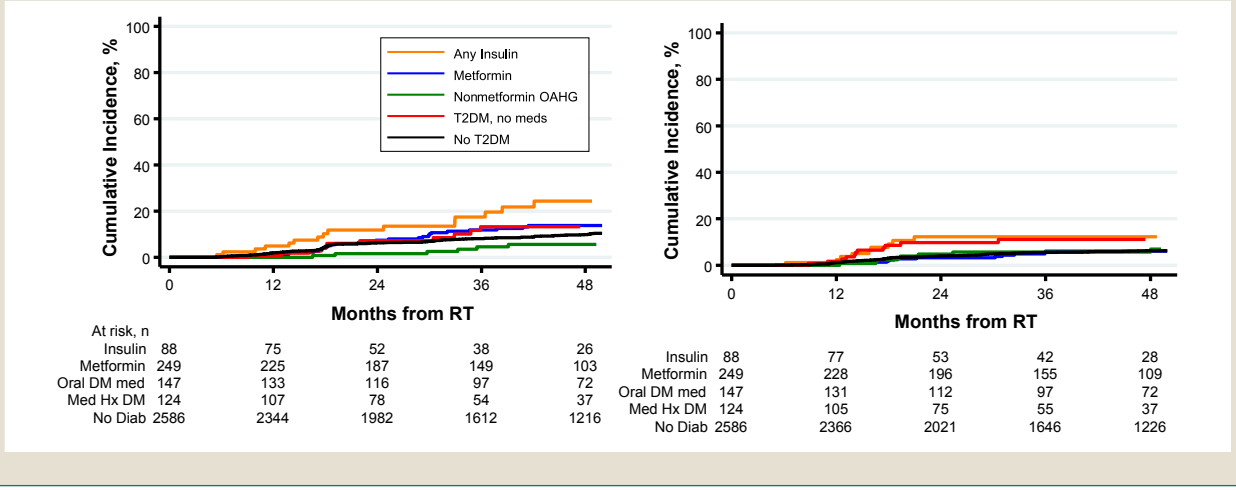
Bold denotes *P* values < .05.
Abbreviations: GI = gastrointestinal; GU = genitourinary; KM = Kaplan–Meier; Ref = reference; RTOG = Radiation Therapy Oncology Group; T2DM = type 2 diabetes mellitus.

compared IMRT with 3D-CRT, we would expect the rate of Grade ≥ 2 toxicities to be < 15% for 3D-CRT and < 6% for IMRT.

In outcomes analysis (Table 2, Figure 1), men in groups III to V had worse OS compared with group I; the significantly worse OS was present in groups IV and V, after controlling for covariates (Table 2, lower portion). Our findings are consistent with data from the United Kingdom, which revealed that T2DM was associated with a 23% increased risk of prostate cancer mortality (hazard ratio [HR], 1.23; 95% confidence interval [CI], 1.04-1.46) and a 25% increased risk in all-cause mortality (HR, 1.25; 95% CI, 1.11-1.40).[37] With respect to cancer-related outcomes, patients in groups II to IV did not have worse FFBF, FFDM, or CSS, before or after adjustment for covariates (Table 2, middle and lower portions, respectively).

Cancer-specific survival was worse for group V, and this might be because distant metastases are relatively common during the disease course of patients (occurring within 5-10 years of diagnosis), versus death from prostate cancer, which is relatively uncommon, occurring in < 5% to 10% of patients treated with RT.[36] Among all patients treated at our institution, almost all who died of prostate cancer were in group V; thus, the corresponding *P* value was low and the CIs were narrow. However, patients with distant metastases were scattered among the groups; thus, for group V, the *P* value was

Figure 2 Kaplan–Meier Curves of the Incidence of Late Genitourinary Toxicities, Grade 2 to 4 (Left); and Late Gastrointestinal Toxicities, Grade 2 to 4 (Right), Among the Type 2 Diabetes Mellitus (T2DM) Groups



Abbreviations: Diab = diabetes; Hx = history; Med = medication; OAHG = oral antihyperglycemic; RT = radiation therapy.

not as low, and CI was relatively wide. Additionally, it is possible that group V and patients with diabetes in general had more comorbidities and therefore received androgen deprivation therapy at a lesser rate (after adjusting for severity of disease) or for a shorter duration; this might also contribute to their apparent increase in cancer-specific mortality and biochemical recurrence rates.

Our findings are consistent with: (1) a Saskatchewan Health database study in which cancer patients with T2DM exposed to sulfonylureas and exogenous insulin had a significantly worse OS compared with patients exposed to metformin[38]; (2) a United Kingdom study, in which the use of metformin was not associated with a change in OS or CSS[39]; and (3) a Mount Sinai study, which revealed no effect of metformin on FFBF, CSS, or OS.[40] Our finding suggest that diabetes should be reported among randomized controlled trials of prostate cancer patients because this might affect outcomes and toxicities.[29]

The MSKCC experience[11] revealed that metformin might prevent the development of castrate-resistant disease. Our results support the hypothesis that insulin is a growth factor and promotes tumor progression, because patients who were receiving oral antihyperglycemic agents (with or without metformin) had improved outcomes compared with those receiving insulin. Thus, oral antihyperglycemic agents might abrogate the negative effect of advanced T2DM; however, hyperinsulinemia further fuels cancer progression.

The mechanisms by which hyperinsulinemia potentiates prostate cancer cell growth are under investigation and have overlap with those of increased obesity and adiposity.[6,41,42] For example, hyperinsulinemia causes a decrease in sex hormone-binding globulins, increasing free unbound androgens, which stimulate hormone-response cancers (eg, breast, prostate).[43,44] Diet-induced hyperinsulinemia accelerates tumor growth in prostate cancer xenograft models,[45] purportedly by increasing insulin receptor expression.[46] Additionally, insulin and IGF-I potentiate the PI3K (phosphoinositide 3-kinase)/Akt (Ak and thymoma)/mammalian target of rapamycin signaling cascade, which regulates cell growth, cell cycle progression, and angiogenesis.[4-6] Finally, diabetic angiopathy might cause tumoral hypoxia, which might stimulate hypoxia inducible factor 1α.[47]

Men receiving insulin had a 50% to 100% greater incidence of acute GU and GI toxicity, an eightfold increase in late GU complications, and a twofold increase in late GI complications (Table 3, lower portion). These results are similar to those of the University of Chicago; such patients had a 1.4 relative risk of Grade $\geq$ 2 GU toxicity.[48] Hypothetically, the presence of T2DM impairs leukocyte function, decreases phagocytosis, impairs bacterial killing, and impairs chemotaxis, thus decreasing host immunity.[49,50] RT also damages endothelial cells, denuding blood vessels, resulting in diminished blood flow and capillary necrosis.[51,52]

Our study has limitations. First, it is retrospective; thus, we might infer association but not causation. Second, we do not have exact start and stop times of medications; and, because 34% of our patients took medications before initiation of RT, we might have some immortal time bias, which was suggested[53] to be present in the MSKCC study.[11] We do not report analyses for immortal time bias because: (1) similar to the MSKCC analysis and subsequent comments of Spratt and colleagues,[54] only 5% of our patients took medications after initiation of RT; in comparison, the time on any event (ie, FFBF, FFDM, CSS) is relatively long (ie, > 10 years from BF to cancer-related mortality) in prostate cancer patients[55]; and (2) men who were receiving any medication did not have improved outcomes. Additionally, we did not evaluate outcomes and toxicities among other fractionation schedules (eg, hypofractionation,[56] stereotactic body RT[57,58]) or treatment modalities (eg, brachytherapy,[59] brachytherapy boost[26,28]), although we hypothesize that outcomes and toxicities of those patients would similarly be affected. Next, we do not have medication dose information. Finally, we do not have information regarding blood glucose concentrations or hemoglobin A1c values (which have been shown to be prognostic for pancreatic cancer[60]); these would have allowed a more robust statistical analysis.

Conclusion

Men with T2DM not receiving medication and men with T2DM receiving insulin have worse prostate cancer outcomes and toxicities than those without T2DM or those receiving oral antihyperglycemic agents. The type of oral antihyperglycemic (ie, presence or absence of metformin) used for control of T2DM might be minimally important for prostate cancer; rather, the development of hyperinsulinemia should be avoided.

Clinical Practice Points

- Type 2 diabetes mellitus is hypothesized to potentiate cancer cell growth and increase all-cause mortality among prostate cancer patients. This association is believed to be rooted on biological evidence of insulin and IGFs potentiating cancer cell growth and cell cycle progression and the clinical findings of increased all-cause mortality among diabetic patients compared with their nondiabetic counterparts.
- For men receiving RT for prostate cancer, those receiving insulin and those not receiving any medication have increased risk of death and toxicity than those without diabetes. The type of oral medication (ie, whether or not it contains metformin) is not as important as avoiding hyperinsulinemia (ie, either from nonmanagement of the disease or the use of insulin).
- Clinicians might use this information to optimally manage diabetes among prostate cancer patients. Additionally, because men not receiving medication and those receiving insulin have the worst outcomes and toxicities among all patients, they would be able to enroll these patients in proper clinical trials (ie, trials that focus on lifestyle management rather than more aggressive fractionation schemes, which might have worse toxicities).

Acknowledgments

This study was approved by the institutional review board, protocol number IRB 03-835. This study was approved by the appropriate ethics committee and has therefore was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent before their inclusion in the study. This is a retrospective analysis, and this article does not contain any studies with human subjects performed by any of the authors.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental tables and text accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clgc.2016.08.020.

References

1. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin* 2012; 62:220-41.
2. Barbieri CE, Bangma CH, Bjartell A, et al. The mutational landscape of prostate cancer. *Eur Urol* 2013; 64:567-76.
3. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care* 2010; 33:1674-85.
4. Song K, Shankar E, Yang J, Bane KL, Wahdan-Alaswad R, Danielpour D. Critical role of a survivin/TGF-beta/mTORC1 axis in IGF-I-mediated growth of prostate epithelial cells. *PLoS One* 2013; 8:e61896.
5. Aggarwal RR, Ryan CJ, Chan JM. Insulin-like growth factor pathway: a link between androgen deprivation therapy (ADT), insulin resistance, and disease progression in patients with prostate cancer? *Urol Oncol* 2013; 31:522-30.
6. Palmer JD, Soule BP, Simone BA, Zaorsky NG, Jin L, Simone NL. MicroRNA expression altered by diet: can food be medicinal? *Ageing Res Rev* 2014; 17:16-24.
7. Gong Y, Ma Y, Sinyuk M, et al. Insulin-mediated signaling promotes proliferation and survival of glioblastoma through Akt activation. *Neuro Oncol* 2016; 18:48-57.
8. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 2008; 300:2754-64.
9. de Beer JC, Liebenberg L. Does cancer risk increase with HbA1c, independent of diabetes? *Br J Cancer* 2014; 110:2361-8.
10. Ma J, Li H, Giovannucci E, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol* 2008; 9:1039-47.
11. Spratt DE, Zhang C, Zumsteg ZS, Pei X, Zhang Z, Zelefsky MJ. Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality. *Eur Urol* 2013; 63:709-16.
12. Margel D, Urbach DR, Lipscombe LL, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. *J Clin Oncol* 2013; 31:3069-75.
13. Mohler JL, Kantoff PW, Armstrong AJ, et al. Prostate cancer, version 1.2014. *J Natl Compr Canc Netw* 2013; 11:1471-9.
14. Zaorsky NG, Li T, Devarajan K, Horwitz EM, Buyyounouski MK. Assessment of the American Joint Committee on Cancer staging (sixth and seventh editions) for clinically localized prostate cancer treated with external beam radiotherapy and comparison with the National Comprehensive Cancer Network risk-stratification method. *Cancer* 2012; 118:5535-43.
15. Currie CJ, Poole CD, Jenkins-Jones S, Gale EA, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. *Diabetes Care* 2012; 35:299-304.
16. He XX, Tu SM, Lee MH, Yeung SC. Thiazolidinediones and metformin associated with improved survival of diabetic prostate cancer patients. *Ann Oncol* 2011; 22:2640-5.
17. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32:193-203.
18. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; 35:1364-79.
19. Pollack A, Hanlon AL, Horwitz EM, et al. Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. *Int J Radiat Oncol Biol Phys* 2006; 64:518-26.
20. Zaorsky NG, Harrison AS, Trabulsi EJ, et al. Evolution of advanced technologies in prostate cancer radiotherapy. *Nat Rev Urol* 2013; 10:565-79.
21. Zaorsky NG, Palmer JD, Hurwitz MD, Keith SW, Dicker AP, Den RB. What is the ideal radiotherapy dose to treat prostate cancer? A meta-analysis of biologically equivalent dose escalation. *Radiother Oncol* 2015; 115:295-300.
22. Zaorsky NG, Raj GV, Trabulsi EJ, et al. The dilemma of a rising prostate-specific antigen level after local therapy: what are our options? *Semin Oncol* 2013; 40:322-36.
23. Zaorsky NG, Yamoah K, Thakur ML, et al. A paradigm shift from anatomic to functional and molecular imaging in the detection of recurrent prostate cancer. *Future Oncol* 2014; 10:457-74.
24. Abramowitz MC, Li TN, Buyyounouski MK, et al. The phoenix definition of biochemical failure predicts for overall survival in patients with prostate cancer. *Cancer* 2008; 112:55-60.
25. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94:496-509.
26. Zaorsky NG, Doyle LA, Yamoah K, et al. High dose rate brachytherapy boost for prostate cancer: a systematic review. *Cancer Treat Rev* 2014; 40:414-25.
27. Zaorsky NG, Shaikh T, Murphy CT, et al. Comparison of outcomes and toxicities among radiation therapy treatment options for prostate cancer. *Cancer Treat Rev* 2016; 48:50-60.
28. Zaorsky NG, Den RB, Doyle LA, et al. Combining theoretical potential and advanced technology in high-dose rate brachytherapy boost therapy for prostate cancer. *Expert Rev Med Devices* 2013; 10:751-63.
29. Zaorsky NG, Egleston BL, Horwitz EM, et al. The missing pieces in reporting of randomized controlled trials of external beam radiation therapy dose escalation for prostate cancer. *Am J Clin Oncol* 2016; 39:321-6.
30. Kowall B, Stang A, Rathmann W, Kostev K. No reduced risk of overall, colorectal, lung, breast, and prostate cancer with metformin therapy in diabetic patients: database analyses from Germany and the UK. *Pharmacoepidemiol Drug Saf* 2015; 24:865-74.
31. Tsilidis KK, Capothanassi D, Allen NE, et al. Metformin does not affect cancer risk: a cohort study in the U.K. Clinical Practice Research Datalink analyzed like an intention-to-treat trial. *Diabetes Care* 2014; 37:2522-32.
32. Margel D, Urbach D, Lipscombe LL, et al. Association between metformin use and risk of prostate cancer and its grade. *J Natl Cancer Inst* 2013; 105:1123-31.
33. Chen YB, Chen Q, Wang Z, Zhou J. Insulin therapy and risk of prostate cancer: a systematic review and meta-analysis of observational studies. *PLoS One* 2013; 8:e81594.
34. Rastmanesh R, Hejazi J, Marotta F, Hara N. Type 2 diabetes: a protective factor for prostate cancer? An overview of proposed mechanisms. *Clin Genitourin Cancer* 2014; 12:143-8.
35. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; 70:1124-9.
36. Zaorsky NG, Keith SW, Shaikh T, et al. Impact of radiation therapy dose escalation on prostate cancer outcomes and toxicities. *Am J Clin Oncol*, Published online March 24, 2016. http://dx.doi.org/10.1097/COC.0000000000000285.
37. Bensimon L, Yin H, Suissa S, Pollak MN, Azoulay L. Type 2 diabetes and the risk of mortality among patients with prostate cancer. *Cancer Causes Control* 2014; 25:329-38.
38. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin: response to Farooki and Schneider. *Diabetes Care* 2006; 29:1990-1.
39. Bensimon L, Yin H, Suissa S, Pollak MN, Azoulay L. The use of metformin in patients with prostate cancer and the risk of death. *Cancer Epidemiol Biomarkers Prev* 2014; 23:2111-8.
40. Taira AV, Merrick GS, Galbreath RW, Morris M, Butler WM, Adamovich E. Metformin is not associated with improved biochemical free survival or cause-specific survival in men with prostate cancer treated with permanent interstitial brachytherapy. *J Contemp Brachytherapy* 2014; 6:254-61.
41. Wang LS, Murphy CT, Ruth K, et al. Impact of obesity on outcomes after definitive dose-escalated intensity-modulated radiotherapy for localized prostate cancer. *Cancer* 2015; 121:3010-7.
42. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. *Eur Urol* 2013; 63:800-9.
43. Jalving M, Gietema JA, Lefrandt JD, et al. Metformin: taking away the candy for cancer? *Eur J Cancer* 2010; 46:2369-80.
44. Zaorsky NG, Trabulsi EJ, Lin J, Den RB. Multimodality therapy for patients with high-risk prostate cancer: current status and future directions. *Semin Oncol* 2013; 40:308-21.
45. Venkateswaran V, Haddad AQ, Fleshner NE, et al. Association of diet-induced hyperinsulinemia with accelerated growth of prostate cancer (LNCaP) xenografts. *J Natl Cancer Inst* 2007; 99:1793-800.
46. Cox ME, Gleave ME, Zakikhani M, et al. Insulin receptor expression by human prostate cancers. *Prostate* 2009; 69:33-40.
47. Fraga A, Ribeiro R, Principe P, Lopes C, Medeiros R. Hypoxia and prostate cancer aggressiveness: a tale with many endings. *Clin Genitourin Cancer* 2015; 13:295-301.
48. Kalakota K, Liauw SL. Toxicity after external beam radiotherapy for prostate cancer: an analysis of late morbidity in men with diabetes mellitus. *Urology* 2013; 81:1196-201.

49. Meng MB, Wang HH, Cui YL, et al. Necroptosis in tumorigenesis, activation of anti-tumor immunity, and cancer therapy. *Oncotarget* 2016 Jul 12. http://dx.doi.org/10.18632/oncotarget.10548 [Epub ahead of print] Review.
50. Turina M, Fry DE, Polk HC Jr. Acute hyperglycemia and the innate immune system: clinical, cellular, and molecular aspects. *Crit Care Med* 2005; 33:1624-33.
51. Stone HB, Coleman CN, Anscher MS, McBride WH. Effects of radiation on normal tissue: consequences and mechanisms. *Lancet Oncol* 2003; 4:529-36.
52. Meng MB, Zaorsky NG, Deng L, et al. Pericytes: a double-edged sword in cancer therapy. *Future Oncol* 2015; 11(1):169-79.
53. Bensimon L, Suissa S, Azoulay L. Re: Daniel E. Spratt, Chi Zhang, Zachary S. Zumsteg, Xin Pei, Zhigang Zhang, Michael J. Zelefsky. Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality. Eur Urol 2013;63:709-16. *Eur Urol* 2013; 64:e28.
54. Spratt DE, Zhang Z, Zelefsky MJ. Reply to Leah Bensimon, Samy Suissa, and Laurent Azoulay's letter to the editor re: Daniel E. Spratt, Chi Zhang, Zachary S. Zumsteg, Xin Pei, Zhigang Zhang, Michael J. Zelefsky. Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality. Eur Urol 2013;63:709-16. *Eur Urol* 2013; 64:e29-30.
55. Zumsteg ZS, Spratt DE, Romesser PB, et al. The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. *Eur Urol* 2015; 67:1009-16.
56. Zaorsky NG, Ohri N, Showalter TN, Dicker AP, Den RB. Systematic review of hypofractionated radiation therapy for prostate cancer. *Cancer Treat Rev* 2013; 39:728-36.
57. Zaorsky NG, Studenski MT, Dicker AP, Gomella L, Den RB. Stereotactic body radiation therapy for prostate cancer: is the technology ready to be the standard of care? *Cancer Treat Rev* 2013; 39:212-8.
58. Zaorsky NG, Hurwitz MD, Dicker AP, Showalter TN, Den RB. Is robotic arm stereotactic body radiation therapy "virtual high dose ratebrachytherapy" for prostate cancer? An analysis of comparative effectiveness using published data [corrected]. *Expert Rev Med Devices* 2015; 12:317-27.
59. Zaorsky NG, Doyle LA, Hurwitz MD, Dicker AP, Den RB. Do theoretical potential and advanced technology justify the use of high-dose rate brachytherapy as monotherapy for prostate cancer? *Expert Rev Anticancer Ther* 2014; 14:39-50.
60. Lu Y, Garcia Rodriguez LA, Malgerud L, et al. New-onset type 2 diabetes, elevated HbA1c, anti-diabetic medications, and risk of pancreatic cancer. *Br J Cancer* 2015; 113:1607-14.

Supplemental Material

Supplemental Materials and Methods

Study Design. All patients had a history and physical examination including digital rectal examination, initial serum PSA level, and histologic confirmation of adenocarcinoma with a Gleason score, reviewed at our National Cancer Institute-designated comprehensive cancer center. T category was established using palpation findings only for 91% of the cohort; the remainder used additional radiographic imaging because of physician preference.

As part of their evaluation, men were specifically asked about their history of T2DM and any medications (including those for T2DM) on preappointment screening questionnaires (open-ended) and then again by members of the health care team. Questionnaires and consultation questions focused on the name of the T2DM (open-ended questions), and whether or not a man was receiving this medication before starting RT (ie, before the first fraction), during RT (ie, between the first and last fraction), or after RT (ie, after the last fraction). For example, if a patient stated he "currently" was receiving a medication (ie, within the past week) during RT, he had used it before RT, and discontinued it during the course of RT then he was counted as having used that medication before and during RT, but not after RT. We unfortunately do not have the start and end dates of medication use, so we cannot provide specific time intervals of medication use. We do not have complete data on blood glucose levels of hemoglobin A1c.

Patients typically had the exact name of the T2DM medications they were taking (either from recall or on a medication list), although most did not have the container of the medication. All medication names provided were queried in an electronic medical record database (which links to outside pharmacies and therefore provides generic and brand names of all drugs) at the time of initial consultation.

Comorbidities were obtained via patient self-report, as well as consultation notes from patient primary care physicians, referring physician (eg, urologists), and involved cardiologists and gastroenterologists. All patients need a biopsy (and sometimes magnetic resonance imaging, and placement of fiducial markers) before RT; thus, appropriate cardiac history from a cardiologist was mandatory. Similarly, gastroenterology records were mandatory. All comorbidities from records were integrated into our database and used in the analysis. We updated information regarding risk data over time during follow-up visits.

The techniques used for 3D-CRT and IMRT have been previously reported.[19] Briefly, patients were immobilized supine in a thermoplastic cast. The planning target volume included the prostatic fossa and a 1-cm margin for 3D-CRT and 8 mm for IMRT, except posteriorly where the margin was smaller to enable better rectal sparing. Daily prostate localization was performed in all patients using either fiducial markers with electronic portal imaging, computed tomography imaging, or radiofrequency beacons. The RT dose was prescribed such that 95% of the planning target volume received 100% of the prescribed dose. ADT, typically with leuprolide acetate, was prescribed at the discretion of the treating physicians, because this is typically recommended for high-risk patients.[40] Of all men, 26% received ADT.

Outcome Measures and Statistical Analysis. If interim PSA levels were missing, subsequent values were used. Patients lost to follow-up were censored. We did not test any interactions, and the assumptions of proportional hazards were tested for the competing risk and Cox models.

Patients who were lost to follow-up were followed until their last known date of contact. In addition to the information we have on patients from follow-up with our multidisciplinary team members (eg, urologic oncologists, medical oncologists, radiation oncologists), our hospital receives information on patient death from patients' primary care physicians (for patients who die outside of the hospital). We review all information on patients to determine the cause of death (ie, cancer vs. other causes).

For patient outcomes, the competing risk regression models adjusted for PSA (log transformed), Gleason score, T stage, and ADT. Cox proportional hazards methods were used to estimate HRs for overall mortality, adjusted for RT dose, RT technique (3D-CRT or IMRT), age at start of RT, treatment year, and comorbidities (heart disease, hypertension), in addition to the covariates included in the FFBF models. For toxicity, adjustments were made for ADT use, RT dose, 3D-CRT versus IMRT, heart disease and hypertension, accounting for the competing risk of death from any cause. We used logistic regression to estimate odds ratios for T2DM medication group use and acute toxicities (occurring during RT and within 3 months of RT), unadjusted and adjusted for hormone use, dose, heart disease and hypertension.

Supplemental Table 1 Type 2 Diabetes Mellitus Groups

Diabetes Group	I: No T2DM	II: Metformin	III: Nonmetformin OAHG	IV: Any Insulin	V: T2DM, No Medication
Criteria	• No diagnosis of T2DM on the basis of records from PCP, urologist, any other associated physician • No history of T2DM provided by patient • Not receiving T2DM medication	• Receiving metformin, or OAHG that contains metformin • Not receiving insulin	• Receiving OAHG that does not contain metformin • Not receiving insulin	• Receiving any injectable insulin • May be receiving OAHG as well	• Diagnosis of T2DM on the basis of records from PCP, urologist, any other associated physician, or provided by patient • Recommended medication, but not taking; or, "diet-controlled" (unknown)
Medications Permitted in Each Group					
Metformin	No	Yes	No	Yes, if receiving insulin	No
Sulfonylureas Dual Peroxisome proliferator-activated receptor delta agonists Meglitinides Thiazolidinediones Dipeptidyl peptidase-4 inhibitors α-Glucosidase inhibitors Sodium-glucose transport protein 2 inhibitors Bile acid sequestrants	No	Yes, if also receiving metformin	Yes, any combination of these drugs	Yes, if receiving insulin	No
Insulin	No	No	No	Yes	No
Examples of Drugs That Patients Might Be Taking	• NA	• Glucophage, Fortamet, Glumetza (metformin) • Janumet (metformin, sitagliptin) • Actoplus MET (metformin, pioglitazone)	• Januvia (sitagliptin) • Amaryl (glimepiride) • Glucotrol (glipizide) • Avandia (rosiglitazone) • Onglyza (saxagliptin) • Prandin (repanglinide) • Starlix (nateglinide)	• Humalog • Humulin • Lantus • Novalog	• NA

Abbreviations: OAHG = oral antihyperglycemic; PCP = primary care provider; T2DM = type 2 diabetes mellitus.

Supplemental Table 2 **Radiation Therapy Oncology Group GU and GI Toxicities**

Grade	0	1	2	3	4
GU	None	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency and dysuria Severe generalized telangiectasia (often with petechiae) Frequent hematuria Reduction in bladder capacity (<150 cc)	Necrosis/contracted bladder (capacity <100 cc) Severe hemorrhagic cystitis
GI	None	Mild diarrhea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/perforation Fistula

Abbreviations: GI = gastrointestinal; GU = genitourinary.