Original Study

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

Nicholas G. Zaorsky,[1] Talha Shaikh,[1] Karen Ruth,[2] Pankaj Sharda,[3] Shelly B. Hayes,[1] Mark L. Sobczak,[1] Mark A. Hallman,[1] Marc C. Smaldone,[4] David Y.T. Chen,[4] Eric M. Horwitz[1]

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

[1]Department of Radiation Oncology
[2]Biostatistics and Bioinformatics Facility
[3]Department of Endocrinology
[4]Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA

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Address for correspondence: Nicholas G. Zaorsky, MD, Department of Radiation Oncology, Fox Chase Cancer Center, 333 Cottman Ave, Philadelphia, PA 19111
Fax: 215-214-4038; e-mail contact: nicholaszaorsky@gmail.com

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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% ($P < .0001$),