Original Study

Association Between Androgen Deprivation Therapy and Patient-reported Depression in Men With Recurrent Prostate Cancer

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Abstract

A multivariate analysis of men with recurrent prostate cancer was conducted to determine whether patient-reported depression differed when stratified by treatment. The receipt of androgen deprivation therapy (ADT) was associated with a threefold greater risk of depression compared with radiation alone. Radical prostatectomy was not associated with a greater risk. Physicians should discuss depression as a possible side effect of ADT and screen patients receiving ADT.

Background: Previous studies have reported conflicting results on the relationship between androgen deprivation therapy (ADT) and the risk of depression. We assessed whether ADT is associated with depression in a unique data set of men with recurrent prostate cancer. **Patients and Methods:** We studied a cohort of 656 men in the prospective COMPARE (Comprehensive, Multicenter, Prostate Adenocarcinoma) registry who experienced biochemical recurrence after radiation therapy (RT) only, radical prostatectomy (RP) with or without RT, or ADT with RP or RT. Multivariable logistic regression was used to determine the relationship between the modality of treatment and patient-reported depression. **Results:** Of 656 men, 44 (6.7%) experienced depression. The prevalence of depression stratified by treatment was 3.2% for RT only, 5.9% for RP with or without RT, and 9.1% for ADT plus RP or RT. Compared with RT-only, ADT plus RP or RT was associated with a significantly increased rate of depression ($P = .031$) and RP with or without RT was not ($P = .195$). On multivariate analysis adjusting for age and baseline comorbidities, the receipt of ADT was associated with an increased risk of depression (odds ratio, 3.29; 95% confidence interval, 1.11-9.76; $P = .032$) compared with RT only. No statistically significant difference was found in the risk of depression for men who received RP with or without RT versus RT only (odds ratio, 2.12; 95% confidence interval, 0.68-6.65; $P = .19$). **Conclusion:** Men with recurrent prostate cancer who underwent ADT were 3 times more likely to report experiencing depression. Treating physicians should discuss depression as a possible side effect when considering the use of ADT and should screen for depression in men who have received ADT.

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Introduction

Prostate cancer is the most common noncutaneous malignancy for men in the United States.[1] The National Cancer Institute has estimated that prostate cancer will have been diagnosed in ~161,360 new patients in 2017.[2] Patients with a new diagnosis of prostate cancer can choose between active surveillance and a variety of interventions, including radical prostatectomy (RP), brachytherapy, external beam radiation therapy (RT), and androgen

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deprivation therapy (ADT). Although the severity and burden of disease will guide the management of the tumor, men will heavily weigh the potential adverse effects of each treatment with their physicians as they choose a preferred plan.[3,4] The long-term post-treatment expectancy of these men make adverse effects a significant determinant of their quality of life.[5]

The long-term side effect profile of ADT has continued to evolve. Although the increased risk of sexual dysfunction and fractures in men treated with ADT is well established, ADT has recently been implicated in increasing the risk of neurocognitive dysfunction.[6-8] However, several studies have reported conflicting results on the association between ADT and depression, with some studies showing an increased risk of depression and others finding no association.[8-13] To help clarify whether such an association exists, we sought to identify a potential association between patient-reported depression and the type of treatment men with prostate cancer had received in a novel cohort.

Patients and Methods

Study Cohort

The COMPARE (Comprehensive, Observational, Multicenter, Prostate Adenocarcinoma) registry enrolled 1129 men with biochemical recurrence after primary treatment for localized prostate cancer from 150 geographically diverse sites in the United States from February 2004 to March 2007.[14] Men of any age presenting with an increasing prostate-specific antigen (PSA) level after treatment of primary nonmetastatic prostate adenocarcinoma were eligible. An increase in PSA level was defined by protocol using the following criteria: (1) an increase of $\geq$ 0.2 ng/mL on repeated testing after RP; or (2) 2 increases greater than the nadir, with a PSA value $\geq$ 50% greater than the nadir and a minimal PSA value of $\geq$ 0.2 ng/mL greater than the post-RT nadir. The exclusion criteria included ongoing treatment of prostate cancer and have been thoroughly detailed previously.[14]

To be included in the present study, the men must have had complete demographic data, treatment data, and data on their perceived experience of depression as assessed by a physician- or patient-completed questionnaire available. All patients must have completed definitive therapy, including RT alone (brachytherapy or external beam RT), RP with or without RT, or adjuvant ADT after RP or RT. A total of 656 men met the inclusion criteria and constituted the study cohort.

Data Collection and Outcomes

Patients' perception of whether they were depressed was assessed by a physician-completed questionnaire on entry into the registry at the time of biochemical recurrence. Physicians were asked "Does the patient have any other complaints" and given a list of symptoms that included depression. For each item, the physicians marked whether the patient had reported depression and noted the severity of the patient's experience, which was listed as "mild," "moderate," or "severe." The responses to the question about depression were dichotomized into "yes" or "no" for the purposes of our analysis, regardless of the severity.

Physicians assessed and documented each patient's comorbidities in the physician questionnaire on entry into the registry. The present study divided the comorbidities into noncardiovascular and cardiovascular comorbidities. The noncardiovascular comorbidities included hypertension, stroke, amputation, diabetes, problems with circulation, chronic obstructive pulmonary disease, asthma, emphysema, ulcers (stomach), inflammatory bowel disease, renal disease, and seizures. Cardiovascular comorbidities were limited to myocardial infarction, congestive heart failure, angina, and chest pain.

Statistical Analysis

A univariate analysis comparing the rate of depression by treatment type (RT alone, RP with or without RT, or ADT plus RT or RP) was conducted using a χ^2 test.[15] Firth's penalized maximum likelihood estimation was then used as a multivariate analysis to determine whether the treatment type was associated with depression, after adjusting for age and comorbidity.[16] This method allowed us to compare the effect of other treatment types to RT alone. Multivariate logistic regression analysis was used to determine whether patient-reported depression was associated with treatment type, after adjusting for age at treatment and comorbidities. We conducted a sensitivity analysis on this model by also controlling for T stage (T1 vs. T2 vs. T3-T4) and Gleason score (6 vs. 7 vs. $\geq$ 8) of the patients' primary tumor. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were computed for the covariates, and $P < .05$ was used as the cutoff to indicate statistical significance. SAS, version 9.3, software (SAS Institute, Cary, NC) was used for all calculations.

Results

Patient Baseline Characteristics

In the COMPARE registry, 656 men surveyed at the time of biochemical recurrence had complete information available on patient-reported depression and were included in the study cohort. The demographic and baseline information is presented in Table 1. No significant difference was found in the baseline characteristics and demographic data of the men who were included and excluded from the cohort. Of the 656 men, with a median time to recurrence of 5.4 years, 129 (20%) were aged < 60 years, 507 (77%) were aged 60 to 80 years, and 20 (3%) were aged > 80 years. Of the 656 patients, 269 (41%) had undergone RP with or without RT as definitive treatment of prostate cancer, 124 (19%) had undergone RT alone, and 263 (40%) had undergone ADT plus RT or RP. Most men had noncardiovascular comorbidities (n = 276 of 656; 42.1%); 217 (33.1%) had cardiovascular comorbidities, and 163 (24.8%) had no comorbidities.

Association of Patient-reported Depression With Treatment

Of the 656 patients, 44 (6.7%) with biochemical recurrence of prostate cancer reported experiencing depression. The prevalence of patient-reported depression by treatment type was 3.2% (4 of 124) for patients who had undergone RT alone, 5.9% (16 of 269) for patients who had undergone RP with or without RT, and 9.1% (24 of 263) for patients who had undergone ADT plus (RT or RP; Figure 1). The ADT with RT or RP group was associated with significantly more complaints of depression ($P = .031$) compared with the RT group alone. The patients who received RP with or without RT also tended to report depression at a lower rate than the