Original Study

Duration of Androgen Deprivation Therapy for High-Risk Prostate Cancer: Application of Randomized Trial Data in a Tertiary Referral Cancer Center

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Abstract

We evaluated the patterns of androgen deprivation therapy (ADT) use for high-risk prostate cancer at a tertiary referral cancer center. Genitourinary oncology specialists tended to prescribe longer course ADT after the 2008-2009 trial publications supporting long-course ADT. However, specialists have continued to weigh the risks and benefits of ADT: 49.4% of patients diagnosed starting in 2010 received shorter course ADT, most often because of side effects, comorbidities, or age.

Introduction: We evaluated the incidence and predictors of the use of long-term (2-3 years) versus shorter term androgen deprivation therapy (ADT) in radiation-managed men with high-risk prostate cancer. **Patients and Methods:** We identified 302 patients from the Dana-Farber Cancer Institute patient registry who had been diagnosed with high-risk prostate cancer (T3a or prostate-specific antigen [PSA] $>$ 20 ng/mL or Gleason score 8-10) from 1993 to 2015. We assessed the intended duration of ADT and used multivariable Cox regression to evaluate the predictors of receiving a shorter course of ADT than recommended by the guidelines ($<$ 2 years). **Results:** The course of ADT intended by physicians increased after the 2008/2009 publication of trials showing the superiority of long-term versus short-term ADT, with 43.5% intending $\geq$ 2 years before versus 61.4% after ($P = .014$). Starting in 2010, 49.4% of patients actually received $<$ 2 years of ADT. The most common reasons for receipt of shorter course ADT were intolerance of ADT side effects, patient comorbidity/age, the presence of T3a on magnetic resonance imaging only as the sole high-risk feature, or participation in a clinical trial. Moderate to severe comorbidity assessed using the Adult Comorbidity Evaluation-27 (adjusted hazard ratio [AHR] = 2.94), Gleason score $<$ 8 (AHR = 5.66), and PSA $<$ 20 ng/mL (AHR = 4.19) all predicted for receipt of shorter course ADT ($P < .05$ for all). **Conclusion:** In a tertiary-care setting, the rates of long-course ADT for high-risk disease have increased since the 2008/2009 trials supporting its use. However, approximately one half of patients continued to receive shorter course ADT, often because of intolerance of side effects, underlying comorbidity, or physician judgment about the aggressiveness of the disease.

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Introduction

The National Comprehensive Cancer Network (NCCN) guidelines currently recommend 2 to 3 years of androgen deprivation therapy (ADT) for patients diagnosed with high-risk prostate cancer.[1] These guidelines are based mainly on the results of 2 randomized trials, Radiation Therapy Oncology Group (RTOG) 92-02 and European Organization for Research and Treatment of Cancer (EORTC) 22,961, published in 2008 and 2009, that demonstrated the cancer-specific and overall survival benefits of 28 to 36 months of ADT versus 4 to 6 months for locally advanced disease.[2,3] Before 2010, before these trials were published, the NCCN guidelines recommended either 4 to 6 months or 2 to 3 years of ADT.[4]

Despite the potential survival benefit, many side effects are associated with ADT use, including weight gain, decreased muscle mass, fatigue, sexual dysfunction, and hot flashes.[5] Also, data have suggested that ADT increases the risk of cardiovascular events, although this issue remains controversial.[5-9] Nevertheless, these concerns could justifiably compel physicians to recommend a shorter course of ADT than is recommended in the high-risk setting. Alternatively, patients might choose to discontinue the drug early if the decreased quality of life due to the side effects or the concern for cardiovascular toxicity outweighs the potential survival advantage of long-course ADT. However, it is unknown what effect the publication of the RTOG and EORTC randomized trial results had on the ADT prescribing patterns of physicians and what the rate of discontinuation is among patients with high-risk disease.

In the present study, we used an institutional cohort from a tertiary care clinic specializing in genitourinary oncology to determine the prescribing patterns of ADT for patients with high-risk prostate cancer before and after the 2008-2009 publications of the randomized trials supporting long-course ADT. In addition, we assessed the reasons and predictors for receipt of shorter course ADT starting in 2010.

Patients and Methods

Patient Population and Outcome Variables

Using an institutional database (Prostate CRIS),[10] we identified 302 patients diagnosed with high-risk prostate cancer defined per the NCCN guidelines as T3a (assessed from physician documentation, usually determined by digital rectal examination or magnetic resonance imaging [MRI]), prostate-specific antigen (PSA) $>$ 20 ng/mL, or Gleason score 8 to 10 between 1993 and 2015 who were seen at the Dana-Farber Cancer Institute's Lank Center for Genitourinary Oncology and had undergone external beam radiation therapy. Patients were excluded if they had N1 or M1 disease. The baseline patient and disease characteristics, including age, PSA level, biopsy Gleason score at diagnosis, and clinical stage, were extracted from the database. All patients were evaluated and treated by medical oncologists and radiation oncologists specifically specializing in genitourinary oncology. Using the physician consultation notes from an electronic medical record, we identified the duration of ADT intended by the medical oncologist at or within 4 months of diagnosis and determined whether the patients had completed their course. We assessed the level of patient comorbidity using the Adult Comorbidity Evaluation-27 (ACE-27) score, a validated instrument that captures the level of comorbidity for patients with newly diagnosed cancer.[11] ACE-27 scores of 0, 1, 2, and 3 signify minimal, mild, moderate, and severe comorbidity, respectively. We determined the duration of ADT received as the time between the first injection of a luteinizing hormone-releasing hormone agonist to the last injection, plus the duration of coverage from the last injection (eg, 3 months from 22.5 mg of leuprolide acetate depot). For patients who received $<$ 2 years of ADT after the 2009 publication of the EORTC 22961 trial, we identified the reasons for the receipt of shorter course ADT using the clinic notes from the follow-up appointments. All patients provided written informed consent, and the Dana-Farber Cancer Institute institutional review board approved the present study.

Statistical Analysis

We determined the proportion of patients who had been scheduled to receive a course of $\leq$ 6 months, 7 to 23 months, and $\geq$ 24 months of ADT after diagnosis and other clinical factors at baseline. For subsequent analyses, shorter course ADT was considered any duration $<$ 24 months. To account for slight variations in the exact duration that can occur owing to timing the ADT injections around holidays, appointments, and patient convenience, we rounded up the duration of ADT of the patients who had completed $>$ 23 months. The analysis of the intended duration of ADT was stratified by the date of diagnosis relative to the 2008 and 2009 publications of randomized trials that supported the use of long-course ADT in this population. For this analysis, patients diagnosed between the 2 trial publication dates were excluded. When analyzing which patients actually received shorter course ADT, patients were included only if they had been diagnosed starting in 2010, when the NCCN guidelines were updated to recommend long-course ADT for all high-risk patients.

The patient characteristics were compared by era of diagnosis using χ^2 tests. The intended duration of use was also compared by era using a χ^2 test. Multivariable logistic regression was used to evaluate which clinical factors predicted a shorter than intended duration of ADT, including the era of diagnosis (before May 2008 vs. after June 2009), patient age at diagnosis ($\leq$ 65 vs. $>$ 65 years), T stage ($\leq$ T2 vs. T3a), Gleason score ($\leq$ 7 vs. 8-10), PSA level at diagnosis ($<$ 20 vs. $\geq$ 20 ng/mL), and comorbidity status at diagnosis (ACE-27 minimal to mild vs. moderate to severe). For the patients diagnosed starting in 2010, the Kaplan-Meier method was used to estimate the duration of ADT actually received, and multivariable Cox regression, including patient age, T stage, Gleason score, PSA level, and comorbidity status, was used to determine which clinical factors predicted an increased risk of receiving less ADT.

Results

Patient and Disease Characteristics at Diagnosis

Of the 302 patients in the cohort, 239 (79.1%) were diagnosed from 1993 to 2009 and 63 (20.9%) were diagnosed from 2010 to 2015. Most patients had Gleason score 8 to 10 disease (241 [79.8%]) and a PSA level $<$ 10 ng/mL (166 [55.0%]). All the characteristics are listed in Table 1.

Intended Duration of ADT Increased After 2008-2009 Trial Publications

We had 251 patients (83.1%) for whom we could determine the intended duration of ADT. Compared with the era before the May 2008 publication of the RTOG 92-02 trial, more patients with high-risk prostate cancer were scheduled for $\geq$ 2 years of ADT after the June 2009 publication of the EORTC 22961 trial (Figure 1; $P = .014$). In earlier years (before May 2008), 63 patients (46.7%) were scheduled for 6 months of ADT, 15 (10.9%) for 7 to 23