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Platinum Priority – Prostate Cancer

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Patterns of Declining Use and the Adverse Effect of Primary Androgen Deprivation on All-cause Mortality in Elderly Men with Prostate Cancer

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Abstract

Background: Primary androgen deprivation therapy (pADT) is commonly used to treat elderly men diagnosed with localized prostate cancer (CaP), despite the lack of evidence supporting its use.
Objective: To examine the effect of pADT on mortality and to assess contemporary trends of pADT use in elderly men with CaP.
Design, setting, and participants: Men older than 65 yr residing in Surveillance, Epidemiology, and End Results (SEER) registry areas diagnosed with localized or locally advanced CaP between 1992 and 2009 and not receiving definitive therapy.
Outcome measurements and statistical analysis: Propensity score (PS)-weighted Cox proportional hazards models were used to estimate the effect of pADT use on overall survival among patients receiving pADT. The interaction between comorbidity-adjusted life expectancy (LE) and pADT use was assessed within the Cox and PS-weighted models. Contemporary (2004–2009) trends for pADT use were analyzed by linear regression.
Results and limitations: The primary cohort included 46 376 men, of whom 17 873 received pADT (39%). Patients with >10 yr LE had lower pADT utilization rates than patients with short LE. Between 2004 and 2009, the use of pADT in men with localized CaP decreased by 14% (from 36% to 22%). Relative to observation, pADT was associated with a survival disadvantage, with a hazard ratio for all-cause mortality of 1.37 (95% confidence interval 1.20–1.56). Limitations included biases not accounted for by the PS-weighted model, changes in CaP staging over the study period, the absence of prostate-specific antigen (PSA) data prior to 2004, and the limits of retrospective analysis to demonstrate causality.
Conclusions: The use of pADT in elderly men with localized CaP has decreased over time. For men forgoing primary definitive therapy, the use of pADT is not associated with a survival benefit compared to observation, and denies men an opportunity for cure with

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definitive therapy. The deleterious effect of pADT is most pronounced in men with prolonged LE.

Patient summary: In this report, we assessed the effect of primary androgen deprivation (pADT) on prostate cancer mortality and determined current trends in the use of pADT. We showed that use of pADT in men aged >65 yr with localized prostate cancer has decreased over time. We also found that pADT is detrimental to men with localized prostate cancer, and particularly men with longer life expectancy. Therefore, we conclude that ADT should not be used as a primary treatment for men with prostate cancer that has not spread beyond the prostate.

1. Introduction

Androgen deprivation therapy (ADT), achieved through disruption of the hypothalamic-pituitary-gonadal axis with either surgical or medical castration, has been the mainstay of treatment for metastatic prostate cancer (mCaP) since the 1940s. The dependence of CaP on circulating androgens was first elaborated by Huggins and Hodges [1] and by a series of randomized controlled trials between 1960 and 1975, which strengthened the role of immediate ADT in the treatment of mCaP [2].

The use of adjuvant ADT in the management of localized CaP has been widely examined and there are several indications for ADT in this setting supported by level I evidence and clinical guidelines [3]. For example, ADT as an adjunct to radiation therapy in men with high risk localized or locally advanced disease [4–6] is associated with increased cancer-specific and overall survival. Limited evidence also supports the use of ADT in men with lymph node metastases at radical prostatectomy (RP) [7]. However, the use of primary ADT (pADT) for localized CaP is largely unsupported by clinical guidelines [3], and has been associated with no survival advantage over observation [8]. Despite the lack of data supporting the treatment of localized CaP with pADT, its use became exceedingly common as an alternative to radiation therapy (RT) or RP. Between 1989 and 2000, pADT was used in 20.4% of men with localized CaP in a large study of community and academic urologists [9].

Concerns over the possible misuse of ADT alone in the treatment of CaP and a growing awareness of its potential harms [10–14] led to changes in Medicare reimbursement policies for ADT in 2004 and were associated with subsequent decreasing pADT use in men aged >65 yr with localized disease [15].

While prior studies have demonstrated the absence of a survival benefit for men aged >65 yr undergoing treatment with pADT [8], we hypothesize that the adverse impacts of ADT may be more pronounced in men with longer life expectancy (LE) at the initiation of treatment, because they would likely be exposed to a longer duration of ADT and possible treatment-related sequelae. Therefore, our primary study objective was to examine the effect of pADT on mortality in men stratified according to LE. Second, we sought to assess the contemporary trends for pADT use, expecting that the downward trend for pADT use reported in previous studies would continue as clinicians develop a broader understanding of the lack of efficacy of pADT and a growing understanding of its harmful effects.

2. Patients and methods

2.1. Population sources

The current study relied on the most recent release of the Surveillance, Epidemiology, and End Results (SEER)-Medicare insurance program linked database. The SEER registries cover approximately 28% of the US population with Medicare administrative data. Medicare insurance includes approximately 97% of Americans aged ≥65 yr. Linkage to the SEER database is complete for approximately 93% of cases [16].

2.2. Study population

Our study comprised men residing in SEER regions diagnosed with localized and locally advanced CaP (T1, T2, T3) between 1992 and 2009 who did not receive local therapy (RP or RT) in the year following diagnosis. Patients were excluded from evaluation if they had stage IV or unknown stage CaP, metastatic disease, more than one cancer diagnosis, incomplete demographic data, absence of both part A and B of Medicare (without HMO coverage), or underwent RP or RT within 1 yr of CaP diagnosis. The final study cohort comprised 46 376 men, 61% of whom underwent observation and 39% of whom underwent ADT (beginning within the first year following diagnosis). Ascertainment of treatment selection was performed using previously published methodology [17,18].

2.3. Covariates

For each patient, age at diagnosis, year of diagnosis, race, population density, marital status, 2000 census tract percentage with 4-yr college education, 2000 census tract annual median income, region, and tumor stage and grade were assigned using the SEER data. The Charlson comorbidity index (CCI) was derived from Medicare claims 1 yr prior to CaP diagnosis, and categorized as 0, 1, 2, and ≥3 using a previously validated algorithm [19]. Before 2003, Gleason grades of 2–4, 5–7, and 8–10 corresponded to well-differentiated, moderately differentiated, and poorly differentiated disease, respectively. Thereafter, a Gleason grade of 2–4, 5–6, and 7–10 corresponded to well-differentiated, moderately differentiated, and poorly differentiated CaP. Clinical extension information provided by SEER was used to determine cancer stage (T1, T2, T3).

Finally, the patients were stratified into three clinicopathologic risk groups. Risk group 1 consisted of localized (T1/T2) low-risk disease (well and moderately differentiated); risk group 2 consisted of localized (T1/T2) high-risk disease (poorly differentiated); and risk group 3 consisted of locally advanced (T3) disease of any grade.