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Platinum Priority – Prostate Cancer

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Does Primary Androgen-Deprivation Therapy Delay the Receipt of Secondary Cancer Therapy for Localized Prostate Cancer?

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Abstract

Background: Despite evidence that shows no survival advantage, many older patients receive primary androgen-deprivation therapy (PADT) shortly after the diagnosis of localized prostate cancer (PCa).
Objective: This study evaluates whether the early use of PADT affects the subsequent receipt of additional palliative cancer treatments such as chemotherapy, palliative radiation therapy, or intervention for spinal cord compression or bladder outlet obstruction.
Design, setting, and participants: This longitudinal population-based cohort study consists of Medicare patients aged ≥66 yr diagnosed with localized PCa from 1992 to 2006 in areas covered by the Surveillance Epidemiology and End Results (SEER) program. SEER-Medicare linked data through 2009 were used to identify the use of PADT and palliative cancer therapy.
Outcome measurements and statistical analysis: Instrumental variable analysis methods were used to minimize confounding effects. Confidence intervals were derived from the bootstrap estimates.
Results and limitations: This study includes 29 775 men who did not receive local therapy for T1–T2 PCa within the first year of cancer diagnosis. Among low-risk patients (Gleason score 2–7 in 1992–2002 and Gleason score 2–6 in 2003–2006) with a median age of 78 yr and a median follow-up of 10.3 yr, PADT was associated with a 25% higher use of chemotherapy (hazard ratio [HR]: 1.25; 95% confidence interval [CI], 1.08–1.44) and a borderline higher use of any palliative cancer treatment (HR: 1.07; 95% CI, 0.97–1.19) within 10 yr of diagnosis in regions with high PADT use compared with regions with low PADT use. Because this study was limited to men >65 yr, the results may not be applicable to younger patients.
Conclusions: Early treatment of low-risk, localized PCa with PADT does not delay the receipt of subsequent palliative therapies and is associated with an increased use of chemotherapy.

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1. Introduction

Prostate cancer (PCa) is the most common nonskin cancer and the second most common cause of cancer death among American men. Because of the widespread use of prostate-specific antigen (PSA) screening, most contemporary patients are diagnosed with localized (T1–T2) PCa [1]. Standard treatment options include surgery, radiation therapy, or active surveillance (ie, deferral of treatment until evidence of progression). Although not supported by any major groups or guidelines, primary androgen-deprivation therapy (PADT) is often initiated shortly after diagnosis as primary treatment of localized PCa, especially in older men [2].

The use of androgen deprivation therapy as an adjunct to radiation therapy for men with high-risk or locally advanced (T3) disease has been shown to improve survival [3,4]. Unfortunately, for men with low-risk disease, the early use of PADT [2,5] or Casodex [6] has been shown to worsen disease-specific and overall survival in the majority of men. Early use of PADT carries significant morbidity, including a 10–50% increase in the risks of fracture, diabetes, weight gain, hot flashes, decreased muscle tone, impotence, coronary heart disease, myocardial infarction, and sudden cardiac death [7–10]. Androgen-deprivation therapy (ADT) not only is associated with numerous treatment-related complications and more severe decline in physical well-being but also is costly [11].

The purpose of this manuscript is to address the question of whether the early use of PADT is beneficial by delaying the receipt of subsequent palliative therapies such as chemotherapy, radiation therapy, or surgical intervention.

2. Materials and methods

2.1. Data sources

Data for this study were obtained from the Surveillance Epidemiology and End Results (SEER) program and linked Medicare files. The Medicare database covers approximately 97% of US persons aged ≥65 yr, and linkage to the SEER database is complete for approximately 93% of the patients [12]. This study has been approved by the Institutional Review Board at the University of Medicine and Dentistry of New Jersey.

2.2. Study participants

The study cohort consisted of men (aged ≥66 yr) who were residents of the SEER areas existing before 2001 and were diagnosed with T1–T2 PCa in 1992–2006 (n = 189 460). We excluded men who died within 1 yr of cancer diagnosis (n = 7253); had other cancers diagnosed before their PCa (n = 18 155); or had surgery, radiation therapy, or chemotherapy within 1 yr of diagnosis (n = 104 797). To ensure that the database accurately documented a patient's clinical course and comorbidity, patients not fully covered by Medicare 1 yr before and 1 yr after cancer diagnosis were excluded (n = 25 430). We also excluded men with unknown health service area (HSA) (n = 809), men with unknown cancer grade (n = 2411), and men who received ADT before cancer diagnosis (n = 830).

2.3. Primary androgen-deprivation therapy

Men who received ADT as primary cancer therapy (eg, no surgery or radiation therapy) within 1 yr of diagnosis were defined as receiving PADT, regardless of whether they subsequently received surgery or radiation therapy >1 yr after diagnosis. Patients who received no therapy within 1 yr of diagnosis were defined as receiving surveillance. Utilizing a previously described algorithm, we reviewed Medicare physician, inpatient, and outpatient claims to identify orchiectomy (Healthcare Common Procedure Coding System [HCPCS] codes 54520, 54521, 54522, 54530, or 54535 or International Classification of Diseases, 9th Revision, code 624) and the use of luteinizing hormone–releasing hormone agonists (HCPCS codes J0128, J1950, J3315, J9202, J9217, J9218, J9219, or J9225) [7].

2.4. Study end points and covariates

In this study, palliative therapy included palliative radiation therapy, chemotherapy, treatment of bladder outlet obstruction, and treatment of spinal cord compression that occurred >1 yr after cancer diagnosis. *Palliative external-beam radiation therapy* was defined as external-beam irradiation that consisted of <20 fractions within a 6-wk period without brachytherapy (pers. comm., A. Zietman, Boston, MA, USA). Chemotherapy was identified from the HCPCS codes published in the literature and by the authors (Appendix 1) [13]. Treatment of bladder outlet obstruction (transurethral resection of the prostate, nephrostomy, or cycstotomy) and treatment of spinal cord compression are defined in Appendix 1. Charlson scores, a powerful predictor of longevity in men with localized PCa, were derived from Medicare inpatient, outpatient, and physician claims during the year prior to PCa diagnosis using a validated algorithm [14]. We used clinical extension information provided by SEER to determine cancer stage (T1, T2). For patients diagnosed in 2003–2006, low risk included those men with Gleason score 2–6 disease. For patients diagnosed in 1992–2002, low risk included those men with Gleason score 2–7 disease, because Gleason scores 5–7 were grouped together during this period. Patients who did not have low-risk cancer were grouped in the high-risk category. We analyzed the data by year of diagnosis (1992–2002 and 2003–2006) and found the patterns of outcomes to be consistent. Accordingly, only the combined results are presented in the study.

2.5. Instrumental variable analysis

Treatment effects estimated from observational studies are often biased because of patient selection. Recently, instrumental variable analysis (IVA), a method of capturing the random component of patient treatment choice, has been applied successfully in several medical studies to mimic the results of randomized trials [15]. We selected HSA, defined as one or more counties that are relatively self-contained with respect to the provision of routine hospital care, as our instrumental variable. The instrumental variable was constructed by first calculating the proportion of patients who received PADT in each HSA. Because some HSAs had small numbers of PCa cases, each HSA with <50 cases was combined with the nearest HSA (in terms of distance between geographic centers) with ≥50 cases. The threshold of ≥50 cases was chosen because lower thresholds were associated with more imbalances in patient characteristics in high- and low-PADT utilization areas. The algorithm produced 48 utilization areas for men with low-risk disease and 30 utilization areas for men with high-risk disease. High- and low-use areas corresponded to the top and bottom tertiles of PADT utilization and were used as the (binary) instrumental variable. Patients who differ in the likelihood of receiving PADT were compared, and the treatment effect on the "marginal" population was calculated as

$$\text{IV Estimate} = \Delta = \frac{\text{Adjusted Outcomes}_{\text{Hi}} - \text{Adjusted Outcomes}_{\text{Lo}}}{\Pr(\text{PADT}|\text{Hi}) - \Pr(\text{PADT}|\text{Lo})}$$

where the following definitions are used: IV, instrumental variable; Hi, a geographic area in the upper tertile of PADT use; Lo, a geographic area in the lower tertile of PADT use. The terms are thus: Pr(PADT|Hi/Low)