Questioning the 10-year Life Expectancy Rule for High-grade Prostate Cancer: Comparative Effectiveness of Aggressive vs Nonaggressive Treatment of High-grade Disease in Older Men With Differing Comorbid Disease Burdens

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OBJECTIVE To determine if the 10-year rule should apply to men with high-grade, clincially localized prostate cancer, we characterized the survival benefits of aggressive (surgery, radiation, brachytherapy) over nonaggressive treatment (watchful waiting, active surveillance) among older men with differing comorbidity at diagnosis.

METHODS We sampled 44,521 men older than 65 with cT1–2, poorly differentiated prostate cancer diagnosed in 1991-2007 from the Surveillance, Epidemiology, and End Results-Medicare database. We used propensity-adjusted, competing-risks regression to calculate 5- and 10-year cancer mortality among those treated aggressively and nonaggressively across comorbidity subgroups. We determined 5- and 10-year absolute risk reduction in cancer mortality and numbers needed to treat to prevent one cancer death at 10 years.

RESULTS In propensity-adjusted, competing-risks regression analysis, aggressive treatment was associated with significantly lower risk of cancer mortality for those with Charlson scores of 0 (sub-hazard ratio (SHR) 0.43, 95% confidence interval [CI] 0.39-0.47), 1 (SHR 0.48, 95% CI 0.40-0.58), and 2 (SHR 0.46, 95% CI 0.34-0.62) but not 3+ (SHR 0.68, 95% CI 0.44-1.07). Absolute reductions in cancer mortality between those treated aggressively and nonaggressively were 7%, 5.5%, 6.9%, and 2.5% at 5 years, and 11.3%, 7.9%, 8.6%, and 2.8% at 10 years for men with Charlson scores of 0, 1, 2, and 3+ , respectively; numbers needed to treat to prevent 1 cancer death at 10 years were 9, 13, 12, and 36 men.

CONCLUSION The 10-year rule may not apply to men with high-grade, clinically localized disease. Older men with Charlson scores ≤2 should consider aggressive treatment of such disease due to its substantial short-term cancer survival benefits. UROLOGY 93: 68–76, 2016. © 2016 Elsevier Inc.

When deciding whether to pursue definitive local therapy for clinically localized prostate cancer, older men must weigh the apparent survival benefits associated with treatment against the likelihood that they will die of something other than prostate cancer. Older men with multiple comorbidities and low- or intermediate-risk prostate cancer have minimal (if any) benefit from aggressive therapy[1,2] and high rates of other-cause mortality within 10 years,[3-5] so the balance of competing risks greatly favors conservative management. This is reflected in national guidelines, which recommend against aggressive treatment of clinically localized disease for men

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with less than 10-year life expectancies,[6-8] widely known as the "10-year rule."

However, the 10-year rule may not apply to men with high-risk prostate cancer. Men with high-risk disease have much higher rates of cancer mortality within 5-10 years if left untreated,[9] so the balance of competing risks may favor aggressive treatment, even for older men with multiple comorbidities. Randomized controlled trials have shown benefit for aggressive over nonaggressive treatment for high-risk disease,[10] but these trials were underpowered to assess survival benefits among comorbidity subgroups. Guidelines for treatment of men with high-risk disease and limited life expectancy are vague as a result of the lack of data: American Urological Association and European Association of Urology guidelines make no distinction for tumor risk in application of the 10-year rule[6,7]; and National Comprehensive Cancer Network guidelines do not incorporate life expectancy into treatment pathways for men with high-risk disease.[8] Individual physicians are therefore left to use their best judgment in deciding whom to treat and whom not to treat, which may result in undertreatment of potentially lethal disease.[11]

To help older patients with high-risk disease better understand competing-risks trade-offs, we sought to quantify the longitudinal survival benefits associated with aggressive treatment of clinically localized, high-grade disease for older men with differing comorbidity burdens at diagnosis. We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data to define the 5- and 10-year absolute risk reduction in cancer mortality associated with aggressive treatment across comorbidity subgroups as well as the number needed to treat to save 1 life at 10 years. We hypothesized that significant survival benefits of aggressive over nonaggressive treatment would be seen early after treatment and that the number needed to treat to save 1 cancer death would be relatively low. Such a finding would call into question the applicability of the 10-year rule for men with high-risk disease.

METHODS

Study Population

We identified men aged >65 years with incident prostate cancer (International Classification of Diseases (ICD)-9 code 185.0) diagnosed between January 1, 1992 and December 31, 2007 using the SEER-Medicare database. This database contains Medicare insurance program files linked to the population-based SEER cancer registries. The Medicare database covers approximately 97% of US persons aged >65 years, and SEER regions encompass approximately 14% of the US population before 2000 and 25% thereafter. Our cohort included only men with poorly differentiated T1 or T2 tumors. We excluded men with T3, T4, and metastatic tumors. We intentionally excluded men with locally advanced and metastatic disease because the current guidelines for application of the 10-year rule only apply to men with clinically localized disease.

Predictor and Outcome Definitions

Sociodemographic Data. We determined sociodemographic information including age at diagnosis, race, marital status, year of diagnosis, and zip code of residence using SEER data from the Patient Entitlement and Diagnosis Summary File of the Medicare dataset.

Comorbidity. Comorbidity burden at diagnosis was ascertained using both inpatient (Medicare Provider Analysis and Review (MEDPAR) Part A and Carrier Part B files) and outpatient claims information for the 12-month period preceding prostate cancer diagnosis. Comorbidity was assessed using the Deyo-Klabunde modification of the Charlson comorbidity index, a validated method of determining Charlson scores using inpatient and outpatient claims data.[12,13] We grouped men by Charlson scores of 0, 1, 2, and 3+ .

Tumor Data. Tumor data including tumor pathology, stage, and histologic grade were obtained using SEER data. We limited our analysis to men with prostatic adenocarcinoma (ICD-9 code 185.0). We used extent-of-disease (EOD) codes corresponding to the American Joint Committee on Cancer 6th edition definitions to define clinical tumor stage as T1 (EOD codes 13-15), T2 (EOD codes 24-29), or T1–T2 (EOD codes 30-34,40,41,48,49). Poorly differentiated tumor grade was defined using ICD for Oncology, Third Edition (ICD-O-3) codes (Gleason score 8-10, ICD-O-3 code 81403/3). Of note, after 2003, SEER coded men with Gleason scores of 7 to the poorly-differentiated code 81403/3. We performed a sensitivity analysis excluding men diagnosed after 2003 to confirm our findings in a group that was exclusively Gleason ≥8.

Type of Treatment. Type of treatment was identified by ICD-9 and Current Procedural Terminology-4 codes within the MEDPAR, National Claims History, and Outpatient files of the Medicare dataset, as previously described.[1] Treatment was categorized as aggressive or nonaggressive. Aggressive treatment was defined as radical prostatectomy, radiation therapy, or brachytherapy within the first year after diagnosis. Nonaggressive treatment was defined as watchful waiting, active surveillance with or without treatment, or immediate or delayed androgen deprivation therapy. Watchful waiting was defined as no aggressive treatment per MEDPAR claims within the first year after diagnosis and no use of prostate-specific antigen (PSA) testing or transrectal ultrasound-guided rebiopsy during the period of follow-up. Active surveillance was defined by use of PSA testing or transrectal ultrasound-guided rebiopsy following diagnosis without aggressive treatment per MEDPAR claims within 1 year of diagnosis. Immediate and/or delayed androgen deprivation therapy was defined as treatment with androgen deprivation or bilateral orchiectomy within and/or after 1 year of diagnosis per MEDPAR claims.

Survival and Cause of Death. Overall survival was defined as the date of diagnosis to the date of death as deter-