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Original article

External beam radiotherapy with or without androgen deprivation therapy in elderly patients with high metastatic risk prostate cancer

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Abstract

Objective: Several randomized controlled trials have documented significant overall survival benefit in high metastatic risk prostate cancer (PCa) patients treated with combination of androgen deprivation therapy (ADT) at radiotherapy (RT) relative to RT alone. Unfortunately, elderly patients are either not included or are underrepresented in these trials. In consequence, the survival benefit of combination of ADT at RT in the elderly warrants detailed reassessment, including its cost.

Methods: Between 1991 and 2009 within the Surveillance Epidemiology and End Results (SEER)-Medicare-linked database, we identified 3,692 patients aged 80 years or more with clinical T1–T2 PCa and WHO histological grade 3, or clinical T3–T4 PCa and any histological grade, treated with or without combination of ADT at RT. Competing risks analyses focused on cancer-specific mortality (CSM) and other-cause mortality, after accounting for confounders. All analyses were repeated in patients with no comorbidity and in most contemporary patients, treated between 2001 and 2009. Finally, we assessed median annual cost according to use of combination of ADT at RT, after adjusting for patient and tumor characteristics.

Results: In competing-risks multivariable analyses, no statistically significant difference was observed in CSM and other-cause mortality between patients treated with or without combination of ADT at RT. Same results were recorded in subgroup analyses of patients with no comorbidity and in most contemporary patients. The median annual costs of $36,140 and of $47,510 were recorded, respectively in patients treated without and with ADT at RT.

Conclusion: Our findings failed to confirm that combination of ADT at RT reduces CSM rates in high metastatic risk PCa patients aged 80 years or more. Moreover, combination of ADT at RT resulted in a significant cost increase, relative to RT alone.

Keywords: Cost; Elderly patients; High metastatic risk; Prostate cancer; RT with ADT; Survival

1. Introduction

Contemporary guidelines recommend the use of combined external beam radiation therapy (RT) with androgen deprivation therapy (ADT) in men with high metastatic risk prostate cancer (PCa) [1–3]. However, most randomized

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controlled trials [4–7] substantiating these guidelines included few, if any, elderly patients within their testing cohorts. Based on the paucity of elderly patients in such trials [4–7], it is debatable whether their findings, as well as the guidelines [1–3] that are based on such trials, are applicable to the elderly. Based on this consideration, we decided to examine RT rates, delivered with or without ADT in elderly patients, within the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Our study had 3 specific objectives. First, we examined cancer-specific mortality (CSM). Here, we postulated that the combination of ADT at RT will exert a protective effect on CSM. Moreover, we hypothesized that other-cause mortality (OCM) will be unaffected by the addition of ADT. Finally, we examined the cost increase related to the treatment of high metastatic risk PCa patients with combination of ADT at RT vs. RT alone.

2. Materials and methods

2.1. Data source and study population

The current study relied on the 1991 to 2009 SEER-Medicare insurance program-linked database with follow-up updated until December 31st, 2011 [8].

Between 1991 and 2009, we identified patients aged ≥80 years with histologically confirmed PCa at prostate biopsy (International Classification of Disease for Oncology [ICD-O] site code 61.9, histologic code 8140). Patients not enrolled in Medicare part A and part B claims, and with a health maintenance organization enrollment throughout the duration of the study, were excluded. Patients were not included if PCa was metastatic, diagnosed at autopsy or on death certificate only or if PCa was not their first malignant disease.

For the present study, we exclusively focused on the original Bolla et al. [4,7] definition of patients with high metastatic risk: patients with clinical T1–T2 PCa and WHO histological grade 3 (G3) or clinical T3–T4 PCa and any histological grade. Active treatment was defined using Common Procedural Terminology, fourth edition (CPT-4), Healthcare Common Procedure Coding System (HCPCS) and International Classification of Disease-Ninth Revision (ICD-9) codes for RT and ADT (Supplementary Table).

To qualify for inclusion, patients needed to receive treatment that consisted of either first-line RT alone or first-line RT combined with concomitant, adjuvant ADT, within 6 months from PCa diagnosis. ADT was defined as GnRH agonist with or without antiandrogens. The final population was represented from 3,692 assessable high metastatic risk PCa patients aged 80 years or more.

2.2. Variable definition

Patient characteristics included age at diagnosis, year of diagnosis, race, marital status, United States (US) regions (Midwest, Northeast, South and West—according to the US Census Bureau), population density. Socioeconomic status (SES) was defined according to 3 county-attribute variables (income, education, and poverty levels) and patients were stratified in 2 groups (high vs. low) according to the median value of the SES, as previously described [9,10]. Comorbidities were identified by classifying inpatient and outpatients claims for the 12-month interval preceding PCa diagnosis into 15 categories [11]. Tumor characteristics included clinical stage (T1, T2, T3, and T4) and WHO histological grade (well differentiated vs. moderately differentiated vs. poorly differentiated).

2.3. Outcomes

The primary endpoint of interest was CSM, which was defined as PCa death (ICD-9 185.9 or ICD-10 C619). The secondary endpoint was OCM, which was defined as death from other causes [12]. The third endpoint was cost related to PCa treatment, based on all Medicare reimbursements related to PCa diagnostic code (185) for the 12 initial months following diagnosis, during each calendar year of the study (1991–2009). Code 185 allowed to identify amounts paid by Medicare for inpatient, outpatient, and physician services related to PCa diagnosis. Expenditures consisted of individual reimbursements.

2.4. Statistical analyses

Our main analyses consisted of 6 steps. First, cumulative incidence plots were constructed to graphically depict 10-year CSM and OCM rates according to treatment type (RT alone vs. combination of ADT at RT). Presence of statistically significant differences in mortality rates were examined with the Gray test [13]. To protect patient confidentiality, only survival outcomes recorded at 10 years of follow-up were reported, according to National Cancer Institute regulations.

Second, multivariable competing-risks analyses were performed to test the effect of treatment type on CSM and OCM, after accounting for confounders and competing cause of mortality [14]. Based on requirements of SEER Medicare administration, we adjusted our model for individual comorbidities, where at least 10 events were recorded (Table 1).

Third, the same analyses were repeated in subgroups of patients with (A) no comorbidity and (B) most contemporary patients, namely individuals identified between 2001 and 2009.

Fourth, we performed power analyses [15] aimed to test whether the sample size available for analyses was sufficient to detect an absolute difference of 5% or 10% in CSM or OCM at 10 years of follow-up, between the 2 treatment groups, for an $\alpha = 0.05$ and a $\beta = 0.1$.

Fifth, we relied on 1:1 propensity score matching to account and to adjust for potential baseline differences in