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Prostate Cancer Death After Radiotherapy or Radical Prostatectomy: A Nationwide Population-based Observational Study

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Abstract

Background: There are no conclusive results from randomized trials on radiotherapy (RT) versus radical prostatectomy (RP) for prostate cancer. Numerous observational studies have suggested that RP is associated with a lower risk of prostate cancer death, but whether results have been biased due to limited adjustments for confounding factors is unknown.
Objective: To compare the risk of prostate cancer death after RT versus RP.
Design, setting, and participants: Nationwide population-based observational study of men in the Prostate Cancer data Base Sweden 3.0 who had undergone RT or RP between 1998 and 2012.
Outcome measurements and statistical analysis: Prostate cancer deaths were compared. Hazard ratios (HRs) were calculated in Cox regression models, including clinical T stage, M stage, Gleason grade group, serum levels of prostate-specific antigen, proportion of biopsy cores with cancer, mode of detection, comorbidity, age, educational level, and civil status. Period analysis with left truncation was performed.
Results and limitations: Primary treatment was RT or RP for 41 503 men. Treatment effect was associated with disease severity. In univariate analysis of RT versus RP, risk of prostate cancer death was higher after RT—low- and intermediate-risk cancer, HR 1.82 (95% confidence interval [CI]: 1.53–2.16), and high-risk cancer, HR 1.57 (95% CI: 1.33–1.85). After full adjustment in period analysis, this difference between the treatments was attenuated—low- and intermediate-risk cancer, HR 1.24 (95% CI: 0.97–1.58), and high-risk cancer, HR 1.03 (95% CI: 0.81–1.31). Confounding remained due to nonrandom allocation to treatment.
Conclusions: In comparison with previous studies, the difference in prostate cancer mortality after RT and RP was much smaller.

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Patient summary: The difference in prostate cancer mortality after contemporary radiotherapy and radical prostatectomy was small in contrast to previous studies, indicating that potential side effects should be more emphasized when selecting treatment.

1. Introduction

Radiotherapy (RT) and radical prostatectomy (RP) are both evidence-based treatments for nonmetastatic prostate cancer (Pca) that decreased Pca mortality compared with noncurative treatment in randomized clinical trials [1,2]. Recently, results from Prostate Testing for Cancer and Treatment, the first randomized clinical trial comparing RT, RP, and active monitoring, were reported [3]. After 10 yr of follow-up, there was no statistically significant difference in cancer-specific survival after RP versus RT, but there were only four deaths from Pca after RT and five after RP. In a meta-analysis of previous observational studies, the adjusted risk for Pca death was twice as high after RT compared with RP [4].

Men treated with RT generally have worse cancer characteristics than those treated with RP, and they are also generally older and have more comorbidities, which may affect the probability of receipt of secondary cancer treatment if disease recurrence occurs [5]. Despite adjustment for covariates to decrease confounding, there remains concern for residual confounding in these previous observational studies comparing RT with RP.

The aim of this study was to provide risk estimates to inform contemporary treatment decision for men with nonmetastatic prostate cancer. We used data in a national population-based prostate cancer registry combined with data from other health care registries and demographic databases that are almost complete. To obtain the most up-to-date risk estimates, we used period analyses to overcome issues regarding incomplete data, misclassification of bone metastasis, and subpar treatment that were present in the early study period.

2. Patients and methods

The study cohort included men in the National Prostate Cancer Register (NPCR) of Sweden diagnosed between January 1, 1998 and December 31, 2012 with Pca in clinical local stage T1c-T3 or Tx, any Gleason grade group (GGG), serum levels of prostate-specific antigen (PSA) <l00 ng/ml, no verified lymph node metastases (N0 or Nx), and no verified bone metastases (M0 or Mx), and treated with primary RT or RP [6].

NPCR captures 98% of all Pca cases in the Swedish Cancer Registry, to which registration is mandated by law [7]. The registration to NPCR has recently been described in detail [7,8]. In brief, NPCR contains information on the date of diagnosis, tumor stage, biopsy Gleason grading, serum PSA level, mode of detection, and executed or planned primary treatment. For men diagnosed before 2008, an audit (Retrospective collection of data on Radiotherapy; RetroRad) collected data from RT dose verification systems at oncological departments throughout Sweden [9]. RPs registered in NPCR were verified by data obtained by linkage to the National Patient Registry. Since 2007, prostate volume, total number of cores obtained at the diagnostic biopsy session, number of cores containing cancer, and extent of cancer in millimeters in all cores combined are registered. For men diagnosed during 1998–2007, data on proportion of cores containing cancer were retrieved from histopathology reports for 14 609 men (74% capture rate).

As previously described, NPCR has been linked to other nationwide population-based health care registries and demographic databases in the Prostate Cancer data Base Sweden (PCBaSe) [7,9]. The National Patient Registry contains information on in-patient care including surgical procedures and discharge diagnoses, coded according to International Classification of Diseases system (ICD-9 or ICD-10) since 1987. Using data on discharge diagnoses for the 10 yr preceding the Pca diagnosis, men were classified into four comorbidity categories according to the Charlson comorbidity index (CCI) [10]. For assessment of socioeconomic status, we used data on civil status and educational level, categorized as low (≤9 yr of school), middle (10–12 yr), and high (≥13 yr).

2.1. Statistical analyses

Inclusion started on January 1, 1998, and follow-up started on the date of surgery for RP and date of start of RT and ended at the date of emigration, date of death, or December 31, 2014, whichever event came first. Cox proportional hazard models with age as time scale were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) [11,12].

Analyses was stratified by two different risk score assessments, National Comprehensive Cancer Network (NCCN) and Cancer of the Prostate Risk Assessment (CAPRA) [13,14]. A Wald test for the interaction between risk category and treatment was performed [15].

Definitions of the modified version of NCCN risk categorization are as follows: for low risk: clinical local stage T1–T2, PSA <10 ng/ml and GGG 1 [16]; intermediate risk: T1–T2 with PSA level 10–20 ng/ml and/or GGG 2 or 3; and high risk: T3 and/or PSA level 20–99 ng/ml and/or GGG 4 or 5. We combined the low- and intermediate-risk categories because we anticipated that there would be very few events in the low-risk category.

CAPRA is a prognostic model with scores from 0 to 10, based on age, PSA, GGG, clinical stage, and percent of biopsy cores with cancer.

To diminish influence from earlier time periods when data quality was poor and to obtain the most representative estimates for the outcome of contemporary RT and RP, period analysis was performed [17]. Period analysis is based on the results from left truncation. We applied left truncation on January 1, 2011. Therefore, depending on date of treatment, our period analysis includes different 4 yr of follow-up for each man. For example, men treated in 2012 contribute with person-years and events to years 0–3, men treated in 2011 contribute to years 1–4, men treated in 2010 contribute to years 2–5, and so on back until men treated in 1998, who contributed to years 13–16 of the total person time.

The models were built stepwise including clinical T stage (T1c, T2, T3), M stage (M0, Mx), GGG (1–5), serum PSA (using linear spline with knots at PSA 3, 10, 20, and 50 ng/ml), interaction between PSA and GGG [18], proportion of biopsy cores with cancer (continuous), mode of detection (screening, lower urinary tract symptoms, other symptoms), CCI (0, 1, 2, 3+), educational level (low, middle, high), and civil status (married, not married). N stage was not included as a covariate, since N

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