available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

Association of Radical Local Treatment with Mortality in Men with Very High-risk Prostate Cancer: A Semiecologic, Nationwide, Population-based Study

Pär Stattin[a,b,*], *Fredrik Sandin*[c], *Frederik Birkebæk Thomsen*[d], *Hans Garmo*[c,e], *David Robinson*[b,f], *Ingela Franck Lissbrant*[g], *Håkan Jonsson*[h], *Ola Bratt*[i,j]

[a] *Department of Surgical Sciences, Uppsala University, Uppsala, Sweden;* [b] *Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University Hospital, Umeå, Sweden;* [c] *Regional Cancer Centre Uppsala Örebro, Uppsala University Hospital, Uppsala, Sweden;* [d] *Copenhagen Prostate Cancer Center, Department of Urology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark;* [e] *King's College London, School of Medicine, Division of Cancer Studies, Cancer Epidemiology Group, London, UK;* [f] *Department of Urology, Ryhov Hospital, Jönköping, Sweden;* [g] *Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden;* [h] *Department of Radiation Sciences, Umeå University, Umeå, Sweden;* [i] *Department of Translational Medicine, Division of Urological Cancer, Lund University, Lund, Sweden;* [j] *CamPARI Clinic, Department of Urology, Cambridge University Hospitals, Cambridge, UK*

Article info

Article history:
Accepted July 15, 2016

Associate Editor:
James Catto

Keywords:
Prostate cancer
Very high-risk
Radical
Treatment
Semiecologic
Nationwide
Population-based
PCBaSe

Abstract

Background: Current guidelines recommend androgen deprivation therapy only for men with very high-risk prostate cancer (PCa), but there is little evidence to support this stance.
Objective: To investigate the association between radical local treatment and mortality in men with very high-risk PCa.
Design, setting, and participants: Semiecologic study of men aged <80 yr within the Prostate Cancer data Base Sweden, diagnosed in 1998–2012 with very high-risk PCa (local clinical stage T4 and/or prostate-specific antigen [PSA] level 50–200 ng/ml, any N, and M0). Men with locally advanced PCa (local clinical stage T3 and PSA level <50 ng/ml, any N, and M0) were used as positive controls.
Intervention: Proportion of men who received prostatectomy or full-dose radiotherapy in 640 experimental units defined by county, diagnostic period, and age at diagnosis.
Outcome measurements and statistical analysis: PCa and all-cause mortality rate ratios (MRRs).
Results and limitations: Both PCa and all-cause mortality were half as high in units in the highest tertile of exposure to radical local treatment compared with units in the lowest tertile (PCa MRR: 0.51; 95% confidence interval [CI], 0.28–0.95; and all-cause MRR: 0.56; 95% CI, 0.33–0.92). The results observed for locally advanced PCa for highest versus lowest tertile of exposure were in agreement with results from randomized trials (PCa MRR: 0.75; 95% CI, 0.60–0.94; and all-cause MRR: 0.85; 95% CI, 0.72–1.00). Although the semiecologic design minimized selection bias on an individual level, the effect of high therapeutic activity could not be separated from that of high diagnostic activity.
Conclusions: The substantially lower mortality in units with the highest exposure to radical local treatment suggests that radical treatment decreases mortality even in men with very high-risk PCa for whom such treatment has been considered ineffective.
Patient summary: Men with very high-risk prostate cancer diagnosed and treated in units with the highest exposure to surgery or radiotherapy had a substantially lower mortality.

* Corresponding author. Department of Surgical Sciences, Uppsala University, Uppsala, Sweden.
Tel. +46 73 620 52 51; Fax: +46 090 12 53 96.
E-mail address: par.stattin@umu.se (P. Stattin).

http://dx.doi.org/10.1016/j.eururo.2016.07.023

1. Introduction

There is no randomized controlled trial (RCT), to our knowledge, on the effect of radical local treatment in men with prostate cancer (PCa) in the "gray zone" between locally advanced and metastatic PCa. This risk category is often referred to as very high-risk PCa and is defined by local invasion into adjacent organs or very high levels of serum prostate-specific antigen (PSA) together with negative imaging findings for metastasis [1–4]. The prognosis is poor, and radical local treatment has generally not been considered beneficial, as the local tumor often is too advanced to eradicate and there is a high likelihood of undetected micrometastases. Consequently, clinical guidelines recommend androgen deprivation therapy (ADT) only for men with very high-risk PCa [1,2]. The only studies on radical local treatment for men with very high-risk PCa are small and retrospective [4–10]. These studies reported longer survival in men who underwent radical prostatectomy or full-dose radiotherapy than in men who received ADT only. The comparisons of treatment effects in observational studies are hampered by selection bias because most patients selected for radical local treatment have less adverse cancer characteristics than patients not receiving that treatment. Even if prognostic factors such as stage, grade, and PSA level are included in the analysis, there will be residual confounding in observational studies based on an analysis of treatment exposure on an individual level [11].

The use of radical local treatment for very high-risk PCa has varied during the past 15 years between Swedish counties, which are geographically well-defined administrative units providing health care to the entire population in their catchment area. This provided a natural experiment, allowing us to investigate the association of radical local treatment with mortality from very high-risk PCa in a semiecologic study in which the effects of selection bias for exposure to treatment on an individual level were minimized and comprehensive individual-level data on cancer characteristics, treatment, and outcome could still be used.

There is consistent evidence from RCTs that radiotherapy combined with ADT improves survival of men with locally advanced PCa [12–17]. To assess the validity of our results for very high-risk PCa, we also investigated the association between radical local treatment for locally advanced PCa and mortality with the same method as a positive control. The plausibility of our observations for the treatment effect on very high-risk PCa would be strengthened if we observed an association between radical local treatment of locally advanced PCa and mortality similar to the effect reported from the RCTs.

The aim of this study was to assess the association between radical local treatment and mortality in men with very high-risk PCa by relating exposure to radical local treatment on a population level in experimental units, defined by county, period, and age at diagnosis, to mortality from PCa and all causes using comprehensive individual-level data on cancer characteristics, treatment, and outcome.

2. Methods

Prostate Cancer data Base Sweden (PCBaSe) 3.0 contains information obtained from the National Prostate Cancer Register (NPCR) of Sweden on cancer characteristics at diagnosis and on primary treatment [18–20]. PCBaSe also includes information on comorbidity, assessed by the Charlson Comorbidity Index (CCI) based on discharge diagnosis from the Patient Registry; education level, income, and marital status from the LISA database; and cause and date of death obtained from the Cause of Death Registry [21–25]. The study population within PCBaSe for this study included men aged <80 yr of age diagnosed in 1998–2012 with very high-risk PCa (T4 and/or PSA level 50–200 ng/ml, any N, and M0). To assess the validity of our method, we separately studied the association of local treatment and mortality in men with locally advanced PCa (local clinical stage T3 and PSA level <50 ng/ml, any N, and M0). Registration in NPCR does not distinguish clinical local stage T3a from T3b.

The following variables in PCBaSe were used: age, year of PCa diagnosis, mode of detection, clinical local tumor stage, N stage, PSA level, Gleason score, CCI, educational level, marital status, primary registered treatment in NPCR, and county of residence. Gleason grade was grouped according to the five-tier Gleason grading groups [26,27]. NPCR includes comprehensive information on radiotherapy since 2008; for men diagnosed before 2008, data were retrieved directly from oncological radiotherapy information systems and local databases in oncology departments on type of radiotherapy, treatment time, total dose, and fractions in RetroRad (Retrospective Registration of Radiotherapy, a nation wide audit) [28]. There are currently 20 counties in Sweden, and a large majority of health care including diagnostic and therapeutic activity for PCa is provided in the county of residence of the patient within a tax-financed equal access system. The study was approved by the Research Ethics Board at Umeå University.

2.1. Statistical methods

Exposure was measured as the proportion of men who received primary radical local treatment, that is, radical prostatectomy or full-dose radiotherapy with or without ADT within 1 yr of diagnosis, for very high-risk and locally advanced PCa in 640 experimental units based on diagnostic county, 2-yr diagnostic periods (plus 2012), and age at diagnosis (<65, 65–69, 70–74, and 75–79 yr). For each experimental unit, the person-years at risk from date of diagnosis until death, emigration, or end of study period (December 31, 2013), whichever event came first, were calculated. In a Poisson model, the logarithm of person-years at risk was used as offset; the numbers of PCa-related deaths and deaths from any cause were used as outcome. Results are presented as mortality rate ratio (MRR) with 95% confidence intervals (CIs) for exposure in tertiles and continuous as a restricted cubic spline. The models included county as a categorical variable, year of diagnosis as a continuous variable, median Gleason grade groups as a