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Review article

Review of the comparative effectiveness of radical prostatectomy, radiation therapy, or expectant management of localized prostate cancer in registry data

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Abstract

Summary: Evidence regarding the effectiveness of treatment for prostate cancer is primarily based on randomized controlled trials. Long-term outcomes are generally difficult to evaluate within experimental studies and may benefit from large pools of observational data. We conducted a systematic review of administrative and registry studies to evaluate the comparative effectiveness of treatment for clinically localized prostate cancer on overall and prostate-cancer specific mortality.

Materials and Methods: In accordance with the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P, 2015), we conducted a systematic search of Ovid Medline and Embase (1946–February 2017) and identified studies that evaluated the relationship between types of treatment for localized prostate cancer and mortality. Additional articles were identified through manual search. Randomized, prospective, and single institution studies were excluded. The risk of bias for each study was evaluated with the Newcastle Ottawa scale. Multivariable adjusted hazard ratios were reported to evaluate overall and cancer-specific mortality.

Results: We screened 4,721 studies and included for review, 19 that were published between 2001 and 2015. The pooled population included 228,444 patients. Countries of origin included the United States, Canada, China, Switzerland, the Netherlands, and Sweden, and the sources included administrative ($n = 6$) and cancer registry or prostate databases ($n = 11$). Overall and cancer-specific mortality were lowest among definitive treatment arms as compared to conservative therapy with no treatment, observation, or active surveillance. Radiotherapy was associated with worse overall and cancer-specific mortality than radical prostatectomy.

Conclusion: Although observational studies using large, population-based cohorts have the potential for bias, we found consistent evidence that high-quality observational studies may be used to evaluate the comparative effectiveness of prostate cancer treatment. Methodologic limitations of observational data should be considered.

Keywords: Prostatic neoplasms; Prostate Cancer; Treatment; Mortality; Observational; Systematic Review

1. Introduction

Prostate cancer is the most common solid-organ malignancy and the third leading cause of cancer-related death in men [1]. Over 90% of disease is clinically localized. Goals of localized prostate cancer treatment are to prevent death and disability while minimizing treatment-related complications. Treatment selection is complicated by the equivocal risks and benefits of curative treatment, making this a patient preference-sensitive decision [2]. Interventions range from no treatment, to active surveillance (AS) with intent to intervene with progression of low-risk disease, or to definitive treatment with radiotherapy (RT) or radical prostatectomy (RP) [3,4].

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Although 3 landmark randomized controlled trials (RCTs) regarding prostate cancer treatment efficacy and outcomes have been performed [5–7], RCTs in general have suffered from high cost, nonrepresentative populations, difficulty enrolling and retaining patients, and changing technology or treatment patterns. These complicate the interpretation of long-term results [8,9], and treatment efficacy of localized prostate cancer remains inconclusive. In the Scandinavian Prostate Cancer Group Trial #4 (SPCG-4; 695 men randomized to RP or watchful waiting (WW) between 1989 and 1999; reported to 18 y) [5] RP was shown to have lower overall mortality (OM) and prostate cancer specific mortality (PCSM). This relationship was not found in the Prostate Cancer Intervention versus Observation Trial (PIVOT; 731 men randomized to RP or observation between 1994 and 2002 in the United States; reported to 18 y) [7]. The only RCT comparing 3 contemporary treatment modalities is Prostate Testing for cancer and Treatment (ProtecT; 1,643 men randomized to RP, RT, or AS between 1999 and 2009 in the United Kingdom; reported to 10 y); this study lacked statistical power and found no significant mortality difference among treatments [6].

In part, owing to the limitations of RCTs examining the treatment of localized prostate cancer, there has been a profusion of epidemiological and outcome studies from large administrative, cancer registry, and institutional datasets in the past 2 decades. Such databases can identify large cohorts of patients, allowing for the observation of correlations between patient characteristics, comparative effectiveness of various therapies, and longitudinal outcomes in large, diverse populations. Nevertheless, critics warn that observational studies should be interpreted cautiously given imperfect data collection and the presence of important biases [10,11]. This review compares 3 management modalities—RT, RP, and no treatment (observation, AS, WW)—for clinically localized prostate cancer within large, population-based administrative and registry data in order to evaluate the status and comparative effectiveness of contemporary treatment.

2. Material and methods

We used preferred reporting items for systematic reviews and meta-analysis protocols 2015 for reporting this systematic review [12].

2.1. Population and exposure

We reviewed studies on men who had a first diagnosis of localized prostate cancer. Exposure included commonly used treatment modality with curative intent including: RP, RT (including external beam RT, intensity-modulated RT, brachytherapy), and AS [4]. Owing to uncertainty regarding administrative and registry data inclusion of AS, exposure was also planned to include management by WW/AS and observation. Studies evaluating primary exposure with nonstandard, neoadjuvant or adjuvant, salvage, or androgen deprivation therapies were excluded.

2.2. Outcome variables

The primary outcome was PCSM. The secondary outcomes were overall/all-cause mortality (OM). Because prostate cancer mortality is susceptible to patient (e.g., age, race, comorbidity) and disease (prostate-specific antigen [PSA], Gleason score, clinical stage) characteristics [13,14], studies that reported only unadjusted outcomes were excluded. Included studies performed multivariable analysis, and treatment effect was measured with adjusted hazard ratios (HRs) from Cox proportional hazards regression models. Studies were included that directly compared effectiveness of RP, RT, or AS/ WW/ observation, as well as those that reported an adjusted mortality HR. Biochemical recurrence was not evaluated as a secondary outcome owing to the low prediction value for eventual PCSM [15], as well as the large variation in definitions among many studies [16].

2.3. Data sources and study selection

Ovid Medline and EMBASE databases were searched from database inception (earliest 1946) to March 18, 2017 for keywords, titles, and text-words including the following terms: “prostate cancer,” “prostate neoplasm,” “radical prostatectomy,” “prostate cancer surgery,” “radiotherapy,” “active surveillance,” “watchful waiting,” “survival,” or “mortality” or any of these (Appendix for full search terminology). No restrictions were imposed for language. Conference abstracts were excluded owing to inability to access source data.

In order to identify registry and administrative data, we included observational cohort, case-control, and cross-sectional trials. RCTs were excluded, as well as review articles and editorials. References from relevant articles were included for cross-reference, and studies were manually extracted for inclusion. Studies that used the same data set were evaluated and included if years of study or outcomes were unique; otherwise the most recent study was included in the reporting of HR ranges.

Two authors performed the study selection independently (D.P. and E.C.S.) by titles and abstracts and then by full text if there was insufficient information to determine if a study should be included or excluded. Disagreements were resolved by consensus.

2.4. Data synthesis

Data were synthesized in Cochrane Collaboration Review Manager software (Revman, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane