

Prostate Cancer

Efficacy of Local Treatment in Prostate Cancer Patients with Clinically Pelvic Lymph Node-positive Disease at Initial Diagnosis

Thomas Seisen^{a,b,1}, Malte W. Vetterlein^{a,b,1}, Patrick Karabon^a, Tarun Jindal^a, Akshay Sood^a, Luigi Nocera^a, Paul L. Nguyen^c, Toni K. Choueiri^d, Quoc-Dien Trinh^b, Mani Menon^a, Firas Abdollah^{a,*}

^a Center for Outcomes Research, Analytics and Evaluation, Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA; ^b Division of Urological Surgery and Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; ^c Department of Radiation Oncology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; ^d Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Article info

Article history:

Accepted August 11, 2017

Associate Editor:

Giacomo Novara

Keywords:

Prostate neoplasms
Lymph nodes
Radiotherapy
Prostatectomy
Castration

Abstract

Background: There is limited evidence supporting the use of local treatment (LT) for prostate cancer (PCa) patients with clinically pelvic lymph node-positive (cN1) disease.

Objective: To examine the efficacy of any form of LT ± androgen deprivation therapy (ADT) in treating these individuals.

Design, setting, and participants: Using the National Cancer Database (2003–2011), we retrospectively identified 2967 individuals who received LT ± ADT versus ADT alone for cN1 PCa. Only radical prostatectomy (RP) and radiation therapy (RT) were considered as definitive LT.

Intervention: LT ± ADT versus ADT alone.

Outcome measurements and statistical analysis: Instrumental variable analyses (IVA) were performed using a two-stage residual inclusion approach to compare overall mortality (OM)-free survival between patients who received LT ± ADT versus ADT alone. The same methodology was used to further compare OM-free survival between patients who received RP ± ADT versus RT ± ADT.

Results and limitations: Overall, 1987 (67%) and 980 (33%) patients received LT ± ADT and ADT alone, respectively. In the LT ± ADT group, 751 (37.8%) and 1236 (62.2%) patients received RP ± ADT and RT ± ADT, respectively. In IVA, LT ± ADT was associated with a significant OM-free survival benefit (hazard ratio = 0.31, 95% confidence interval [CI] = 0.13–0.74, $p = 0.007$), when compared with ADT alone. At 5 yr, OM-free survival was 78.8% (95% CI: 74.1–83.9%) versus 49.2% (95% CI: 33.9–71.4%) in the LT ± ADT versus ADT alone groups. When comparing RP ± ADT versus RT ± ADT, IVA showed no significant difference in OM-free survival between the two treatment modalities (hazard ratio = 0.54, 95% CI = 0.19–1.52, $p = 0.2$). Despite the use of an IVA, our study may be limited by residual unmeasured confounding.

Conclusions: Our findings show that PCa patients with clinically pelvic lymph node-positive disease may benefit from any form of LT ± ADT over ADT alone. While not necessarily curative by itself, the use of RP or RT could be the first step in a multi-modality approach aiming at providing the best cancer control outcomes for these individuals.

Patients summary: We examined the role of local treatment for clinically pelvic lymph node-positive prostate cancer. We found that the delivery of radical prostatectomy or radiation therapy may be associated with an overall mortality-free survival benefit compared with androgen deprivation therapy alone.

© 2017 European Association of Urology. Published by Elsevier B.V. All rights reserved.

¹ These authors contributed equally.

* Corresponding author. Vattikuti Urology Institute, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202, USA. Tel. +13487357124; Fax: +13139169539.

E-mail address: firm.abdollah@gmail.com (F. Abdollah).

1. Introduction

With an estimated 161 360 new cases in 2017, prostate cancer (PCa) is the most common malignancy in US men [1]. Although the initiation of widespread prostate-specific antigen screening in the early 1990s has resulted in a dramatic drop in the incidence of metastatic disease over the past few decades [2], approximately 12% of these patients still present with clinically pelvic lymph node-positive (cN1) disease at the time of diagnosis [1]. This rate is likely to increase within the next few years, given the greater utilization of advanced imaging [3], and the recent United States Preventive Services Task Force recommendations against prostate-specific antigen screening [4,5].

Unfortunately, evidence to guide treatment decision-making for patients with cN1 PCa remains highly limited. Based on the assumption that cancer cells could have spread concomitantly to the pelvic lymph nodes and other distant sites throughout the body, the American Joint Committee on Cancer groups cN1 and cM1 PCa together as stage IV disease [6]. Accordingly, the current National Comprehensive Cancer Network guidelines predominantly advocate the use of androgen deprivation therapy (ADT) alone as first-line treatment in individuals with such disease, regardless of the metastases site [7].

As a result, care providers may be reluctant to deliver any form of local treatment (LT) to these patients. Nonetheless, the paradigm of treating the primary tumor burden for metastatic PCa is continuously evolving, with increasing evidence suggesting a benefit of LT for men with extrapelvic lymph nodes, and/or bone/visceral involvement at initial diagnosis [8,9]. Surprisingly, very few studies addressed this research question in patients with nodal metastasis confined to the pelvis [10–12]. It is noteworthy that these reports exclusively assessed the role of radiation therapy (RT), given that patients who received radical prostatectomy (RP) were systematically excluded from the analyses. Additionally, no attempt was made to adjust for potentially unmeasured confounders, such as the granular general condition, and/or the clinical extent of pelvic lymph node involvement at initial diagnosis.

Against this backdrop, we sought to examine the efficacy of LT (RP or RT) ± ADT versus ADT alone in treating PCa patients with cN1 disease. We relied on the National Cancer Database (NCDB), and performed an instrumental variable analysis (IVA) to account for measurable, as well as unmeasurable confounders. We hypothesized that LT ± ADT confers more favorable overall mortality (OM)-free survival outcomes in comparison to ADT alone. Moreover, we hypothesized that OM-free survival outcomes are similar in cN1 PCa patients treated with RP ± ADT versus RT ± ADT.

2. Materials and methods

2.1. Data source

The NCDB is a joint program of the American College of Surgeons and the American Cancer Society. Clinical oncological registry data are collected

from more than 1500 Commission on Cancer-accredited facilities and represent approximately 70% of newly diagnosed cancer cases in the US.

2.2. Study population and definition of treatment groups

Using the American Joint Committee on Cancer classification and the Collaborative Staging System, we identified 6599 individuals diagnosed with clinically pelvic lymph node-positive PCa (International Classification of Diseases-O-3 site code: C61.9) and no evidence of distant metastasis, between 2004 and 2012. Further inclusion/exclusion criteria are depicted in Figure 1. Our final study population consisted of 2967 patients, who were stratified based on treatment type: LT ± ADT group versus ADT alone group. We defined LT as the receipt of either RP or RT with a total dose (regional + boost) ≥68.4 Gy delivered to the prostate using external beam modality [13], both within 180 d following initial diagnosis. Available covariates were categorized as indicated in Table 1.

2.3. Endpoint

Our main endpoint was OM defined as the death from any cause as reported by the NCDB. As such, survival time was calculated from the time of initial diagnosis to the date of death from any cause or last follow-up.

2.4. Statistical analyses

First, we examined the distribution of baseline characteristics between the two treatment groups using a two-sample *t* test and a chi-square test to compare continuous and categorical variables, respectively. Continuous variables were presented using means and corresponding standard deviations, while categorical variables were reported using frequencies and proportions.

Second, to account for selection bias between patients who received LT ± ADT versus ADT alone, we used an IVA to account for measured differences in baseline characteristics, as well as unmeasured confounders. After exploring several eligible instruments, the yearly regional utilization rate of LT ± ADT was selected to perform a two-stage residual inclusion analysis [14,15]. This instrument was previously used in the literature [16–19] and calculated for each of the nine United States Census Division as follows:

$$\frac{LT \pm ADT \text{ cases/region/yr}}{(LT \pm ADT \text{ cases/region/yr}) + (ADT \text{ alone cases/region/yr})}$$

The F-statistic was computed to confirm its adequate correlation with the receipt of LT ± ADT, while the second IVA assumption was assumed to be met, as the absence of correlation between the instrument and the outcome of interest other than through the exposure of interest cannot be formally tested. A multivariable logistic regression was further used to identify the independent predictors of receiving LT ± ADT versus ADT alone in the first-stage model. The residual, defined as the observed minus the predicted probability of receiving LT ± ADT was calculated and included in the second-stage model to assess the impact of LT ± ADT versus ADT alone on OM-free survival using a multivariable Cox regression analysis with robust standard errors clustered at the facility level. Results were compared with those obtained from an inverse probability of treatment weighting (IPTW)-adjusted Cox model. We subsequently plotted instrumental variable (IV)-adjusted Kaplan-Meier curves with their corresponding 95% confidence interval (CI) bands to depict OM-free survival in the two treatment groups and compare 5-yr OM-free survival. In addition, we assessed whether the treatment effect of LT ± ADT versus ADT alone varied according to available baseline clinical characteristics by using a locally weighted regression method.

Download English Version:

<https://daneshyari.com/en/article/8778535>

Download Persian Version:

<https://daneshyari.com/article/8778535>

[Daneshyari.com](https://daneshyari.com)