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

European Association of Urology

Prostate Cancer

Local Therapy Improves Survival in Metastatic Prostate Cancer

Sami-Ramzi Leyh-Bannurah[a,b,c,1,*], *Stéphanie Gazdovich*[a,d,1], *Lars Budäus*[b], *Emanuele Zaffuto*[a,e], *Alberto Briganti*[e], *Firas Abdollah*[e,f], *Francesco Montorsi*[e], *Jonas Schiffmann*[g], *Mani Menon*[f], *Shahrokh F. Shariat*[h], *Margit Fisch*[c], *Felix Chun*[c], *Thomas Steuber*[b], *Hartwig Huland*[b], *Markus Graefen*[b], *Pierre I. Karakiewicz*[a,d]

[a] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Canada;* [b] *Martini-Clinic, Prostate Cancer Center Hamburg-Eppendorf, Hamburg, Germany;* [c] *Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [d] *Department of Urology, University of Montreal Health Center, Montreal, Canada;* [e] *Department of Urology and Division of Experimental Oncology, URI, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Milan, Italy;* [f] *Vattikuti Urology Institute and VUI Center for Outcomes Research Analytics and Evaluation (VCORE), Henry Ford Hospital, Henry Ford Health System, Detroit, MI, USA;* [g] *Department of Urology, Academic Hospital Braunschweig, Braunschweig, Germany;* [h] *Department of Urology Medical University of Vienna, Vienna, Austria*

Article info

Article history:
Accepted March 14, 2017

Associate Editor:
James Catto

Keywords:
Standard of care
Local radiotherapy
Radical prostatectomy
Cytoreductive prostatectomy
Brachytherapy

Abstract

Background: Treatment of the primary, termed local therapy (LT), may improve survival in metastatic prostate cancer (mPCa) versus no local therapy (NLT).
Objective: To assess cancer-specific mortality (CSM) after LT versus NLT in mPCa.
Design, setting, and participants: Within the Surveillance, Epidemiology and End Results database (2004–2013), 13 692 mPCa patients were treated with LT (radical prostatectomy [RP] or radiation therapy [RT]) or NLT.
Outcome measurements and statistical analysis: Multivariable competing risk regression analyses (MVA CRR) tested CSM after propensity score matching (PSM) in two analyses, (1) NLT versus LT and (2) RP versus RT, and were complemented with interaction, sensitivity, unmeasured confounder, and landmark analyses.
Results and limitations: Of 13 692 mPCa patients, 474 received LT: 313 underwent RP and 161 RT. In MVA CRR, after PSM, LT (n = 474) results in lower CSM (subhazard ratio [SHR] 0.40, 95% confidence interval [CI] 0.32–0.50) versus NLT (n = 1896). In MVA CRR after PSM, RP (n = 161) results in lower CSM (SHR 0.59, 95% CI 0.35–0.99) versus RT (n = 161). Invariably, lowest CSM rates were recorded for Gleason $\leq$7, $\leq$cT3, and M1a substage. Interaction and sensitivity analyses confirmed the robustness of results, and landmark analyses rejected the bias favouring LT. A strong unmeasured confounder (HR = 5), affecting 30% of NLT patients, could obliterate LT benefit. Data were retrospective.
Conclusions: In mPCa, LT results in lower mortality relative to NLT. Within LT, lower mortality is recorded after RP than RT. Patients with most favourable grade, local stage, and metastatic substage derive most benefit from LT. They also derive most benefit from RP, when LT types are compared (RP vs RT). It is important to consider study limitations until ongoing clinical trials confirm the proposed benefits.
Patient summary: Individuals with prostate cancer that spreads outside of the prostate might still benefit from prostate-directed treatments, such as radiation or surgery, in addition to receiving androgen deprivation therapy.

[1] These authors shared the first authorship.
[*] Corresponding author. Cancer Prognostics and Health Outcomes Unit, 264 Blvd. Rene-Levesque E. Room 228, Montreal QC H2X 1P1, Canada. Tel. +1 514 806 5044; Fax: +1 514 227 5103.
E-mail address: S.Bannurah@googlemail.com (S.-R. Leyh-Bannurah).

http://dx.doi.org/10.1016/j.eururo.2017.03.020
0302-2838/

1. Introduction

Treatment of the primary tumour, termed local treatment (LT), reduces mortality rates in several malignancies (renal, colon, and ovarian cancer), despite established metastatic spread [1–6]. LT may also improve survival in metastatic prostate cancer (mPCa), relative to standard of care: androgen deprivation therapy (ADT) with no LT (NLT) [7]. Evidence stems from six studies within four data repositories: the Surveillance, Epidemiology and End Results (SEER) database [8–10], the SEER-Medicare database [11], the National Cancer Database (NCDB) [12], and the Munich Cancer Registry [13]. Four studies reported improved survival with radical prostatectomy (RP) versus NLT [8,9,11,13]. However, none directly examined RP against radiotherapy (RT). Additionally, three institutional studies confirmed RP safety in select mPCa patients [14–16].

Methodological limitations apply to all six reports: four failed to account for other-cause mortality that may irreversibly confound all-cause mortality rates and lacked competing risk regression (CRR) [8,10,12,13]. Three failed to fully adjust for patient characteristics with propensity score matching [9,13]. One combined CRR and propensity score matching but had a limited sample size: 47 RP patients [11].

We combined CRR with propensity score matching, within the largest possible patient sample: the SEER database to test for differences in CSM according to LT versus NLT. Moreover, unlike previously, we tested for CSM differences according to LT type: RP versus RT.

2. Patients and methods

2.1. Patient selection

Within the SEER database (18 cancer registries, accounting for 26% of the US population), we identified patients diagnosed with adenocarcinoma of the prostate (International Classification of Disease for Oncology [61.9]; histological code: 8140) with metastatic disease at diagnosis (ie, SEER field "CS Mets at DX") and stages M1a–c (sixth edition of American Joint Committee on Cancer [AJCC] Cancer Staging Manual). All underwent LT: (1) RP (surgery site codes 50 and 70) with or without RT or (2) RT (ie, brachytherapy) with or without external beam radiation therapy (EBRT) or (3) NLT, between 2004 and 2013. Prostate-specific antigen (PSA) values were available for patients diagnosed between 2010 and 2013, and were included in subgroup analysis.

Patients were stratified according to RP versus RT versus NLT status, as described earlier [8,9]. EBRT was excluded; it lacked target site information distinguishing local from extraprostatic treatment. Other surgical treatments than RP, for example, transurethral resection of the prostate, were also excluded. These selection criteria yielded 13 692 patients.

2.2. Propensity score matching

Propensity score matching (4:1 ratio, with nearest-neighbour matching or calliper width of 0.1 of the standard deviation of the logit) yielded similar patient characteristics between LT (n = 474) and NLT cohorts (n = 13 218), emulated randomised trial design, minimised residual bias, and increased precision [17]. Adjustment variables consisted of age, race, biopsy Gleason score, clinical tumour stage, nodal stage, and metastatic substages. Standardised mean difference measurements were performed to confirm sufficient matching. Propensity score matching (1:1 ratio due to sample size) was repeated for RT versus RP tests.

2.3. Statistical analyses

To ensure intergroup comparability, we exclusively relied on metrics applicable to all patients, regardless of LT versus NLT status or of LT type (RP vs RT): biopsy Gleason score, clinical tumour, nodes, and metastatic substages were used in propensity score matching and in all analyses.

Covariates consisted of age, race, marital status, biopsy Gleason score, clinical tumour, nodes, and metastatic substages. Subsequently, clinical variables that qualified as independent cancer-specific mortality (CSM) predictors were used in a risk stratification scheme of $\leq$1 versus $\geq$2 risk factors. To further examine the effect of risk factors ($\leq$1 vs $\geq$2 risk factors), we refitted the Cox model by adding an interaction term: risk stratification scheme and treatment status. Landmark analyses were performed at 6, 12, 18, and 24 mo after the time of diagnosis, to address the potential effect of immortal time bias, which may favourably affect patients treated with either RP or RT, relative to NLT patients [18]. Sensitivity analyses tested the effect of a potential unmeasured confounder by (1) computing the prevalence required to render our result statistically insignificant assuming that such a confounder has a moderate subhazard ratio (SHR; eg, 2), and (2) computing the SHR required to render our results statistically insignificant assuming a moderate prevalence ratio (eg, 30% in LT and 10% in NLT) [19,20].

All tests were two sided with a statistical significance set at $p < 0.05$. Analyses were performed with the statistical package for R (version 3.2.2; the R foundation for Statistical Computing, Vienna, Austria).

3. Results

Prior to propensity score matching, NLT patients were oldest (72 yr), relative to RT (68 yr) and RP patients (63 yr, Tables 1 and 2). The rate for biopsy Gleason score $\leq$7 was lowest in NLT patients (18%), followed by RP (47%) and RT patients (48%). The rate for clinical stage $\leq$T3 was highest in RP (97%), followed by in RT (94%) and NLT (89%) patients. Node stage N0/NX was virtually the same in RP (92%) and RT (91%) patients and lower in NLT patients (80%). Finally, metastatic substage M1a was also virtually the same in RP (11%) and RT (12%) patients and lower in NLT group (6.1%).

After propensity score matching (NLT vs LT and RP vs RT), residual statistically significant differences remained only for year of diagnosis in RP versus RT comparisons: 17% and 6.2% of the population in year 2013, respectively, in RP and RT arms. After propensity score matching, the median follow-up of NLT versus LT and RP versus RT patients without CSM or other-cause mortality was 31.0 mo (interquartile range [IQR] 12.0–58.0) versus 43.5 (IQR 18.0–80.0) and 39.0 mo (IQR 16–72) versus 56.0 mo (IQR 28.0–86.0), respectively.

In propensity score–matched multivariable competing risk regression analyses (MVA CRR), both LT types, RP and RT, yielded lower CSM rates (65% and 52%, respectively) relative to NLT (SHR 0.35, 95% CI 0.26–0.46 and SHR 0.48, 95% CI 0.35–0.66; both $p < 0.001$; Table 3). Additionally, CSM was also lower with Gleason $\leq$7 (vs GS $\geq$8; SHR 1.84, 95% CI 1.59–2.13; $p < 0.001$), $\leq$cT3 (vs T4; SHR 1.85, 95% CI 1.39–2.46; $p < 0.001$), and substage M1a (vs M1c; SHR 1.98, 95% CI 1.52–2.58; $p < 0.001$) and in married men (vs divorced/widowed; SHR 1.25, 95% CI 1.03–1.51; $p < 0.024$).

Please cite this article in press as: Leyh-Bannurah S-R, et al. Local Therapy Improves Survival in Metastatic Prostate Cancer. Eur Urol (2017), http://dx.doi.org/10.1016/j.eururo.2017.03.020