Editorial

Adjuvant radiotherapy and mortality in lymph node-positive prostate cancer

Michael Froehner, Manfred P. Wirth

Department of Urology, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

Correspondence to: Michael Froehner, MD. Department of Urology, University Hospital "Carl Gustav Carus", Technische Universität Dresden, Fetscherstrasse 74, D-01307 Dresden, Germany. Email: Michael.Froehner@uniklinikum-dresden.de.

Comment on: Touijer KA, Karnes RJ, Passoni N, *et al.* Survival Outcomes of Men with Lymph Node-positive Prostate Cancer After Radical Prostatectomy: A Comparative Analysis of Different Postoperative Management Strategies. Eur Urol 2017. [Epub ahead of print].

Received: 08 January 2018; Accepted: 01 February 2018; Published: 06 March 2018.

doi: 10.21037/amj.2018.02.06

View this article at: http://dx.doi.org/10.21037/amj.2018.02.06

In a retrospective study, Touijer and co-workers investigated mortality in 1,338 patients with lymph-node positive prostate cancer who underwent radical prostatectomy between 1988 and 2010 in two centers in the US and one in Italy (1). The patients were stratified into three groups by the receipt of adjuvant treatment (radical prostatectomy alone versus adjuvant androgen deprivation treatment, ADT, versus adjuvant androgen deprivation treatment plus external beam radiotherapy, EBRT) (1). The combination of adjuvant ADT + EBRT was associated with lower mortality compared with either observation or adjuvant ADT alone (1). The difference was higher among higher risk groups (1). An earlier study with patients recruited during the same time frame in the same institutions revealed similar results (2). Beside the observed mortality differences favoring combined ADT + EBRT, the differences in demographic data were impressive. Patients who underwent combined ADT + EBRT had adverse parameters concerning Gleason score, number of involved lymph nodes, pathological stage, prostate-specific antigen level, and positive surgical margins rate (each $P<0.0001$) (1). The authors addressed the problem of possible unmeasured confounders arguing that such confounders are usually correlated with measured covariates thus making bias less likely and concluded that combined ADT + EBRT improved survival over either observation or adjuvant ADT alone (1).

Frequently, unmeasured confounders will indeed be correlated with measured variables. The setting of adjuvant radiotherapy for lymph node-positive prostate cancer, however, might be a different situation. For this indication, adjuvant radiotherapy became popular in more recent times. Therefore, such treatment is more likely of being administered to more contemporarily treated patients. It is conceivable that those patients have undergone more critical staging (imaging and/or removal and/or histopathological investigation of more lymph nodes) and might have been assigned higher Gleason scores (pretending higher risk) compared with their earlier treated counterparts. It has been reported that such Gleason score shift may confound retrospective series which recruited patients during the 1990s (3,4). The resulting bias (apparently improved outcome in all risk classes) is called Will Rogers phenomenon (3,4). Furthermore, a stage shift by an earlier detection of prostate cancer might have enriched more recently treated subgroups with good risks. Finally, since the year 2004, several effective systemic treatment options for castration-resistant prostate cancer have become available from which more recently treated patients might have benefited more. Unfortunately, the authors provided no information on the timing of treatment (1). The higher proportion of patients at risk after 10 years of follow-up among patients with ADT (more traditional management strategy) compared with the combined ADT + EBRT subgroup [the novel approach; 41% versus 15% (1)], however, suggests that the latter option was indeed used more frequently in more recent times.

In view of these points, was it surprising that mortality was lower among more recently treated patients? No. Was lower mortality an effect of combined ADT + EBRT?

© AME Medical Journal. All rights reserved.

Not necessarily. In contrast to the therapeutic effect of adjuvant (systemic) ADT for lymph node-positive disease (5), that of additional local measures [more extensive lymph node dissection in patients with lymph node metastases (6) or supplementary radiotherapy of the pelvic lymph nodes in patients with high risk disease treated with external beam radiotherapy (7)] has not been convincingly demonstrated yet.

Toxicity is another important point. Adjuvant pelvic radiotherapy is associated with increased acute and late gastrointestinal toxicity as well as with urinary incontinence (8). The current study (1) did not provide data on adverse effects of combined ADT + EBRT. Despite concern on the lack of data from randomized trials, current prostate cancer guidelines recommend considering adjuvant combined ADT + EBRT as an option (9-11). Candidates for such treatment should, however, be informed on the remaining uncertainties and should be encouraged to participate in randomized trials.

Acknowledgements

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xiao Li (Department of Urologic Surgery, The Affiliated Cancer Hospital of Jiangsu Province of Nanjing Medical University, Nanjing, China).

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2018.02.06). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Touijer KA, Karnes RJ, Passoni N, et al. Survival Outcomes of Men with Lymph Node-positive Prostate Cancer After Radical Prostatectomy: A Comparative Analysis of Different Postoperative Management Strategies. Eur Urol 2017. [Epub ahead of print].
2. Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. J Clin Oncol 2014;32:3939-47.
3. Chism DB, Hanlon AL, Troncoso P, et al. The Gleason score shift: score four and seven years ago. Int J Radiat Oncol Biol Phys 2003;56:1241-7.
4. Albertsen PC, Hanley JA, Barrows GH, et al. Prostate cancer and the Will Rogers phenomenon. J Natl Cancer Inst 2005;97:1248-53.
5. Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med 1999;341:1781-8.
6. Lawton CA, DeSilvio M, Roach M 3rd, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. Int J Radiat Oncol Biol Phys 2007;69:646-55.
7. Mandel P, Kriegmair MC, Bogdan K, et al. Association between Lymph Node Counts and Oncological Outcomes in Lymph Node Positive Prostate Cancer. Eur Urol Focus. 2017 Apr;3:248-55.
8. Daly T, Hickey BE, Lehman M, et al. Adjuvant radiotherapy following radical prostatectomy for prostate cancer. Cochrane Database Syst Rev 2011;(12):CD007234.
9. Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF), Deutschen Krebsgesellschaft e.V. (DKG) und Deutschen Krebshilfe (DKH). Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms Version 0.5.0 (Konsultationsfassung) – September 2017. Interdisciplinary S3 guidelines on early detection, diagnostics and treatment of different stages of prostate cancer; Guidelines in German. AWMF-Registernummer: 043/022OL. Available online: http://

© AME Medical Journal. All rights reserved.

www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Prostata_5_0/LL_Prostata_Langversion_0_5_0.pdf
10. Mottet N, Bellmunt J, Briers E, et al. European Association of Urology (EAU) guidelines on prostate cancer. Update 2017. (accessed: January 2, 2018). Available online: http://uroweb.org/guideline/prostate-cancer/
11. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines (NCCN Guidelines®) Prostate Cancer. Version 2.2017. (accessed: January 2, 2018). Available online: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

doi: 10.21037/amj.2018.02.06
Cite this article as: Froehner M, Wirth MP. Adjuvant radiotherapy and mortality in lymph node-positive prostate cancer. AME Med J 2018;3:31.

© AME Medical Journal. All rights reserved.