Editorial

Lymph node positive prostate cancer: the evolving role of adjuvant therapy

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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].

Submitted Jan 19, 2018. Accepted for publication Jan 23, 2018.
doi: 10.21037/tcr.2018.01.33
View this article at: http://dx.doi.org/10.21037/tcr.2018.01.33

For decades, lymph node metastasis (LNM) at the time of radical prostatectomy (RP) has been considered as a poor prognostic sign. Currently, the appropriate timing for androgen deprivation therapy (ADT) remains controversial. Only one small prospective randomized study (ECOG 3886) has shown improved survival for immediate *vs.* delayed ADT in this select group of patients (1). However, given that most urologists will not delay hormone therapy for evidence of bulky metastatic disease as was done in that trial, the study's findings do not apply to the contemporary management of biochemically recurrent (BCR) prostate cancer. In today's PSA era, immediate ADT would lead to overtreatment for a significant number of patients along with its associated risks and adverse effects (2,3).

The presence of LNM, or pN+ disease, has traditionally been seen as a sign of disseminated disease with lymphadenectomy playing more of a staging rather than therapeutic role. However, emerging evidence has provided insight into this complex issue; with longitudinal data demonstrating a considerable subset of men can be free of disease at 10 years with lymphadenectomy alone (4). Patients with low Gleason score and low number of metastatic lymph nodes appear to be a favorable group for whom an extended pelvic lymph node dissection (PLND) may be beneficial (5,6). The need and timing of adjuvant treatments remains less clear with current national comprehensive guidelines labeling ADT and ADT plus pelvic radiotherapy (RT) as a category 1 and 2B, respectively (7). Only one retrospective report from the Vita-Salute San Raffaele University (Milan, Italy) demonstrated improved BCR-free and cancer specific survival for men treated with ADT plus RT *vs.* ADT alone after RP and PLND (8).

This same center partnered with the Mayo Clinic and Memorial Sloan-Kettering Cancer Center in the latest issue of *European Urology* examining long term outcomes between different management strategies for pN+ men (9). Based on practice patterns at each institution, their large cohort of 1,388 men was comprised of three arms: observation (28%), ADT (49%), and ADT + RT (23%). Of note was their median follow-up of 69 months with 368 (26%) men followed longer than 10 years. Their results showed ADT + RT was associated with better overall survival than ADT [hazard ratio (HR): 0.46, 95% CI: 0.32–0.66; P<0.01] or observation alone (HR: 0.41, 0.27–0.64; P<0.01). This benefit seemed greater for those with high-risk disease features such as high Gleason score, pathologic T3b/T4 stage, and positive surgical margin; which correspond with previously reported data that also included Milan and Mayo Clinic patients (10).

Interestingly, there were no differences in survival between ADT and observation alone; with lifelong adjuvant ADT associated with increased risk of death from other causes (HR: 3.05, 1.45–6.40; P=0.003). However, it is noteworthy that approximately 77% of patients in the ADT arm came from US centers which tracked deaths using the Social Security Death Index (as opposed to the Italian National Civil Registry) so these results may be affected by spurious differences in coding between the two registries. Additionally, most of the ADT + RT patients (83%) came from Milan so these findings may not necessarily translate to North American cohorts with distinct lifestyle, medical, and environmental factors which can confound retrospective studies such as this one. Nevertheless, the authors are to be congratulated for providing the largest experience to date on the post-operative management of pN+ disease after RP and PLND. These findings add to the evidence for the benefit of surgical resection and local control for a complex and heterogeneous disease state in which prospective data is unlikely to be forthcoming given the downward stage migration caused by widespread PSA screening (11,12).

Selecting patients who would benefit from adjuvant treatments remains difficult. What is clearer, as data continues to show, is the dogma that pelvic LMN is invariably a 'game-

over' for prostate cancer patients. Even those with ominous pathologic features may derive benefit from aggressive local consolidation, and referral to centers of experience with multidisciplinary management of high-risk prostate cancer should be considered. With advances in systemic therapy targeting the androgen receptor, there is also an opportunity to improve hormonal manipulation and assess oncologic benefit in both adjuvant and salvage settings. What remains to be better defined is the subset of patients who may not require or benefit from adjuvant therapies, thus also sparing them the adverse consequences of castration and radiation effects on quality of life. Additionally, there is an opportunity to evaluate novel molecular biomarkers which could allow for better risk stratification with the goals of maximizing oncologic benefit while minimizing morbidity of overtreatment.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Peng Zhang, MD, PhD (Department of Urology, Zhongnan Hospital of Wuhan University, Wuhan, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.01.33). 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.

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Cite this article as: Chipollini JJ, Pow-Sang JM. Lymph node positive prostate cancer: the evolving role of adjuvant therapy. Transl Cancer Res 2018;7(Suppl 1):S94-S95. doi: 10.21037/tcr.2018.01.33

