



Should we treat cN+ prostate cancer patients with surgery as part of multimodal approach?

Lorenzo Bianchi^{1,2}, Federico Mineo Bianchi¹, Marco Borghesi^{1,2}, Francesco Chessa^{1,2}, Marco Garofalo^{1,2}, Riccardo Schiavina^{1,2}, Eugenio Brunocilla^{1,2}

¹Department of Urology, ²Department of Specialistic, Diagnostic and Sperimental Medicine (DIMES), University of Bologna, Bologna, Italy

Correspondence to: Lorenzo Bianchi, MD. Department of Urology, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.

Email: lorenzo.bianchi3@gmail.com.

Comment on: Gandaglia G, Soligo M, Battaglia A, *et al.* Which Patients with Clinically Node-positive Prostate Cancer Should Be Considered for Radical Prostatectomy as Part of Multimodal Treatment? The Impact of Nodal Burden on Long-term Outcomes. *Eur Urol* 2018. [Epub ahead of print].

Received: 17 January 2019; Accepted: 28 January 2019; Published: 11 February 2019.

doi: [10.21037/amj.2019.01.10](https://doi.org/10.21037/amj.2019.01.10)

View this article at: <http://dx.doi.org/10.21037/amj.2019.01.10>

The optimal management of prostate cancer (PCa) patients with clinical positive lymph nodes (cN+) is still matter of debate. Historically, cN+ as well as metastatic PCa men were scheduled for androgen deprivation therapy (ADT). However, despite the lack of prospective randomized controlled trials, some authors recently reported improved survival outcomes in PCa patients who underwent local therapies (LT) for cN+ disease as compared to long-term ADT alone (1). As consequence, current guidelines include radical prostatectomy (RP) with extended pelvic lymph node dissection as a part of a multi-modal therapy for cN+ PCa patients (2). As previously stated, PCa with nodal metastases doesn't necessarily translate in a poor prognosis (3), since node positive PCa men represent a highly heterogeneous group and each man should be counseled accordingly to choose the most suitable management on individualized level (4-7).

For example, patients with 2 or less positive nodes at final pathology have a significantly better cancer specific survival (CSS) at 15-year follow-up compared to patients with more than two positive lymph nodes (84% *vs.* 62%; $P < 0.001$) (8). Moreover, both age and the number of positive nodes are significant competing cause of mortality (8,9). However, as Briganti *et al.* reported (10), patients with retroperitoneal N+ had a poor prognosis and should be considered as affected by a systemic disease, since the retroperitoneal lymphatic chains are not a regional drainage area for PCa. Of note, the landing of PCa cells to retroperitoneal

nodes itself represents the expression of a more aggressive phenotype (11).

Recent evidences suggest that patients diagnosed with an oligo-metastatic disease have a better prognosis and response to systemic therapy compared with those with extensive metastatic burden (12). Furthermore, the precise identification oligo-metastases in high risk PCa patients at time of presentation has given rise to emerging trials aimed to evaluate the survival benefit of radical treatments even in oligo-metastatic individuals and initial oncologic results are encouraging (13). Therefore, those oligo-metastatic patients selected by imaging would be effectively managed with curative intent, using multimodal treatments such as debulking surgery and radiotherapy targeted to lesions, including lymph nodes and skeletal metastases

The crucial point is how to correctly identify men with cN+ disease. In fact, the diagnostic performance of the conventional imaging to detect nodal metastases in staging setting is similar to the flip of the coin (14). Thus, lymph node dissection remains the gold standard procedure for nodal staging. Even with the use of prostate specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT), despite better diagnostic performance as compared to conventional imaging in intermediate and high-risk men (15), still shows suboptimal accuracy to identify cN+ PCa patients (16,17). As consequence, many individuals are wrongly classified as cN+ and are scheduled to ADT losing the chance to be

cured with radical treatments. In this context, in this issue of European Urology, Gandaglia *et al.* (18) attempted to identify men with cN+ disease, who would have a “real” CSS benefit with multimodal treatments including surgery. Out of 162 cN+ men, at final examination 127 patients had confirmed pathologic nodal involvement, while 45 individuals had pN0 status. The main limitation of this study consists of the use of conventional imaging to identify cN+ patients that could lead to perform surgery in patients with metastatic disease. Perhaps the use of PSMA PET/CT would result in better selection of oligometastatic men who could benefit for surgery. The authors proposed to stratify cN+ men in five “risk groups” according to clinical grade group, the number of positive lymph nodes and the site of nodal involvement. At 8 years follow-up clinical recurrence (CR) ranged from 9% of group 1 (namely, 1–3 clinical Gleason grade group and <2 positive lymph nodes at pre-operative imaging) to 59% (4–5 Gleason grade group and suspicious retroperitoneal lymph nodes). With the aim to answer the question whenever to select cN+ patients for surgery, they found that only PSA, high Gleason grade group, high number of lymph nodes identified by imaging and retroperitoneal localization of suspicious nodes were predictor of cancer recurrence. As consequence, we agree that surgery as part of a multi-modal approach for cN+ Pca men, should be reserved only to very selected individuals. Aside from men with suspicious retroperitoneal disease and clinical Gleason grade group 4–5, who did not receive any advantage from surgery and should be schedule to systemic therapy up front, patients with Gleason grade group 1–3 and <2 suspicious lymph nodes with pelvic localization should be offered a multi-modal approach to give best chance to survive.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xiao Li (Department of Urology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/amj.2019.01.10>).

The authors have no conflicts of interest 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

- Hsu CY, Joniau S, Oyen R, et al. Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. *Eur Urol* 2007;51:121-8; discussion 128-9.
- Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2017;71:618-29.
- Bianchi L, Nini A, Bianchi M, et al. The Role of Prostate-specific Antigen Persistence After Radical Prostatectomy for the Prediction of Clinical Progression and Cancer-specific Mortality in Node-positive Prostate Cancer Patients. *Eur Urol* 2016;69:1142-8.
- Moschini M, Briganti A, Murphy CR, et al. Outcomes for Patients with Clinical Lymphadenopathy Treated with Radical Prostatectomy. *Eur Urol* 2016;69:193-6.
- James ND, Spears MR, Clarke NW, et al. Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer: Data From Patients in the Control Arm of the STAMPEDE Trial. *JAMA Oncol* 2016;2:348-57.
- Seisen T, Vetterlein MW, Karabon P, et al. Efficacy of Local Treatment in Prostate Cancer Patients with Clinically Pelvic Lymph Node-positive Disease at Initial Diagnosis. *Eur Urol* 2017. [Epub ahead of print].
- Rusthoven CG, Carlson JA, Waxweiler TV, et al. The impact of definitive local therapy for lymph node-positive prostate cancer: a population-based study. *Int J Radiat Oncol Biol Phys* 2014;88:1064-73.

8. Briganti A, Karnes JR, Da Pozzo LF, et al. Two positive nodes represent a significant cut-off value for cancer specific survival in patients with node positive prostate cancer. A new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. *Eur Urol* 2009;55:261-70.
9. Schiavina R, Bianchi L, Borghesi M, et al. Predicting survival in node-positive prostate cancer after open, laparoscopic or robotic radical prostatectomy: A competing risk analysis of a multi-institutional database. *Int J Urol* 2016;23:1000-8.
10. Briganti A, Suardi N, Capogrosso P, et al. Lymphatic spread of nodal metastases in high-risk prostate cancer: The ascending pathway from the pelvis to the retroperitoneum. *Prostate* 2012;72:186-92.
11. Pereira ER, Kedrin D, Seano G, et al. Lymph node metastases can invade local blood vessels, exit the node, and colonize distant organs in mice. *Science* 2018;359:1403-7.
12. van Soest RJ, de Wit R. Irrefutable evidence for the use of docetaxel in newly diagnosed metastatic prostate cancer: results from the STAMPEDE and CHAARTED trials. *BMC Med* 2015;13:304.
13. Heidenreich A, Pfister D, Porres D. Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. *J Urol* 2015;193:832-8.
14. Hövels AM, Heesakkers RA, Adang EM, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. *Clin Radiol* 2008;63:387-95.
15. Maurer T, Gschwend JE, Rauscher I, et al. Diagnostic Efficacy of (68)Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. *J Urol* 2016;195:1436-43.
16. Schiavina R, Bianchi L, Mineo Bianchi F, et al. Preoperative Staging With 11C-Choline PET/CT Is Adequately Accurate in Patients With Very High-Risk Prostate Cancer. *Clin Genitourin Cancer* 2018;16:305-312.e1.
17. Vagnoni V, Brunocilla E, Bianchi L, et al. State of the art of PET/CT with 11-choline and 18F-fluorocholine in the diagnosis and follow-up of localized and locally advanced prostate cancer. *Arch Esp Urol* 2015;68:354-70.
18. Gandaglia G, Soligo M, Battaglia A, et al. Which Patients with Clinically Node-positive Prostate Cancer Should Be Considered for Radical Prostatectomy as Part of Multimodal Treatment? The Impact of Nodal Burden on Long-term Outcomes. *Eur Urol* 2018. [Epub ahead of print].

doi: 10.21037/amj.2019.01.10

Cite this article as: Bianchi L, Bianchi FM, Borghesi M, Chessa F, Garofalo M, Schiavina R, Brunocilla E. Should we treat cN+ prostate cancer patients with surgery as part of multimodal approach? *AME Med J* 2019;4:12.