Editorial

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

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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 results 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.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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