Commentary

Risk stratification in prostate cancer treated with radiation therapy: a window of opportunity for new clinical trials

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Prostate cancer (PCa) is the most incident male cancer in USA and in Europe (1,2). Among malignant solid tumors that constantly require careful and specialized management planning, PCa is a multifaceted disease for which the decision making process has to precisely evaluate several variables concerning the tumor and its host. PCa may present a wide spectrum of clinical situations that require different interventional options. Due to the prostate specific antigen (PSA) "revolution", in the past years, the health operators' community has mainly focused on the identification of the indolent disease in order to avoid overtreatment; and active surveillance has been considered as a reasonable and primary choice for a substantial portion of patients. On the other hand, more recently, the definition of PCa subtypes with a clinical behavior more comparable to other aggressive solid tumors calls for different considerations about this kind of disease, especially in light of the new therapeutic agents' availability. In particular, clinical studies aimed at defining the comparative validity of the current treatment approaches in high-risk localized disease and possibly exploring alternative therapeutic strategies, are urgently needed.

In this framework, the paper by Narang *et al*. (3) valuably explores the prognostic power of a classification method based on the National Comprehensive Cancer Network (NCCN) high-risk parameters in PCa patients consecutively treated with definitive radiation therapy (RT). This risk stratification tool was originally defined on a NCCN high-risk PCa patients treated by radical prostatectomy (RP). A combination of pre-treatment clinical variables (multiple NCCN high-risk factors, and/or primary Gleason pattern 5 disease, and/or 5 or more biopsy samples with Gleason score 8–10) that identify a subset of men at very high risk (VHR) for poor oncologic outcomes was developed (4). Of note, the validation was made on patients treated with RT at the same institution (Johns Hopkins University School of Medicine) from which the patients of the surgical series were coming.

The key findings reported by the above paper are that the VHR status is significantly associated with higher rates of biochemical failure (BF), distant metastases (DM) and prostate cancer specific mortality (PCSM) when compared with the NCCN high-risk status even in radiation treated subjects. Thus, the VHR classification works irrespectively of the type of therapeutic intervention chosen, i.e., RP or RT. Moreover, the authors demonstrated whether a detectable end-of-radiation (EOR) PSA level correlates with greater DM and PCSM if compared with undetectable EOR PSA in VHR group.

With regard to PSA level relative to risk stratification, it should be mentioned the study by Mahal *et al*. (5) showing that in men with high grade disease (Gleason score 8–10), also a low pre-treatment PSA (≤2.5 ng/mL) resulted in greater PCSM (5).

As previously underlined, a remarkable point of the work by Narang *et al*. (3) is the same institutional origin of the RT and the RP database making the two differently treated populations meaningfully analyzable. Many suggestions

can be drawn from jointly considering the paper by Narang *et al*. (3) and the paper by Sundi *et al*. (4). The resulting observations have, of course, only a speculative value, but some of the arguments that can be raised are sensitive issues in the PCa field. The percentage of high-risk patients and, within this group, of VHR patients is greater in RT (34%) than in RP (15%) patients. The NCCN high-risk patients purged from the VHR subgroup have a prostate cancer specific survival at ten years of about 90%, irrespective of the therapeutic option (RT 93.4% *vs.* RP 89.5%), whereas, as expected by the patients selection, the overall survival seems to be better for RP (RT 73% *vs.* RP 83.3%).

The VHR subgroup appears to have benefitted more from RT as suggested by the data about metastases free survival (RT 58.7% *vs.* RP 36.9%) and PCa specific survival (RT 79.4% *vs.* RP 62.2%). Interestingly, in the VHR, subgroup the overall survival seems to be at least equal in the RT compared to RP group, and, although only a suggestion, this is the most intriguing point.

Not surprisingly, the biochemical control is better with RT (6), but this may be due to the different criteria used to define biochemical recurrences that are not uniform in surgical and in radiation series due to the presence of a potentially functional prostatic tissue in radiation treated patients.

The comparison of data coming from different studies is often unfair and may be misleading. On the one hand, we have to consider that in RP series only 52% of VHR patients underwent post-operative (and prior to metastasis) treatment, hence introducing a negative bias that may favor the RT treatment. The androgen deprivation therapy (ADT) seems to be more used in RT patients and generally it is started earlier than in RP patients. In locally advanced disease, it has been shown that the early use of ADT provides a better control of the disease (7). On the other hand, the median dose of radiation administered in the report by Narang *et al*. (3) is lower than the dose presently recommended as a standard. This may introduce a bias that favors the RP group. Indeed, the significant effect of the dose on the control of the disease has been demonstrated (8,9).

The present NCCN guidelines foster a non-surgical approach for VHR patients with RT combined with ADT considered as the standard. However, the outcome achieved by the current therapeutic strategy, with more than 20% PCSM and more than 40% of metastatic patients at 10 years, is unsatisfactory for VHR patients even in the RT group.

Dose escalation represents the current practice in high-risk patients, and current evidence demonstrates that the better approach for dose intensification is the combined RT modality, namely external beam RT plus brachytherapy (10). Some additional remarks could be made concerning the target volumes. The present trend seems to be in the direction of their extension. The ongoing RTOG 0924 trial assesses the benefits of the extended pelvic RT (superior border field L4/L5) coupled with ADT in unfavorable intermediate or favorable high risk PCa patients. Recently, Spratt *et al*. reported the results on the patterns of lymph node failure in a large cohort of patients with localized PCa, demonstrating that the current recommendations for pelvic irradiation field may provide an inadequate coverage of common sites of recurrences such as the common iliac nodes. Thus, the authors conclude that an extended field approach is recommended, in particular for ≥ T3a diseases when pelvic irradiation is indicated (11).

Given the high DM rate in VHR subjects, a different treatment approach would be more appropriate for this subset of patients. Indeed, these patients are likely to present a microscopic metastatic disease at the time of diagnosis. As a consequence, an alternative first line therapy might be taken into consideration in order to improve the prognosis of the VHR patients, possibly combining the standard therapy with drugs, such as docetaxel, abiraterone, enzalutamide or cabazitaxel, that have been shown active in advanced stage patients (12).

Finally, a hot topic in cancer research is immunotherapy. Nowadays, sipuleucel-T is the only immunotherapeutic procedure approved by the Food and Drug Administration for the metastatic setting (13). PCa represents an interesting candidate for testing immune check-point inhibitors, such as ipilimumab and nivolumab (14). The immune-modulating activity of ADT and the combination of immunotherapy and RT have to be taken into account in order to explore new multimodal therapeutic approaches (15). Against this background, the VHR classification could represent an effective tool for patient selection even in the immunotherapy scenario.

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Footnote

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