



Vascular-targeted photodynamic therapy: a glimpse in the future of Urology?

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Background

The technological development and the continuous research in the field of prostate cancer (PCa) have not overcome significant clinical questions and ethical dilemmas related to the treatment of the disease. Current efforts to provide recommendations in the optimal treatment of PCa patients has provided significant standardization of the current knowledge and eventually produced guidelines which are widely acceptable. Nevertheless, a plethora of clinical issues commonly met in the everyday clinical practice such as the optimal management of low risk prostate cancer patients remain inadequately addressed by the literature (1,2). These patients are considered to have a low risk for disease progression and their management by radical approaches may expose them to risk of significant morbidity. In an attempt to optimize the care of this PCa population, different approaches have been proposed (2).

During the recent years, active surveillance (AS) has been documented as a viable management option for very low and low risk patients (3-7). The option of managing these patients with AS could be considered as intriguing and the favorable disease profile of these patients could advocate the reduction of the indications of the radical treatments to a minimal number of patients. Nevertheless, the approach has been hampered by a variety of issues that are currently inadequately addressed by the available evidence. Specifically, there is significant variation in the patient selection criteria among the AS studies while the follow-up schedule and the criteria for the consultation to treatment remain variable and not well defined (8). Solid patient

classification criteria have not been established yet (3-5) and adequate evidence on the appropriate follow-up strategies including modern diagnostic modalities are not currently available (8-10). Moreover, recently published clinical investigations proposed AS only to patients that could be classified as very low risk and do not have a very long life expectancy since these are the only patients that will not miss their chance for cure and more importantly they are not endangered to die from PCa (10). Consequently, significant concerns have been raised on the role of AS in the management of PCa patients (11). These concerns are strengthened by the evidence suggesting that pT3 stage tumors are present in 17-44% of the prostatectomy specimens of patients initially managed by AS (8). The latter observation may represent the most important challenge for AS since patients which were categorized as low risk were eventually diagnosed with advanced high risk for progression PCa. Thus, the option of treating these patients with an organ-preserving approach reflects the need to contain a malignant condition and to minimize the morbidity related to the radical treatments.

Focal therapy has been introduced as a management option for these low risk patients and includes different approaches such as high intensity focused ultrasound (HIFU) and cryosurgery (2). These modalities aim to provide treatment of PCa with lower morbidity than the radical treatments or delay to perform a radical approach (12). Nevertheless, these approaches have not been established in the urological practice and may be considered for the treatment of selected patients in a

clinical trial setting only (2,8). Solid long-term evidence is not available and these focal treatment options may represent a viable approach for the management of low risk patients in the future.

Considering the above, it is clear that the available approaches for the management of low risk PCa patients without using any of the radical treatments are lacking and the introduction for more efficient treatment modalities is a constant need of the urological practice.

Comment on the study

The authors present a very interesting randomized trial comparing the safety and efficacy of a focal treatment approach to the active surveillance in PCa in patients recruited by 47 University centers (13). Patients with one positive biopsy core without Gleason four or five patterns and a core length between 3 and 5 mm were included. Patients with up to three positive cores with a maximal length of 5 mm were also eligible. Important inclusion criteria were the clinical stage up to t2c, PSA ≤ 10 ng/mL and a prostate volume between 25 and 70 cm³. It should be noted that all the cases had a life expectancy of at least 10 years and did not have contraindications for general anesthesia. The patients were either assigned to AS (n=207) or to the vascular-targeted photodynamic therapy with padeliporfin (VTPT, n=206). The latter is a prostate-preserving approach during which a number of optical fibers are placed under guidance in the prostate at the desired treatment zone with the patient in general anesthesia. The photosensitizing substance padeliporfin is then administered intravenously. The process requires 2 hours operating theater allocation. Patients could be retreated if cancer is present in the biopsy performed 12 months after the procedure. A strict follow-up schedule was considered for both patient groups of the study.

The results showed that the patients treated with VTPT had a longer time to progression, higher proportion of negative biopsies at 24 months and a smaller proportion had disease progression in comparison to the patients managed with AS. These results provide evidence on the efficacy of the procedure in the treatment of patients with low-risk disease. The patient and the physician would expect from a focal therapeutic approach to delay or even to avoid any radical treatment. The VTPT seemed to delay the progression of a patient to a status that the radical prostatectomy or radiotherapy would be rendered as imperative management options. Moreover, the progression

to the latter status was avoided in some cases due to the effectiveness of the approach. At this point, it is important to clarify that the currently available methods for following these patients, classifying the stage of their disease and triggering a definitive treatment remain problematic as in the case of AS. Thus, the presented results require careful interpretation and extrapolation to larger populations and wider clinical practice settings would require significant additional investigational effort. The centers included in the study were all academic institution and probably had access to latest diagnostic equipment and they could provide a state of the art follow-up of the included patients.

The adverse events were more common in the VTPT than the AS group. The majority of the patients of the VTPT group had an adverse event which resolved quickly within the first days after the procedure. The most common adverse event was urinary retention which resolved within a period of 2 months while perineal pain was observed in 15% of the patients of the VTPT group. It should be noted that these events did not result in discontinuation of the treatment protocol. Transient erectile dysfunction and lower urinary tract symptomatology were more common in the case of the VTPT. Nevertheless, the results were similar at 24 months among the groups. The quality of life was also similar among the groups. Thus, the approach could be considered as safe and significant aspects such as the erectile function and the quality of life seemed to be preserved with the approach. It is important to note that the presented results were obtained by inexperienced study sites in the majority of the cases. Thus, these results could be expected to provide a lower incidence of adverse events in experienced hands.

When considering the above, it is becoming clear that focal treatments has promising potential to slowly become a viable treatment option for selected cases, especially for cases which could be also considered for AS. The decision of the authors to randomize the VTPT with AS reflects an important need of the current urological practice to optimally manage a specific subpopulation of PCa patients. On the other hand, a significant question remains: What is the long-term oncological outcome and how it compares to the radical treatment approaches? The only answer is: "Time will tell". Still, we should applaud the hard work and the innovative concept of the authors for the glimpse in the future of Urology that they provided us.

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