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Selection for Focal Therapy: Is It Too Early to Judge?

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The advent of novel focal therapies theoretically opens up new treatment avenues for patients with localised prostate cancer (PCa). Presently, management is dichotomised between active surveillance and radical, whole-gland therapy, such as prostatectomy and radiotherapy. While the former burdens patients with the detrimental diagnosis of cancer without the reassurance of treatment, the latter is too often associated with long-term incontinence and/or impotence [1]. The ultimate aim in PCa treatment is effective cure with minimal morbidity and maintenance of quality of life. Through targeted treatment and resultant tissue preservation, focal therapy has been hypothesised to achieve this difficult goal in certain patients. However, the interminable challenge of patient selection remains.

In this month's issue of *European Urology*, Singh and colleagues report an interesting and important study that retrospectively looked at all patients who had undergone transperineal template prostate-mapping biopsies over a 4-yr period [2]. Their creditable aim was to estimate the proportion of patients with PCa who are appropriate for focal therapy. Their optimistic conclusion was that 92% of 239 patients (220 men) with PCa were potentially suitable for focal treatments.

The presence of substantial selection bias in a population-based study must, however, be acknowledged, with the authors only analysing men who had been referred to their tertiary centre with a special interest in focal therapy. Furthermore, and crucially, how do we define suitability for what are currently evolving and experimental treatments? Singh et al. [2] used broad criteria for suitability, requiring the cancer to be (1) unifocal, (2) unilateral, (3) bilateral/bifocal with at least one neurovascular bundle avoided, or (4) bilateral/multifocal with one dominant index lesion and secondary lesions with Gleason $\leq 3+3$ and cancer core involvement <3 mm. Evidently, the broader the eligibility criteria, the greater the proportion of patients deemed suitable. The crux, however, is that success in these groups is presently uncertain and hypothetical. Moreover, these criteria neglect an integral factor in treatment decision: individual patient health and life expectancy [3].

The core tenet of focal therapy is that the targeted removal of detectable local disease results in oncologic control. The secondary assumption is that any undetected secondary tumours will remain inconsequential. Multifocality is highly prevalent (up to 87% in radical prostatectomy series [4]) and many urologists would question the use of focal therapy where multifocal, intermediate- to high-risk disease has been detected. Singh's group and others rely on the *index theory* to advocate focal therapy in these groups [2]. This is the belief that a dominant, index lesion drives malignant and metastatic potential and that eradication of this results in effective treatment [5]. This is supported by the idea of the monoclonal origin of prostatic metastases [6]. Although intuitive, this remains a theoretical and as-yet unproven concept that requires long-term outcome data. Therefore, it is perhaps too early to surmise that all of these men identified by Singh et al. are suitable for focal therapy [2]. Furthermore, pending robust validation, it is difficult to counsel patients regarding the effectiveness of focal treatment.

The success of focal therapy also depends on the accuracy of the diagnostic technique used and the subsequent ability to precisely ablate the identified targets. Investigative methods have improved in tandem with evolving focal therapies [7,8], but there is still no ideal tool for diagnosing and localising PCa. Multiparametric magnetic resonance imaging has been demonstrated to accurately identify PCa foci when compared against

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whole-mount radical prostatectomy [7]. However, uncertainties remain about consistent analysis, and invariably biopsy is needed for definitive pathologic diagnosis. Singh's group reasonably used transperineal template biopsy in their study, but, unfortunately, even extended biopsy is not infallible [2]. In a large series of 414 men, a noteworthy 25.6% were upgraded in Gleason grade when correlating the transperineal biopsy with the final radical prostatectomy specimen [8]. The implication, therefore, is that many men may be incorrectly allocated to focal rather than radical treatments. Notably, biopsy is also inherently invasive and not without morbidity. Singh's group, for example, reported haematuria in 2% and urinary retention in 7% of 291 men biopsied [2]. Arguably, these complications partly undermine the supposed low side-effect advantage of focal therapy. This is compounded by difficulties in monitoring for recurrence after focal treatment; with imaging and prostate-specific antigen levels typically difficult to analyse, additional biopsies are often necessary. The arrival of focused treatments only emphasises the need for a gold standard and safe test for PCa.

The potential urinary and sexual dysfunction that can arise from radical prostate treatment weighs heavily on patient and physician decision making [1]. This need for acceptable morbidity is key to the interest in focal therapy. Early findings are promising; however, side effects such as urinary retention, dysuria, urinary tract infection, urethral strictures, and, rarely, rectal fistulas have been reported [9]. Erectile function is also not assured, with a series ($n = 70$) reporting impotence in 14% of patients after cryotherapy [10]. Nonetheless, morbidity rates associated with focal therapy are better than those reported for radical treatments, and functional outcomes are likely to improve with experience. An understanding of prostatic neuroanatomy is specifically needed to limit erectile dysfunction. Traditionally, preservation of a single neurovascular bundle was thought to confer potency and it is this doctrine that these authors used to guide their selection criteria [2]. This is perhaps too reductionist, with recent dissection studies demonstrating a more complex periprostatic neural network [3,11]. The presence of pro-erectile fibres at the prostatic apex and anterolaterally is of particular interest and should perhaps guide future selection criteria [11]. Another issue in focal therapy selection is that patients with low-volume disease may, in actuality, still be better suited to side effect-free, active surveillance.

Focal therapy's position, as a low-morbidity bridge between the gulf of surveillance and radical treatment is highly appealing. Although Singh et al. further our understanding of focal therapy selection, it is too early to judge how many patients would benefit. Clearly, before we can identify the proportion of men best suited, we need validated, evidence-based eligibility criteria. Unnecessary treatment of insignificant disease and, in turn, undertreatment of serious disease must be avoided. Consequently, patient selection for focal modalities presents several hurdles that only anticipated, long-term outcome studies can traverse.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Bill-Axelson A, Garmo H, Holmberg L, et al. Long-term distress after radical prostatectomy versus watchful waiting in prostate cancer: a longitudinal study from the Scandinavian Prostate Cancer Group-4 randomized clinical trial. Eur Urol 2013;64:920–8.

[2] Singh PB, Anele C, Dalton E, et al. Prostate cancer tumour features on template prostate-mapping biopsies: implications for focal therapy. Eur Urol 2014;66:12–9.

[3] Ward JF, Pisters LL. Considerations for patient selection for focal therapy. Ther Adv Urol 2013;5:330–7.

[4] Meiers I, Waters DJ, Bostwick DG. Preoperative prediction of multifocal prostate cancer and application of focal therapy: review 2007. Urology 2007;70:3–8.

[5] Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med 2009;361:1704–6.

[6] Liu W, Laitinen S, Khan S, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nat Med 2009;15:559–65.

[7] Turkbey B, Mani H, Aras O, et al. Correlation of magnetic resonance imaging tumor volume with histopathology. J Urol 2012;188:1157–63.

[8] Huo AS, Hossack T, Symons JL, et al. Accuracy of primary systematic template guided transperineal biopsy of the prostate for locating prostate cancer: a comparison with radical prostatectomy specimens. J Urol 2012;187:2044–9.

[9] Barret E, Ahallal Y, Sanchez-Salas R, et al. Morbidity of focal therapy in the treatment of localized prostate cancer. Eur Urol 2013;63:618–22.

[10] Bahn D, de Castro Abreu AL, Gill IS, et al. Focal cryotherapy for clinically unilateral, low-intermediate risk prostate cancer in 73 men with a median follow-up of 3.7 years. Eur Urol 2012;62:55–63.

[11] Alsaid B, Bessede T, Diallo D, et al. Division of autonomic nerves within the neurovascular bundles distally into corpora cavernosa and corpus spongiosum components: immunohistochemical confirmation with three-dimensional reconstruction. Eur Urol 2011;59:902–9.