EDITORIAL

Focal therapy for localized prostate cancer: not all that glitters is gold

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In past years we are experiencing a shift toward earlier diagnosis of prostate cancer (PCa). The driving dynamics behind that are twofold. On one hand there is a greater public awareness in parallel to advancing professional insights, leading to the adoption of (in)formal screening strategies. Hence, numerous improved non-invasive enhanced diagnostic imaging modalities have become available.

Traditionally the detection of PCa has been fuelled by prostate-specific antigen (PSA) and image-guided prostate tissue sampling. A proactive attitude towards decreasing the threshold of performing diagnostic investigations has led to an increase in making the (early) diagnosis of PCa. Consequently, this has led to an increase in the number of patients presenting with clinically organ-confined PCa.

Currently we are on a crossroad regarding the treatment of localized PCa. On one hand we aim at an excellent oncological outcome while preserving functional outcomes and thus quality of life. While active surveillance (AS) and whole-gland treatments such as radical prostatectomy or radiotherapy remain standard options, these approaches are often associated with significant morbidity, including urinary, sexual, and bowel dysfunction, with a consequent impact on quality of life. As for radical prostatectomy we may safely conclude that at present time we have reached the limitations of our surgical capabilities, and outcomes are established by the skills of the surgeon rather than on the technology used. Notably, long-term data suggest no clear survival advantage of radical treatments over AS in low- and intermediate-risk disease, despite a higher risk of progression with surveillance [1].

In line with this the urological community is increasingly studying different ablative technologies for treatment of localized PCa. This goes along with advances in improved visualization of the tumor. In this context, focal therapy (FT) has emerged as a promising alternative to radical prostate treatment aimed at improving the balance between oncological control and functional preservation. By only targeting the index lesion—considered the main driver of disease progression—FT seeks to minimize damage to surrounding structures and reduce treatment-related morbidity [2]. Current evidence supports its use in intermediate-risk patients, while AS remains preferable in low-risk disease. Over the past decade, multiple FT modalities have faced the surface, including amongst others high-intensity focused ultrasound (HIFU), cryotherapy, and irreversible electroporation (IRE). Early evidence suggests favourable safety and functional outcomes; however, most studies have been limited to early-phase (IDEAL stage 2b) designs [3]. While high-quality evidence supports the role of FT in improving functional outcomes and reducing adverse events, conclusive evidence demonstrating its oncological efficacy compared with the current standard of care is still lacking. Therefore, major guidelines still recommend that FT, even with established modalities, should be performed at least within a prospective registry [4].

This special collection of Prostate Cancer and Prostatic Diseases (PCAN) provides a timely overview of where the field currently stands—from mature evidence on established modalities to the emergence of novel energy platforms and the increasingly important role of salvage strategies. The collection was performed in collaboration between editors of PCAN and members of the scientific committee of the Société Internationale d'Urologie.

One of the key contributions in this collection is the systematic review and meta-analysis by Tay et al. [5], which offers perhaps the most comprehensive contemporary assessment of established FT modalities, namely HIFU, cryotherapy, and IRE, which have the longest history of use. By pooling 49 cohorts across more than a decade of clinical experience, the authors report excellent short- to intermediate-term oncological outcomes, with pooled overall survival, cancer-specific survival, and metastasis-free survival rates all approaching 99%. Biochemical progression was reported in only 30% of the cohorts, with a mean annual biochemical progression rate of 9%. No significant differences were observed among the three different modalities or across FT ablation patterns, although the authors noted a temporal shift toward more focal and targeted ablation strategies compared with hemi-ablation approaches. Regarding treatment failure, owing to the heterogeneity in its definition across studies, the authors adopted a composite endpoint including radical or whole-gland treatment, initiation of hormonal therapy, or transition to watchful waiting, while excluding repeat FT procedures. Using this definition, 19 of 49 cohorts (38.8%) reported a pooled failure rate of 14%. Overall, these findings are highly reassuring and support the oncological feasibility of FT in carefully selected patients. At the same time, the heterogeneity in surveillance protocols, treatment margins, and follow-up biopsy strategies remains a major limitation, highlighting the urgent need for standardized clinical pathways [5].

Equally important is the review by Ghai et al. [6], which focuses on the "new kids on the block" in FT: MRI-guided focused ultrasound, transurethral ultrasound ablation (TULSA), focal laser ablation (FLA), and histotripsy. Among these modalities, MRI-guided approaches are particularly compelling because they offer real-time thermal monitoring, precise treatment margins, and potentially superior reproducibility. In particular, MR-guided focused ultrasound surgery (MRgFUS) is a non-invasive technique that uses focused ultrasound waves under real-time MRI guidance to induce thermal coagulative necrosis, allowing precise targeting while preserving surrounding healthy tissue. Similarly, TULSA delivers directional ultrasound energy through a transurethral applicator under MRI thermometry guidance, enabling controlled whole-gland or subtotal ablation with favourable oncological and functional outcomes. FLA, performed either under MRI or ultrasound guidance, uses laser-induced thermal energy to achieve highly localized tissue destruction and has shown

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promising short- to intermediate-term cancer control with minimal impact on urinary and sexual function. Finally, histotripsy represents a novel non-thermal technology based on pulsed high-intensity ultrasound, which mechanically fractionates tissue through cavitation bubble activity while potentially preserving surrounding extracellular structures. Overall, these modalities have demonstrated encouraging oncological efficacy together with excellent functional preservation, particularly regarding continence and erectile function, supporting their role as minimally invasive alternatives for selected patients with localized prostate cancer. To note, several limitations still hinder the widespread adoption of these technologies. Most available studies are small, non-randomized, single-center series with relatively short follow-up, limiting the strength of current evidence regarding long-term oncological durability. In addition, heterogeneity in patient selection, treatment margins, surveillance protocols, and follow-up biopsy strategies makes comparisons across studies challenging. Furthermore, MRI-guided procedures are associated with increased procedural complexity, longer operative times, and higher costs, while some techniques may have technical limitations related to tumor location, prostate calcifications, or the need for multiple treatment applicators to achieve adequate ablation coverage [6].

Across all studies included in this collection, mpMRI emerges as the cornerstone of focal therapy. Its role extends beyond diagnosis to include lesion localization, treatment planning, margin definition and post-treatment surveillance. This tight integration between imaging and therapy highlights that FT cannot exist without a robust diagnostic pathway. As such, improvements in imaging accuracy will directly translate into more accurate patient selection and consequently better oncological outcomes. Correas et al. [7] examined the potential added value of multiparametric ultrasound (mpUS) and micro-ultrasound (mUS) as a complementary tool combined with MRI. By integrating structural, vascular, and tissue-characterization information derived from non-linear B-mode imaging, Doppler and micro-Doppler techniques, elastography, and CEUS, mpUS provides superior diagnostic performance over standard B-mode TRUS in the detection of prostate cancer. Shear wave elastography (SWE) has potential in the era of FT, as it improves detection of stiff lesions not seen with other imaging techniques and real-time targeting of biopsy cores. It is mainly available on a single US platform; accuracy, sensitivity, and NPV ranged from 70 to 96%, 92 to 96%, and 83 to 99% respectively. The stiffness value correlated to the ISUP grade the Gleason score. Having said this, some concerns may arise from this topic. First of all, the authors emphasize that mpMRI and advanced ultrasound can accurately select patients and guide FT. However, they themselves acknowledge that MRI misses secondary csPCa in up to 50% of cases and that lesion size and extent are frequently underestimated. Therefore, a key counterargument is that if the imaging modality used to define the treatment target fails to identify all clinically significant disease, then the biological rationale of FT becomes weaker. In other words, the limitation is not the ablation technology itself, but the ability to accurately map the disease before treatment. Furthermore, does micro-ultrasound truly improve clinically meaningful endpoints (treatment planning, recurrence rates, metastasis-free survival), or does it merely identify more lesions without changing long-term outcomes? Certainly, Correas et al. [7] demonstrates that imaging has improved dramatically, but it does not yet support an image-only approach to patient. In fact, biopsy remains indispensable for both patient selection and post-treatment surveillance, highlighting that accurate disease characterization—rather than energy delivery—continues to represent the principal challenge for the future development and validation of FT. As a matter of fact, there is currently no universally accepted "best" biopsy strategy for selecting patients for FT in prostate cancer. While transperineal template mapping biopsy (TTPM) and the Ginsburg protocol are often considered reference standards because of their high diagnostic accuracy, they are invasive, require general anaesthesia, are costly, and may increase biopsy-related morbidity due to the high number of cores obtained. Consequently, several studies have investigated whether less invasive approaches combining multiparametric MRI, MRI-targeted biopsy (MRI-TB), and systematic biopsy (SB) can adequately identify clinically significant prostate cancer (csPCa) and appropriately select candidates for FT. In the narrative review by Windisch et al. [8] MRI-TB combined with systematic TRUS biopsy achieved approximately 80% sensitivity and 75% overall accuracy for FT eligibility when compared with whole-mount histopathology (WMH). On the other hand, nearly half of patients initially considered eligible for FT based on MRI-targeted biopsies were later deemed unsuitable after final pathology assessment, mainly because of undetected contralateral or more extensive disease. Similarly, studies using more extensive biopsy approaches, such as TTPM combined with MRI-TB, demonstrated improved staging accuracy and better identification of bilateral or higher-grade tumours, although at the cost of significantly higher biopsy burden and the need for anesthesia [8].

The review by Ghoreifi et al. [9] addresses one of the most important unresolved questions in FT for localized prostate cancer: whether genomic biomarkers can improve patient selection and oncological risk stratification beyond conventional clinical, imaging, and pathological variables. As FT aims to eradicate the index lesion while preserving surrounding tissue, accurate characterization of tumour biology is essential to minimize the risk of undertreating clinically significant disease. The authors therefore sought to summarize the current evidence supporting the use of tissue-based genomic classifiers and molecular biomarkers in the context of FT. Commercially available genomic assays, including Decipher, Oncotype DX Genomic Prostate Score, and Prolaris, which have demonstrated prognostic value for adverse pathology, biochemical recurrence, metastasis, and prostate cancer-specific mortality in men with localized disease. By integrating molecular information with established clinical and radiological parameters, these tools may refine risk assessment and potentially improve the identification of suitable FT candidates. However, most genomic classifiers have been validated in cohorts undergoing active surveillance, radical prostatectomy, or radiotherapy rather than FT. Consequently, evidence supporting their specific use in FT remains largely indirect. Furthermore, it is still unclear whether genomic testing can reliably identify untreated clinically significant cancer outside the ablation zone or accurately characterize the biological relevance of secondary lesions. Most importantly, there is currently no prospective evidence demonstrating that the addition of genomic classifiers to contemporary MRI-guided patient selection translates into improved oncological outcomes [9].

In the end, a major theme emerging from this collection is the management of recurrence after primary FT. The review by Ramacciotti et al. [10] addresses one of the most clinically relevant and underexplored issues in the FT pathway: what happens when focal therapy fails? The authors elegantly summarize the available salvage options, including repeat focal treatment, salvage radical prostatectomy, and salvage radiotherapy. More specifically, 21 studies with a total of 1012 patients were included. The most reported salvage treatments were salvage radical prostatectomy followed by re-do ablation therapy, whereas only one study evaluated salvage radiation therapy. Except for one prospective study, all studies were retrospective. Oncological outcomes showed acceptable biochemical recurrence rates. Functional outcomes varied, with significant impacts observed on erectile function across modalities, though continence rates were less impacted. Complications were generally low across all treatment options. The primary endpoint of FT in prostate cancer remains undefined, with considerable variability in how outcomes are measured across studies. Proposed endpoints include biochemical recurrence-free survival, absence of detectable lesions on imaging or biopsy, avoidance of radical or systemic treatment, absence of metastasis, and prostate cancer–specific mortality. In many cases, a composite definition of failure is used, encompassing the need for

radical or systemic therapy, development of metastases, or cancer-specific death.

In contrast, expert consensus has defined FT success more strictly as complete eradication of all biopsy-proven clinically significant disease (Gleason Grade ≥2 lesions). However, this creates a conceptual mismatch, as patients with low-volume GG2 disease may still be appropriately managed with active surveillance, meaning that "failure" of FT does not always equate to meaningful clinical progression. Importantly, there is also no standardized approach to managing recurrence after primary FT. Salvage options—including radical prostatectomy, radiotherapy, or repeat focal ablation—are currently selected on a case-by-case basis rather than guided by established consensus or evidence-based algorithms.

Taken together, the articles highlight both the promise and the current limitations of FT. Nevertheless, several critical questions remain unanswered:

- Can FT achieve durable oncological control comparable to radical treatment in intermediate-risk disease?
- Should recurrence after FT be considered treatment failure or part of an organ-preserving strategy?
- Will emerging technologies such as TULSA and histotripsy outperform established HIFU and cryotherapy platforms? Can surveillance protocols finally be standardized?

Focal therapy has many faces and is no longer an experimental niche but an increasingly mature field in uro-oncology. The challenge ahead is no longer proving feasibility, but defining durability, standardization, and patient selection. Eventually, the road to success for focal therapy is paved by improvements in enhanced prostate imaging.

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AUTHOR CONTRIBUTIONS

AF. writing - original draft preparation - conceptualization; JdlR. writing - review and editing; CDN. supervision – conceptualization.

COMPETING INTERESTS

The authors declare no competing interests.