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PROSTATE CANCER (A KIBEL, SECTION EDITOR)

# Current Trends and New Frontiers in Focal Therapy for Localized Prostate Cancer

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**Abstract** Prostate cancer (PCa) care is an ever-evolving field. Research and technological developments continue to refine our definitions and management of this disease. Now, with a greater understanding of the natural history of PCa, the prevention of overtreatment has shaped a new era with the adoption of active surveillance (AS) and advancement of focal therapy (FT). Multiparametric magnetic resonance imaging (mpMRI) allows us to define, locate, and monitor cancers in a way never before possible. These capabilities combined with promising results from current prospective studies have changed the face of FT. This review presents the latest developments, current trends, and next steps in FT.

**Keywords** Prostate cancer · Focal therapy · Multiparametric MRI · PI-RADS · Cryotherapy · High-intensity-focused ultrasound

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## Introduction

Over the last 20 years, there has been a 40 % reduction in prostate cancer (PCa)-related deaths [1]; however, this has been coupled with a significant increase in the diagnosis and treatment of potentially insignificant disease. At present, the mainstay of treatment involves radical whole-gland therapy (RWGT) with radical prostatectomy (RP) or radiotherapy, versus active surveillance (AS). The dichotomous nature of these management options challenges clinical decision-making. While RWGT provides the greatest confidence in durable outcomes, complications can have a detrimental impact on a patient's quality of life (QoL) [2]. AS avoids these therapeutic side effects, but given the poor accuracy of conventional biopsy for diagnosis [3], it carries potential for under-treatment, disease progression, and the psychological burden of untreated cancer. Focal therapy (FT) has emerged as an innovative strategy in the treatment of clinically localized PCa, poised to address the aforementioned limitations. FT aims to target and eradicate the index tumor (IT) and significant secondary lesions (SL) to minimize treatment-induced damage of adjacent structures (e.g., bladder, rectum, neurovascular bundles). Advancements in mpMRI have driven FT forward by providing functional characterization and localization of PCa foci, refined patient selection, precise targeting, and a reliable tool in post-treatment surveillance. Herein, we review the most significant advances and latest trends pertaining to the role of FT in the management of clinically localized PCa.

## Redefining Patient Selection

In the balance between over-detection and over-treatment, patient selection is the fulcrum to optimal PCa care. However, the heterogeneous nature of this disease makes this a major

challenge. To date, we cannot predict cancer behavior nor what drives metastasis. For the last 20 years, we have utilized Epstein's criteria of significant versus insignificant cancer to guide clinical decisions [4], yet these definitions have recently been questioned. van der Kwast and Roobol argue the current definition of insignificant disease is too narrow, citing many studies supporting the indolent behavior of pure Gleason score (GS) 6 disease [5•]. While this would greatly expand AS eligibility, other studies have demonstrated variations in GS6 behavior particularly within certain populations such as African American and obese men that may counter this argument [6, 7]. Initially, FT was encouraged for unilateral or unifocal low-risk disease, but by today's standards, this may be overtreatment. Expert consensus panels (ECPs) now agree patients with intermediate risk disease, including those with multifocal disease, are appropriate candidates for FT [8, 9••, 10•]. In addition, FT ECPs agree insignificant lesions by Epstein criteria do not necessarily need to be targeted for FT but can be monitored by AS, including GS6<3 mm length within the FT treatment zone [9••, 11]. This shift in thought is likely the product of the AS movement and evolving definitions of significant versus insignificant disease.

## Multifocality and FT: Incongruent Concepts?

A longstanding criticism of FT holds that the multifocal nature of PCa inherently contradicts the ability of a focal approach to provide adequate oncological control. The current practice in FT targets the IT as well as significant SL to achieve oncological control [9••, 10•]. A growing body of literature supports this approach having identified the IT as the determinant factor in disease behavior while the development of a lethal clone of cells are likely responsible for the development of metastatic disease [12–15]. In addition, recent studies have found little to no effect of multifocality on overall pathological and biochemical outcomes for PCa [16–20]. Iremashvili et al. evaluated 1400 men treated with RP and found no difference between singular and multifocal lesions in biochemical recurrence (BCR) [19]. A recent study by Le et al. found 87 % of SL to be GS6 and 82 % to be <1 cm [21•] highlighting the likely indolent nature of most SL. Therefore, it is not the presence of multifocality but rather the ability to target and eliminate the IT and significant SL that define oncological control in FT. The high specificity and negative predictive value (NPV) of mpMRI provides the key to this success [22••].

## Current mpMRI Capabilities: Seeing the Significance

Prostatic MRI was introduced approximately 30 years ago; however, over the past 10 years, multiparametric techniques have revolutionized the field. mpMRI enables clinicians to assess functional characteristics of suspicious lesions, subsequently increasing both its sensitivity and specificity over isolated anatomical T2-weighted imaging (T2w). According to the 2012 European Society of Urogenital Radiology (ESUR) prostate MR guidelines, it is recommended that high-resolution T2w be paired with at least two functional techniques, most often including diffusion-weighted imaging (DWI)—adding specificity to lesion characterization and dynamic contrast-enhanced MRI (DCE)—having a high sensitivity in both lesion and recurrence detection [23]. Futterer et al. highlighted the benefit of pairing these imaging techniques demonstrating an area under the curve of 0.9 for the localization of PCa [24]. Each imaging technique utilizes a different characteristic of PCa to aid identification. For example, a hyperintense defect on DWI is produced by limited water diffusion secondary to the high cellular density and complex microstructure of cancer [25]. Apparent diffusion coefficient (ADC) maps, derived from DWI, have a strong inverse relationship to GS [26–29]. However, given the overlap of ADC values for a given GS along with differences in equipment and techniques across practices, a definitive correlation scale is yet to be established. In addition to DWI and ADC mapping, DCE-MRI detects vascular differences often present in malignancies via increased blood flow, microvascular density, and capillary leakiness [30] and is the imaging modality of choice to identify PCa recurrence [31].

Comparison to whole mount pathology can validate mpMRI's discernment for lesion identification/localization. While theoretically straightforward, this has proved challenging. Initial studies did not account for the significant degree of deformation resulting from free-hand slicing or non-uniform shrinkage occurring with fixation [8]. To address these challenges, Turkbey et al. sliced the prostate sections at the same interval as the MRI slices using a customized 3D mold. The subsequent positive predictive value (PPV) of mpMRI using this comparative method was 98 % overall, 98 % in the peripheral zone, and 100 % in the central zone [32]. Given the demands of this process, almost all studies utilize a non-stepped whole mount specimen approach. A summary of recent studies examining mpMRI performance parameters can be found in Table 1. A recent study by Le et al. specifically examines the current capabilities of mpMRI in the detection of index and non-index lesions against non-step sectioned whole mount histopathology. Of 122 patients, 36 % had solitary and 64 % had multifocal lesions with 283 unique lesions identified on pathology. Altogether, 80 % of ITs and 72 % of ≥GS7 lesions were identified, while 86 % of tumors less than 0.5 cc were not. Of 60.7 % SL not identified, 83 % were <1 cm and 78.6 % were low grade [21•]. Arguments could be made that this supports the goal of not detecting insignificant lesions or that standard transrectal ultrasound biopsy (TRUSBx) should still be paired with mpMRI guided biopsy

**Table 1** Outcomes of studies examining mpMRI's capabilities validated by various histopathological methods

| Reference | Number | MRI | Sequence | ERC | Analysis | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) | PA |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Turkbey et al. [33] | 70 | 3 T Achieva, Philips | T2w, T1w, MRSI, DCE | Yes | Individual review | 73 | 89 | – | – | – | Whole mount HP |
| Rosenkrantz et al. [34] | 38 | 1.5 T Magnetom Avanto, Siemens | T2w, T1w | No | Individual review | 67.4 | 71.1 | 58.6 | 78.3 | 69.7 | Whole mount HP |
| Kitajima et al. [35] | 53 | 3 T Magnetom Trio Tim, Siemens | T2w, T1w, DWI, DCE | No | 1–5 scoring scale | 80.8 | 95.7 | 85.1 | 95.4 | 92.2 | TRUSBx |
| Vilanova et al. [36] | 70 | 1.5 T Signa HDx, GE | T2w, DWI, DCE, MRSI | Yes | 1–5 scoring scale | 72.5 | 91 | 82.2 | 85.3 | 87.3 | 57 TRUSBx and 13 whole mount HP |
| Turkbey et al. [32] | 48 | 3 T Intera Achieva, Philips | T2w, T1w, DWI, DCE, MRSI | Yes | DWI toolkit | 58 | 100 | 93 | 90 | – | Whole mount HP |
| Portalez et al. [37] | 129 | 1.5 T Acheiva, Philips and 1.5 T Avanto, Siemens | T2w, DWI, DCE | Yes and no | ESUR-S<br>Likert | 69.1<br>73.5 | 92.2<br>81.5 | 58.0<br>38.2 | 95.1<br>95.2 | 89.1<br>80.4 | TRUSBx and MRGB |
| Gray et al. [38] | 201 | 1.5 T Signa Excite, GE and 1.5 T Magnetom Symphony, Siemens AG | T2w, DWI | No | PI-RADS | 97 | 60 | 67.5 | 97.7 | – | TTMB |
| Pokorny et al. [39] | 223 | 3 T Magnetom Skyra, Siemens | T2w, DWI, ADC, DCE | No | PI-RADS | 92.3<br>70.4 | 96.9<br>93.6 | 92.3<br>93.2 | 96.9<br>71.9 | –<br>– | MRGB<br>TRUSBx |
| Pepe et al. [40] | 100 | 3 T Achieva, Philips | T2w, DWI, DCE, MRSI | No | PI-RADS | 82.2 | 77.8 | 65.4 | 95.5 | 82.6 | SPBx and MRGB |
| Jambor et al. [41] | 55 | 3 T Megnetom Verio, Siemens | T2w, DWI<br>T2w, DWI, DCE, MRSI | No<br>No | 1–5 scoring system | 61<br>72 | 96<br>89 | –<br>– | –<br>– | 87<br>85 | TRUSBx and MRGB |
| Gupta et al. [42] | 60 | 3 T GE HDx, GE | T2w, DWI, DCE | Yes | T2a/b vs T2c vs T3a vs T3b | 82.6 | 86.4 | 91.2 | 73.1 | – | Whole mount HP |
| Panebianco et al. [43•] | 570 | 3 T Discovery MR750, GE and Magnetom Verio, Siemens | T2w, DWI, DCE | Yes | PI-RADS | 86 | 94 | 99 | 78 | 97 | TRUSBx and MRGB and whole mount HP |

Adapted and updated from: Muller BG, Futterer JJ, Gupta RT, Katz A, Kirkham A, Kurhanewicz J et al. The role of magnetic resonance imaging (MRI) in focal therapy for prostate cancer: recommendations from a consensus panel. BJU international. 2014;113 (2):218–27

(−) not reported, *MRSI* magnetic resonance spectroscopic imaging, *HP* histopathology, *SPBx* transperineal saturation biopsy, *ESUR-S* European Society of Urogenital Radiology scoring system

(MRGB) to detect potential small volume GS≥7 disease. Since mpMRI and MRGB are both new skills, ECPs agree that 6–12-core TRUSBx still be paired with targeted specimens while technology and learning curves improve [44••, 45].

## Improving Diagnostic Accuracy with mpMRI-Guided Biopsy

A key advantage of MRGB is the ability to localize lesions, describe their characteristics, and confirm these findings with targeted biopsy. This offers both physician and patient assurance that the significant cancer was identified and the appropriate management options can be confidently recommended. TRUSBx inadequately characterizes the extent and grade of disease for a FT approach [46]. Noguchi et al. report TRUSBx underestimated tumor grade in 46 % and overestimated it in 18 % as compared to RP specimens [47]. Comparatively, Hambrock et al. found MRGB to be highly representative of tumor grade exactly matching 88 % of RP specimens [48]. In a prospective study, Pokorny et al. found the MRGB pathway reduced the need for biopsy by 51 %, decreased the diagnosis of low-risk PCa by 89.4 %, and increased the detection of intermediate/high-risk PCa by 17.7 % over a standard TRUSBx approach [39]. Baco el al. utilized step-sectioned RP specimens to evaluate the accuracy of elastic MR/3D TRUS. Twenty-seven regions of interest (ROI) were identified on mpMRI and labeled IT for MRGB. They found a 95 % concordance between the IT location on MRGB and RP specimen and 90 % concordance for tumor grade [49]. Another important application of MRGB applies to men with rising PSAs with repetitive negative TRUSBx. Sonn et al. identified 105 subjects with previous negative TRUSBx and elevated PSA. Each patient underwent standard 12-core TRUSBx followed by MRGB of mpMRI lesions. MRGB revealed newly diagnosed PCa in 34 %, 72 % of whom had clinically significant disease. Importantly, MRGB identified significant disease in 91 % of cases, whereas TRUSBx identified insignificant disease in 46 % [50]. These findings correlate with similar studies reporting a 39–59 % cancer detection range utilizing MRGB for this "dilemma group" of previously undiagnosed men [51–53]. These findings have important implications on patient care and demonstrate the strength of MRGB for disease classification.

## Is There Still a Role for Transperineal Template Mapping Biopsies?

Transperineal template mapping biopsy (TTMB) has been a gold standard for patient selection and FT planning. While TTMB yields a similar cancer detection rate to mpMRI, the detection of ≤GS6 and likely insignificant disease is considerably higher [54]. The strong data supporting mpMRI in the localization and characterization of suspicious lesions has led consensus panels to agree that MRGB is a suitable alternative to TTMB [44••] Additional potential benefits of MRGB over TTMB include reduced burden on clinical and OR resources, no anesthesia, and lower post-procedure rates of urinary retention [55]. In this rapidly developing field, mpMRI will likely emerge as the gold standard method for both initial planning and follow-up strategies in all approaches of FT.

## Next Steps: Adopting a Standardized Language for Reading and Reporting of mpMRI

The volume of data and number of imaging modalities available through mpMRI inherently leads to variation in interpretation, reporting, and understanding if not guided by a validated scoring system. Accurate interdisciplinary communication between urology, radiology, and research is also dependent on this adoption. The ESUR released the Prostate Imaging-Reporting and Data System (PI-RADS) guidelines in 2012, and subsequent studies have shown great promise of this evolving scoring system. In brief, the PI-RADS score is assigned a 1–5 score to reflect the likelihood of significant disease of an identified lesion, 1 being least likely and 5 most likely. A score is assigned for each lesion in every sequence; a separate composite score reflects the overall likelihood of significant cancer [56••]. Schimmoller et al. evaluating the diagnostic value of PI-RADS found using a summed score of T2w, DWI, and DCE (PSsum) ≥10 the sensitivity of MRGB was 86.0 % and the NPV was 86.2 %. For higher grade PCa, sensitivity was 98.6 %, and NPV was 99.5 %. Overall, a PSsum below 9 excluded a higher grade PCa, whereas lesions with a PSsum≥13 represented in 88 % PCa, 42 % of which were higher grade [57]. However, given the variable importance of each sequence for a given context, a simple summed score may not reflect these variations. A consensus between the ESUR and the PI-RADS steering committee of the American College of Radiology stated the overall score should be weighted to reflect the "dominant" sequence which is DWI for lesions in the PZ, T2w for lesions in the TZ, and DCE when evaluating for recurrence [56••]. The newest PI-RADS guidelines are pending publication and highlight this recent development.

## Consensus Panels and the Current Practice of FT

FT comprises a diverse armamentarium of energy modalities that includes cryotherapy, high-intensity-focused ultrasound (HIFU), irreversible electroporation (IRE), radiotherapy, photodynamic therapy (PDT), and laser interstitial therapy (LIT)

among others. The incorporation of imaging advances, greater cumulative clinical experience, and in some cases newer generations of instrumentation have together fueled the rapid evolution of the field. Indeed, this growth is reflected by the increasing number of focal therapy clinical trials that have emerged over the last decade (Fig. 1). To validate focal techniques, several studies with short- to mid-term follow-up are ongoing to ultimately inform the design of future long-term trials that would provide the strongest evidence for or against the implementation of FT as an established alternative to RWGT or AS. A critical perquisite is the standardization of patient selection, the interpretation/reporting of mpMRIs, and post-treatment follow-up.

## Irreversible Electroporation

IRE is among the most novel of prostate FTs and has the advantage of being able to be combined with real-time MRI visual and thermometry monitoring during treatment. Lee et al. describe their initial experience with MRI in-bore IRE therapy for 21 patients highlighting patient selection, therapeutic procedure—in-bore ablation of 150 % of the target volume with confirmed destruction using intravenous Gadolinium and follow-up practice [58]. At the time of publication, 13 patients had undergone post-procedure MRGB, 12 (92.3 %) had no evidence of disease, and 1 had residual 3+4 disease which was reablated. Additionally, no incontinence or significant changes from baseline AUA symptom scores (AUASS), International Prostate Symptom Scores (IPSS), or Sexual Health Inventory for Men (SHIM) scores were observed 3–6 months post-procedure. A retrospective analysis by Valerio et al. also demonstrated encouraging functional outcomes in 34 patients at 6 months with 100 % continence and 95 % preservation potency of pretreatment potent patients [59]. These authors are conducting a prospective analysis (NEAT trial) evaluating both functional and disease outcome measures after treating anterior prostate lesions [60]. A shorter pilot study in the USA is aimed at evaluating the short-term (3 month) efficacy, adverse events, and functional outcomes, and will be presented to the FDA for safety and efficacy evaluation (NCT01972867). Efforts are also in place to correlate histopathological and imaging analysis with treatment efficacy, as evidenced by a multi-center prospective investigation involving patients receiving IRE 1 month prior to RP [61]. A phase II trial currently underway is utilizing real-time MRI-guided IRE treatment and MRGB for oncological follow-up at 3 and 12 months post treatment (NCT01792024). Finally, the most ambitious study to date (CROES) will randomize 200 patients into hemi-ablation versus complete ablation therapy (NCT01835977) [62].

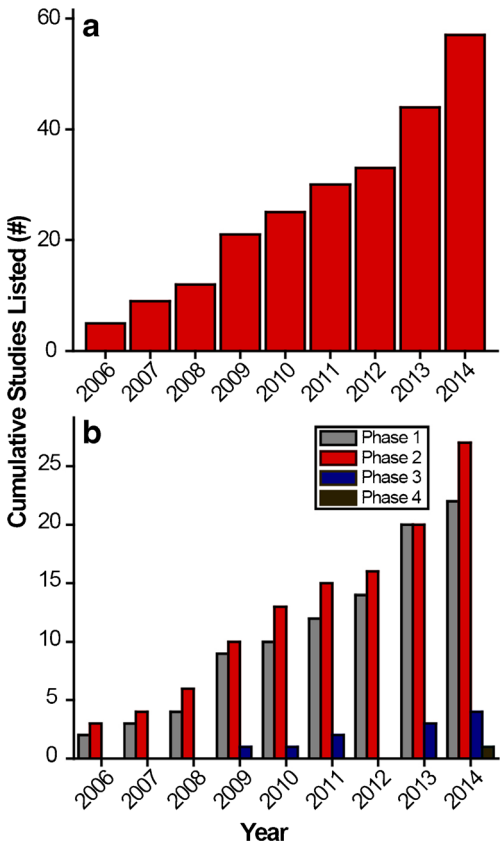


**Fig. 1** The increase in focal therapy trials over time. **a** Cumulative number of focal therapy trials listed on clinicaltrials.gov from 2006 to 2014. **b** Cumulative number of focal therapy trials from 2006 to 2014 organized by phase

## Radiotherapy

Brachytherapy has been used for decades for whole-gland irradiation with well-characterized efficacy and toxicity rates, and this approach is now being considered for targeting cancer foci. A study by Nguyen et al. examined 318 men with GS≤(3+4) and PSA <15 ng/ml whom underwent MRI-guided peripheral zone (PZ) brachytherapy found that failure-free survival was 91.9 % at 5 years and 86.2 % at 8 years using a failure definition of PSA velocity >0.75 ng/mL per year with a PSA elevation of >2 ng/mL; this definition improved detection of local failure over PSA thresholds alone [63]. Furthermore, the authors observed that for low-risk patients, local failure rates with PZ therapy were similar to those described for WG therapy. However, intermediate-risk patients showed higher local failure rates for a PZ versus WG approach. The GEC-ESTRO Brachytherapy Committee held a consensus meeting in 2012 to develop recommendations on patient selection, treatment, and follow-up for focal monotherapy [64]. These guidelines informed a recently published clinical series on focal brachytherapy in low-risk prostate cancer that showed favorable toxicity profiles in 21 patients with unilateral disease, as determined by functional outcome assessments (ICS, IIEF-5, IPSS) [65]. A separate phase II trial

is currently ongoing (NCT01354951) to assess the late toxicity outcomes, QoL measures, tumor control, and radiological-histopathological correlation in patients with low-risk PCa receiving focal brachytherapy. Complementing these developments, groups are developing new treatment plans and dosimetry models appropriate for focal brachytherapy (NCT01830166, NCT01902680). Focal brachytherapy is also being considered as an option for salvage following local recurrence (NCT01583920). While partial prostate irradiation using an external beam as monotherapy has not been established clinically, Riches et al. recently showed that focal boosts with IMRT to mpMRI-defined dominant lesions significantly improved tumor control probability while maintaining dose constraints to healthy tissue [66]. At present, stereotactic body radiotherapy (SBRT) seems poised for a monotherapy approach given its image-tracking capability and highly precise delivery of radiation [67]. There is currently only one trial exploring the possibility of SBRT monotherapy for FT, involving MRI-guided SBRT in low- and intermediate-risk patients (NCT02163317).

### Photodynamic Therapy

PDT utilizes the combination of targeted light administration in the presence of photosensitizing agents that together potentiate oxygen radical formation against cancer cells. Recently, the results of a multicenter phase II prospective study were published that determined the likely optimal drug and light dose in men with low-risk prostate cancer treated with WST-11 (TOOKAD; Steba Biotech, Luxembourg) [68]. Based on imaging, biopsy, and safety data, the authors made recommendations on the optimal treatment conditions. As a result, a randomized phase III study involving 413 patients has been initiated to compare WST-11 PDT versus active surveillance (NCT01310894 [end date September 2015]). Furthermore, a separate group has just completed a phase III multicenter single-arm trial to further characterize the safety and efficacy of this modality by assessing patient-reported outcomes together with serial laboratory and biopsy evaluations up to 1 year (NCT01875393 [end date July 2014]), with results pending.

### High-Intensity-Focused Ultrasound

As a FT, HIFU is being investigated for use in primary and salvage treatment. Several efforts are ongoing to validate the use of HIFU for PCa with longer-term data. Having established reassuring functional outcomes and evidence of early PCa control through short-term single-center studies [69], Dickinson et al. announced the INDEX trial, a single-arm multicenter prospective study with the primary end point of determining the proportion of those free of all PCa and also those free of clinically significant disease in untreated areas at intermediate-term (36 months) post-treatment [70]. This study will feature 5-mm transperineal template mapping biopsy at study entry and exit that offers the potential for histopathological examination of both treated and untreated tissue. The STAR trial will assess for BCR in 200 patients treated with HIFU for locally recurrent PCa status post primary radiation therapy (NCT00772317). An emerging research direction is the integration of MRI guidance with HIFU; to this end, several phase I trials have been detailed (NCT01522118, NCT01686958).

Recently, market approval for whole-gland HIFU ablation of localized PCa was denied in the USA based on the need for more clinical data. However, the use of HIFU for PCa has greatly matured, as evidenced by more recently published long-term single-arm studies showing durable clinical outcomes and morbidity profiles of whole-gland HIFU primary therapy [71, 72] and with neoadjuvant transurethral prostate resection [73]. Functional outcomes and morbidity profiles of primary and salvage HIFU has also been described [74], with outcomes on the latter most recently being shown in patients with radiorecurrent lesions [75]. Combined, these recent developments in whole-gland HIFU, together with ongoing studies in focal ablation described above will likely offer useful comparative data and add value to future focal HIFU therapy trials.

### Cryotherapy

A recently published systematic review on primary focal cryotherapy (PFC) examined outcomes of >1500 patients from nine different studies. The analysis suggested that BCR post PFC (71–93 % at 9–70 months) was similar to that of RWGT in the short to medium term, with comparatively lower side effects [76]. Furthermore the Cryo Online-Data Registry (COLD), pooling the experience from multiple institutions, has thus far suggested similar oncological efficacy yet a favorable morbidity profile with PFC compared to RWGT [77]. A favorable safety and efficacy profile was demonstrated in a prospective study involving GS≤(3+4) disease treated with PFC [78]. These results were particularly interesting as the incidence of positive biopsies at routine 12-month follow-up was comparable to those reported in a 2012 study utilizing a hemiablative approach [79]. The most recent data from COLD showed that patients with radiorecurrent disease treated with salvage focal cryotherapy have similar efficacy (based on BCR and positive biopsy) and better preservation of sexual function as compared to salvage RWG cryotherapy; rates of incontinence and rectourethral fistula were similar [80]. At present, there are two phase IIb trials evaluating PFC (NCT00774436, NCT00877682). The FORECAST trial is utilizing whole body MRI together with targeted/template biopsies to determine suitability of focal salvage therapy in patients with radiorecurrent disease (NCT01883128).

### Laser Interstitial Therapy

LIT involves the delivery of photothermal energy through laser fibers, and leverages the advantages of real-time visualization and temperature monitoring with MRI during treatment. Several phase I trials have demonstrated feasibility and reassuring functional outcomes via a transperineal approach [81, 82]. Significantly, Feller et al. are conducting the first pilot evaluation of safety and efficacy (assessed by MRI-guided biopsy) of transrectally delivered LIT at 1 year post-treatment (NCT02243033). At present, the LIT field has advanced to several ongoing phase II investigations, one of which is investigating the feasibility of ablation with MRI-guidance (NCT01377753), and others aimed at short-term treatment efficacy and intermediate term disease-free survival based on biopsy (NCT01792024, NCT02200809).

## Recommendations in the Follow-up of FT

The utilization of mpMRI, augmented by MRGB, has taken on a prominent role in post-treatment surveillance of FT. While the PI-RADS system has made progress in the standardization in the interpretation and reporting of mpMRI, the rapid succession of guidelines makes it difficult to stay abreast with the latest recommendations. Education of physicians to understand a PI-RADS report would increase comfort and appropriate utilization of the information. Similar to AS, there has been a wide array of how physicians and even institutions choose to follow-up their patients. To standardize FT follow-up protocols, ECPs have made the following recommendations: (1) PSA is a non-validated measure for recurrence in FT and should not be used in isolation [10•]; (2) mpMRI should be obtained prior to procedure to serve as a baseline, 6 months after treatment (allowing for resolution of confounding hemorrhage and/or inflammation), and yearly thereafter [44••, 8]; and (3) any areas of suspicion on DCE-MRI should undergo MRGB for tissue confirmation [8]. The question of FT retreatment was addressed by a separate ECP and agreed that ≤3 mm of GS6 did not require further treatment but should continue to be monitored, retreatment rates ≤20 % were acceptable, and any subsequent RWGT represents a failure of FT [9••, 11]. Inarguably, the next major step for FT will be the conduct of randomized controlled trials; however, exactly what that will look like and entail has been a matter of debate.

## Randomized Controlled Trials: the Time Is Right

While preliminary work to date has suggested encouraging oncologic control and side effect profiles with FT, translation to clinical practice is currently limited by the lack of randomized comparative studies. At present, most experts seem to favor a non-inferiority trial design for the comparison of FT to RWGT. Trial design with standardized methodology is necessary to facilitate meaningful comparisons between studies, ultimately informing clinical decision-making with the highest level of evidence.

A four-stage consensus project based on a modified Delphi algorithm recently published recommendations on FT trial design [83]. Inclusion and exclusion criteria were described, and the authors presented optimal timeframes for single-arm prospective phase II (18–36 months) and randomized prospective comparative phase III (3–5 years) trials. A separate consensus meeting utilizing the two-stage RAND/UCLA Appropriateness Methodology process further developed recommendations on patient eligibility, treatment planning, and oncologic outcomes with FT [9••]. Notably, not only this meeting arrived at similar recommendations and expanded upon many conclusions of the aforementioned Delphi model-based meeting, but also some key differences were presented that reflected a shift in expert opinion on the role of FT in treating localized PCa. One major difference was that the authors agreed that FT should be recommended to patients with intermediate-risk disease. Another difference in selection criteria was that previous treatment to the prostate and radiorecurrent disease were not sufficient to exclude patients from FT.

While standard head-to-head randomized clinical trials (RCTs) offer the greatest level of evidence, several attempts at standard RCTs have been abandoned. Difficulties in patient recruitment, overwhelming financial and logistical burden, and lack of clinical equipoise present barriers to successful and timely delivery of standard RCTs. The PCa RCT Consensus Group (PCRCG) recently advocated for cohort-embedded randomized controlled trials (cmRCT) as a potential alternative to standard head-to-head randomized trials (RCT) [84•]. The details of cmRCT is described extensively elsewhere [85]. In brief, this approach involves recruitment of a large observational cohort with a condition of interest whose outcomes are regularly assessed in a prospective manner. Trial interventions are offered at random to patients meeting inclusion criteria, and their outcomes are measured against eligible patients receiving the standard of care. One unique advantage of cmRCT is that it allows multiple randomized trials over time and thus may enable timely execution of FT trials. cmRCT are well-suited for trials where the standard of care is evaluated against an experimental intervention (e.g. focal versus RWGT), settings involving multiple available interventions (e.g. HIFU, cryotherapy, PDT, etc.), and where easily measured outcomes are evaluated (e.g., patient-reported outcomes). The PCRCG recommended that primary outcomes should be based on composite medium-term outcome measures (3–5 years) and supported the use of database registries to collect long-term (10–15 years) oncologic and QoL data. These mid- to long-term measures are essential to the widespread implementation of FT as it is critically dependent on the hypothesis that tissue sparing reduces morbidity. Taken

together, the current trajectory of FT toward developing higher-level evidence may establish the role of FT as a standard of care for localized PCa.

## Conclusion

Advancements in mpMRI have allowed for rapid progression in every stage of FT from patient selection to post-treatment surveillance in just a few short years. Now, with the power to accurately identify, target, and ablate the IT and significant SL utilizing a combination of mpMRI and MRGB, FT stands to completely revolutionize the management of localized PCa. Greater understanding of the natural history of PCa and shifting consensus on the definition of clinically significant disease have together expanded the eligibility criteria to include intermediate-risk and multifocal lesions. Key next steps in the advancement of this field include universal adoption of standardized interpretation and reporting system for mpMRI, evaluation of intermediate-term outcomes in trials that are currently underway, and ultimately, the establishment of cmRCTs to definitively assess non-inferiority of FT as compared to RWGT in the management of localized PCa.

### Compliance with Ethics Guidelines

**Conflict of Interest** Melissa H. Mendez, Daniel Y. Joh, and Rajan Gupta each declare no potential conflicts of interest.

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**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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