REVIEW ARTICLE

Clinical

Surveillance after Focal Therapy – a Comprehensive Review

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BACKGROUND: to date, no standardized, evidence-based follow-up schemes exist for the monitoring of patients who underwent focal therapy (FT) and expert centers rely mainly on their own experience and/or institutional protocols. We aimed to perform a comprehensive review of the most advantageous follow-up strategies and their rationale after FT for prostate cancer (PCa).
METHODS: a narrative review of the literature was conducted to investigate different follow-up protocols of FT for PCa. Outcomes of interest were post-ablation oncological and functional outcomes and complications.
RESULTS: Oncological success after FT was generally defined as the biopsy-confirmed absence of clinically significant PCa in the treated zone. De novo PCa in the untreated area usually reflects an inaccurate patient selection and should be treated as primary PCa. During follow-up, oncological outcomes should be evaluated with periodic PSA, multiparametric MRI and prostate biopsy. The use of PSA derivatives and new biomarkers is still controversial and therefore not recommended. The first MRI after FT should be performed between 6-12 months to avoid ablation-related artifacts and diagnostic delay in case of FT failure. Other imaging modalities, such as PSMA PET/CT scan, are promising but still need to be validated in the post-FT setting. A 12-month "for-protocol" prostate biopsy, including targeted and systematic biopsy, was generally considered the preferred biopsy method to rule out tumor persistence/recurrence. Subsequent mpMRIs and biopsies should follow a risk-adapted approach depending on the clinical scenario. Functional outcomes should be periodically assessed using validated questionnaires within the first year, when typically recover to a new baseline. Complications, despite uncommon, should be strictly monitored mainly in the first month.
CONCLUSIONS: FT follow-up is a multifaceted process involving clinical, radiological, and histological assessment. Studies evaluating the impact of different follow-up strategies and ideal timings are needed to produce standardized protocols following FT.

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INTRODUCTION

Focal therapy (FT) has emerged as a minimally invasive modality to selectively treat only the cancerous regions within the prostate gland, sparing the remaining tissue. By treating only a portion of the prostate, the impact is less severe than with traditional whole gland radical treatments, improving functional outcomes and decreasing complication rates [1, 2].

In terms of oncological outcomes, current data on FT are promising and, at a medium-term follow-up, have revealed comparable results to radical treatments in well-selected patients [2, 3]. Nevertheless, while FT leads to greater tissue preservation, it can also expose a non-negligible rate of local tumor persistence with or without the opportunity to repeat focal treatment and/or consider radical treatment [4]. In this light, patients who have undergone FT need to be carefully monitored to timely identify any disease persistence or de novo tumors, avoiding cancer progression and not jeopardizing the oncological outcome. At the same time, urinary and sexual functional outcomes, including any perioperative complications, also deserve to be adequately monitored.

Whilst evidence on medium to long-term efficacy of FT is increasing, to date no standardized ways of following patients have been adopted as expert centers rely mainly on their own experience and/or institutional protocols rather than on standardized and/or evidence-based follow-up schemes. The ideal follow-up after FT should balance a reasonable number of meaningful consecutive assessments, thus minimizing the impact on patients' QoL and related costs to the healthcare system, with the need to ensure enough visits to provide optimal monitoring for cancer progression and mortality while avoiding a missed opportunity to optimally retreat the patient, if necessary.

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This work aims to perform a comprehensive review of the most advantageous follow-up strategies and their rationale after FT for PCa.

METHODS/EVIDENCE ACQUISITION

Herein, a narrative review of the literature was conducted to investigate different follow-up protocols of FT for PCa. PubMed-MEDLINE database was investigated on 1st March 2024 using the terms "focal therapy" and "prostate cancer". The outcome of interest was surveillance after FT, focusing on post-treatment oncological and functional outcomes along with complication rates. A manual web search was implemented based on the references of included records and authors' consultation.

EVIDENCE SYNTHESIS

Oncological follow-up

Definition of in-field and out-of-field failures. The main reason for careful oncologic follow-up is the early detection of csPCa recurrence or persistence to optimize the likelihood of cancer control or cure. Thus, it is important to understand why FT can fail and the different failure scenarios.

From a spatial perspective, PCa detected in the treated zone(s) after treatment is defined as "in-field failure (IFF)" or "ablation failure", whilst tumor in the untreated gland is defined as "out-of-field failures (OFF)". IFF are generally considered to be the result of either insufficient energy delivery or targeting error [5, 6]. This may happen if the temperature does not reach the appropriate threshold in thermal ablative therapies, due to host related (e.g. presence of calcification between the energy source and the lesion in the case of HIFU) or inappropriate parameter settings resulting in suboptimal energy delivery, or inadequate coverage of the index lesion to name but a few. Conversely, OFF typically occurs in an untreated area of the prostate on AS and by definition is not related to previous FT delivery and can be the result of "de novo" disease development reaching a clinically significant volume, grade group progression of known GG 1 cancer, or identification of previously unrecognized tumor (suboptimal sampling). The latter are also defined as "selection failures" since they may be the result of poor patient selection, especially when they occur within the first year after treatment [5, 6].

From a time-related perspective, early imaging and/or biopsy identifying disease in the treatment zone can be considered as disease persistence, whilst late onsets are generally considered as recurrence after a cancer-free window [5].

Definition of success. The ideal result of FT relies on oncological and functional principles. Namely, FT success would be the achievement of a histologically documented clinically significant (cs) cancer-free status with minimal adverse effect and/or impact on patients' quality of life [5, 7].

Different definitions have been proposed to define FT success and failure.

As per active surveillance (AS), the highest degree of certitude in exclusion of recurrence remains histology-based and some groups rely on treatment success being based on histology-related definitions.

Historically, when FT was first introduced, success was considered as the absence of any PCa within the prostate at the first control biopsy [8]. However, because of the widespread utilization of AS and the absence of hallmarks of malignancy and metastatic potential of Grade Group (GG) 1 disease, it is now internationally recognized that indolent PCa does not require treatment in the vast majority of cases [9, 10]. Modern FT principles generally do not comprise the treatment of GG 1 lesions anymore, both if alone or contralateral from a main index lesion of a higher grade group, but rather allow surveillance. Of course, there may be exceptions such as a large, MRI-visible GG1 tumor with extraprostatic extension but in general, the presence of some degree of GG 1 disease should not necessarily be regarded as a failure anymore.

FT success is rather defined with histological criteria and consists of biopsy-documented eradication of all identified GG ≥ 2 cancerous lesions at the post-treatment biopsy, with GG 1 tumor in the ablation zone not representing an FT failure [7]. Other international consensuses agreed with this definition, stating that if residual tumor is present in the treatment field, this should be of a lower grade or smaller volume than the original index lesion [5, 11, 12]. Nonetheless, for research purposes, it is important that all publications report treatment success differentiating an "absence of residual tumor" from a "low-risk tumor persistence".

Some authors consider FT success not histology-based but rather using a broader definition that does not rely on the presence of clinically significant disease but as a durable disease control and the absence of the requirement for further whole gland or radical treatment including androgen deprivation therapy (ADT) [2, 13]. This definition involves the success of FT as a strategy rather than that of the primary ablation itself. In this light, a patient with csPCa who presents with residual disease after an initial ablation and no disease after the second round of FT is not considered a failure in the traditional sense [14]. Hence, whilst after radical treatments success is thought of as the eradicating of the tumor with a single treatment, focal ablation offers the possibility of repeating treatment due to its low morbidity.

In urology, there is precedent to repeat treatment when necessary for some malignancies, such as kidney cancer, where a second ablation is allowed [15], and a similar concept can be extended to the prostate, changing the concept of success from "eliminating cancer in a single treatment" to controlling cancer over time possibly with repeat application and low morbidity. However, re-do FT has been observed to be a predictor for FT failure over time [16]. Furthermore, in-field recurrence was associated with PCa progression (biochemical relapse and need for additional treatment) after salvage RP [17]. Therefore, when proposing an additional FT, it is important to determine why the initial FT did not succeed and whether there is a means to apply additional FT in an attempt to maintain cancer control, without delaying the timing of curative salvage whole-gland treatment in aggressive cancers. Nevertheless, while being clinically reasonable, this way of evaluating FT success may pose challenges to the definition of success since it tends to overestimate FT efficacy.

Follow-up timing. Overall, the timing of surveillance should follow a risk-adapted strategy depending on pre- and post-operative factors, keeping in mind the long natural history of localized PCa [3], and initial PCa risk at baseline remains the key driver.

To date, expert recommendations suggest considering FT in the context of discreetly localized GG 2(-3) disease and, more generally, in the context of localized intermediate-risk patients [9, 10]. For GG 1 disease, current guidelines favor AS [9, 10]. However, approximately 10% of AS patients exit surveillance protocols to undergo radical treatments due to cancer-related anxiety, without disease progression, and despite appropriate counseling efforts to reduce these rates [18]. There are other men who discontinue AS and need treatment for csPCa and they remain candidates for FT due to grade, location, and other patient and disease factors. If FT is offered to these men, post-ablation surveillance, whilst relying on the same principles of GG 2 disease, may/might be based on a less intense follow-up schedule compared to those of higher-grade disease due to the lower PCa risk. In contrast, in the case of ablating GG 3 disease, which currently is not standard, a more stringent follow-up should be considered.

PSA and other biomarkers. The use of PSA for post-treatment surveillance following whole-gland RT or RP is well-established [5]. Nonetheless, even in these contexts, the use of biochemical recurrence (BCR) has been recently challenged as it does not always correlate with a worse prognosis and thus may not require treatment [9]. Also, current criteria used to define BCR after RT may not be appropriate anymore with the introduction of novel imaging modalities, as up to half of patients scanned with PSMA-PET/TC below the Phoenix threshold may harbor metastatic PCa [19].

This context is even more challenging with FT due to the presence of untreated benign parenchyma which varies depending on the treated area (FT technique and extension of surrounding margin) but also on the prostate volume left untreated.

Hence, the prostate continues to secrete PSA, with an estimated contribution to PSA for benign tissue ranging between 0.04 and 0.06 ng/ml/cc, impairing accurate post-FT interpretation [20, 21]. Furthermore, the post-treatment serum PSA trend may be affected by age, benign prostatic hypertrophy, and other nonmalignant entities, such as prostatitis [5].

Therefore, PSA is less reliable at identifying recurrence or triggering salvage therapy than after traditional radical treatments. To date, no widely accepted BCR definitions after FT are available [5, 22]. Nonetheless, PSA remains the preferred biomarker after FT, and several consensus panels agreed that it should be recommended in post-procedural surveillance every three months during the first year, and then every six months thereafter [7, 11, 22].

The utility of PSA-related derivatives has also and continues to be investigated in the context of FT.

A %PSA reduction (ratio between PSA nadir and preoperative PSA) of 50-80% has been proposed as suggestive of successful focal hemi-ablation using cryotherapy [23, 24]. In a large multicenter cohort of partial HIFU, only 20% of patients with %PSA reduction >90% were observed to require additional treatment, compared to 70% of men with a %PSA reduction <10%. In this study, %PSA reduction was an independent predictor of the presence of csPCa at follow-up biopsy and of any additional treatments needed after FT at multivariable analysis [25].

A PSA nadir of 1 ng/mL at 12 months and 1.5 ng/mL at 24-36 months has shown a sensitivity of 100% and a negative predictive value (NPV) of 96.1-100% in the detection of failure, defined as any secondary treatment, GG ≥ 2 PCa recurrence on prostate biopsy without further treatment, metastasis and/or PCa-related mortality [26]. Conversely, post-ablation PSA nadir or 6-month PSA levels have been found to have a poor correlation with residual disease identified at biopsy post-focal HIFU [27].

PSA density (PSA-d) assumes relevance, as a notable volumetric decrease of the gland is frequently observed after FT; false negative mpMRI generally have higher PSA-d [28]. Higher median pretreatment PSA-d also relates to increased biochemical progression and positive post-cryoablation biopsy rates [29]. Nonetheless, others showed only moderate ability of PSA-d to predict residual Gleason pattern 4 (AUC 0.78) or residual cancer core length >3 mm any grade PCas (AUC 0.67) [27].

Finally, it is important to recall neither PSA nor its derivatives have been validated in terms of survival and/or disease progression, which constitute stronger and more meaningful endpoints compared to histologically confirmed disease recurrence [3].

Other biomarkers have been recently investigated in a Delphi consensus from the Focal Therapy Society. This work in 2019 revealed the vast opportunity for discovery in the field of biomarkers and FT and, not surprisingly, a low rate of agreement among experts due to the current lack of data [30]. Whilst all panelists recognized research in this context as a priority to improve FT follow-up precision to reduce biopsies and their invasiveness, to date, meaningful clinical interpretation of biomarkers beyond PSA should not be routinely done in the FT setting [5].

Recent work showed the Oncotype DX GPS assay appears to be a prognostic indicator of time to failure-free survival (FFS) and biopsy recurrence (> GG2) in men undergoing FT for PCa. GPS assay is a strong predictor of treatment failure and in-field recurrence beyond NCCN categories. This information can be used to increase the frequency of surveillance and low-threshold for suspicion of recurrence among men with higher GPS score (41-100). Further multi-center studies are required to validate these findings [31].

Imaging. Imaging is a cornerstone of the entire FT process, including patient selection, assessment biopsy, treatment, and follow-up. After FT, its role consists of delineating the contours of the treated area, allowing identification as to whether ablation had an appropriate effect on the location and margins and, more importantly, identifying any elements suggestive of tumor recurrence [5, 7]. Today, the conventional imaging modality for surveillance after FT is mpMRI, although new imaging modalities, such as PSMA PET scans, contrast-enhanced ultrasound (CEUS), and micro-ultrasound, are promising [7].

Multiparametric MRI: Immediate post-FT mpMRI in the first post-interventional period is generally not recommended since it may lead to misinterpretation due to inflammatory reaction and possibly bleeding and has low clinical value. Surgeons at the beginning of their learning curve or suspecting to have missed the target may consider it to confirm a satisfactory ablation field with appropriate margins (Fig. 1) [32–34].

Similarly, early post-FT mpMRI, within 1-3 months, [32, 33, 35] generally shows edema, tissue necrosis, inflammation, and other radiological artifacts including the presence of peripheral rim-like contrast enhancement due to reparative tissue dynamic contrast enhancement (DCE), patchy areas of intermediate-high intensity signal representing hemorrhage on T1-weighted sequence or loss of the zonal anatomy of the prostate on T2- weighted (T2W) sequence are temporary findings but can persist even after 6 months [32, 33, 35, 36]. This may lead to misinterpretation, false positive imaging, and an incorrect trigger for early re-biopsy [5]. Thus, mpMRI should be taken at least 6 months after FT [37] (Fig. 1). Dickinson et al. showed that after focal HIFU 6-month mpMRI has greater accuracy than <3 weeks in identifying residual cancer (AUC 0.77-0.85 vs 0.75-0.76 respectively) [27].

Hence, the initial mpMRI should be performed ideally at 9-12 months post-treatment [7, 20, 38].

Afterward, the timing of further mpMRI is not clear, with some suggesting its use as a consequence of triggering factors, while others suggesting annual or biannual controls, or adapting to AS protocols [7, 13, 39–41].

Normal recurrence-free post-ablation MRI findings consist of a heterogeneous, hypointense area on T2W sequence with no sign of perfusion within it on DCE images [36, 42]. After 6 months, with the resolution of inflammatory effects and formation of scar tissue, the effects of focal ablation usually manifest with fibrosis, fluid-filled cavities, size reduction of the ablated lobe, and midline shift [35, 43, 44] (Fig. 2).

Overall, IFF are best detected using functional sequences and are often characterized by early enhancement on DCE, restricted diffusion, and hyperintense signal on high b-value on diffusion-weighted imaging (DWI), and hypointensity on T2W [7, 32, 36, 42] (Fig. 3). Koopman et al. described DCE imaging as the most conclusive sequence for detecting cancer progression/recurrence, especially after HIFU and cryoablation [36]. Conversely, OFF are new-onset cancer foci outside the ablated region and thus present the same radiological characteristics of primary PCa [5, 38].

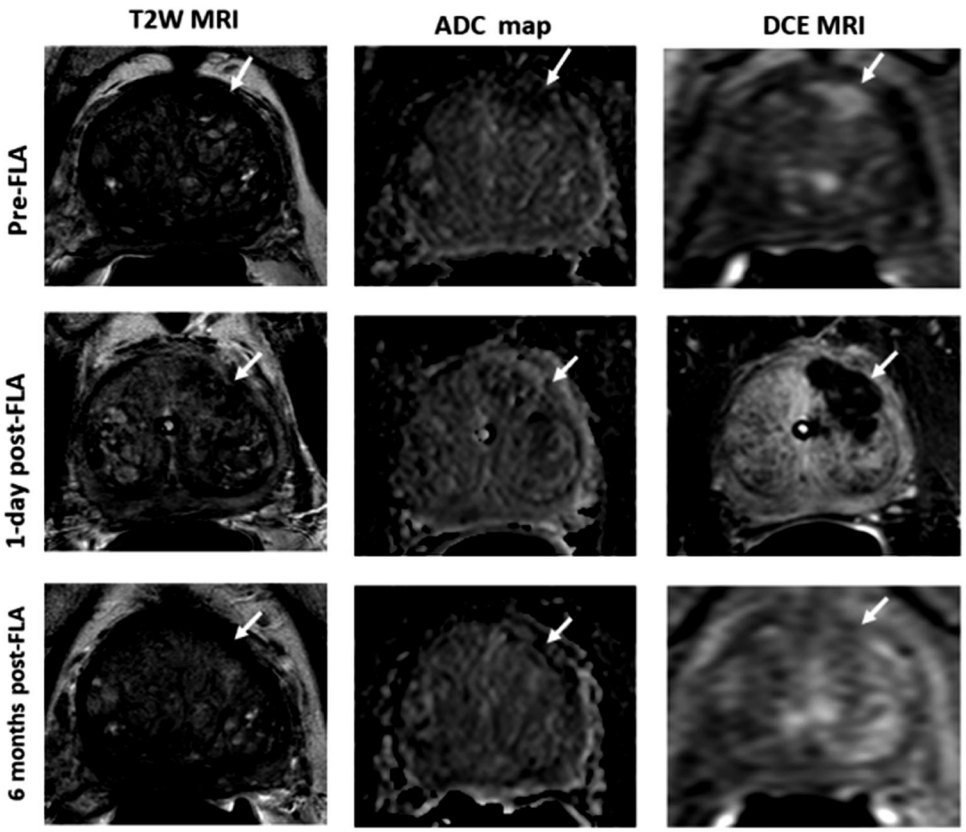

Fig. 1 Multiparametric MRI images showing a Gleason Grade 2 left mid-anterior transition zone lesion treated with focal laser ablation (FLA) without tumor recurrence. From top to bottom: MRI before FLA, 1-day post-FLA MRI with early findings of necrosis and edema, and 6 months post-FLA MRI without evidence of residual/recurrent disease confirmed with fusion targeted guided biopsy.

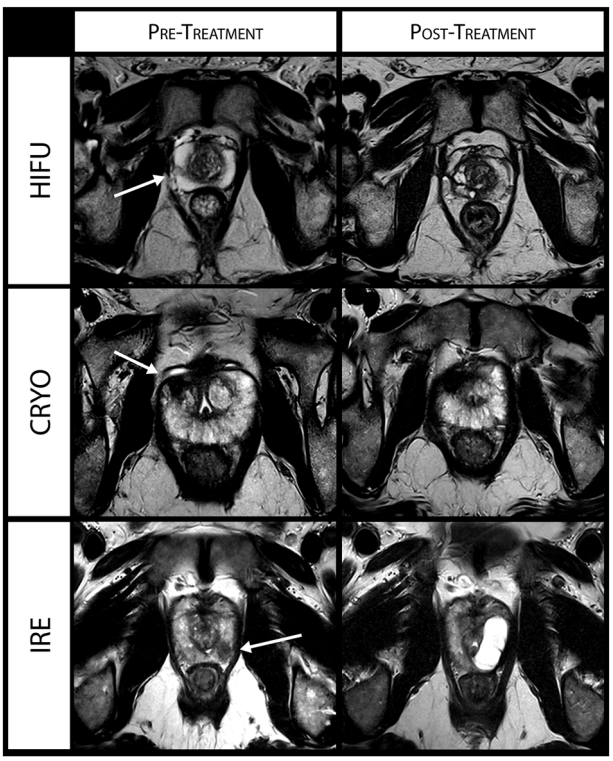

Fig. 2 One-year post-ablation MRI changes using different energies. Size reduction of the ablated lobe, scar tissue, fibrosis, midline shift and fluid-filled cavities are the most common findings at MRI after ablation.

The traditional PI-RADS v2.1 scoring system was developed for treatment-naïve patients and its application is felt as inappropriate in the post-FT setting as it does not take into account treatment-induced changes [45]. More recently, two classification systems have been proposed to evaluate treatment response after FT: the PI-FAB and the TARGET score (Fig. 4) [38, 46]. Both scoring systems use DCE as the main sequence, reflecting the higher importance of contrast images in the post-ablation setting rather than in a treatment-naïve gland. Using a more limited numerical point scale, the PI-FAB score may be easier to adopt than the TARGET score. Conversely, a 5-point scale may allow better stratification of patients into the proper risk category. Both scores still need to be validated before their use in clinical practice.

When there is a suspicious area in the treated zone on mpMRI, histological assessment is necessary as PPV ranges from 14%-47% [47–49]. Additionally, the NPV of mpMRI after FT is not optimal, ranging from 72%-98% [47–49].

The post-FT context may represent a middle ground between the treatment-naïve and post-radiation settings as there will be sections of the prostate that will be untreated. Although the PROMIS group showed that in treatment-naïve patients mpMRI can accurately predict csPCa potentially avoiding systematic biopsy, the same group with the FORECAST trial revealed that in the post-radiation setting MRI-targeted biopsy alone is insufficient for prostate mapping, with 59% of the patients harboring cancer in unsampled (MRI-negative) quadrants [50, 51]. However, to date, there are no high-quality studies investigating this topic and current evidence varies widely among studies, showing contradictory results [48, 49, 52, 53]. A recent systematic review evaluating the diagnostic accuracy for recurrent in-field cancer after late (>6 months) mpMRI post-ablation reported suspicious in-

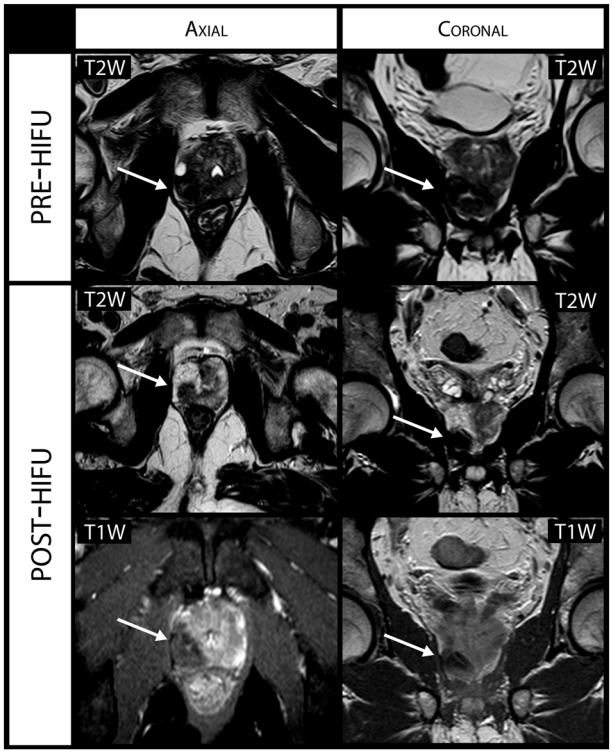

Fig. 3 Multiparametric MRI images (T2-weighted [T2W] and T1-weighted [T1W]) showing 1-year tumor recurrence after HIFU right lobe hemiablation for a right posterior tumor. Transurethral resection of the prostate was performed before the ablation.

field MRI in 0-60% of cases, and in-field cancer being detected on biopsy in 0–57% [35].

In a study comparing post-ablation mpMRI accuracy to RP pathology specimens, Thompson et al. analyzed a series of 35 men who underwent salvage robot-assisted RP after partial ablation HIFU. They reported a moderate (81.8%) sensitivity for IFF, with all 6 missed cases presenting with GG 3 PCa. Interestingly, at final pathology, the overall pT3 rate increased to 60% (location unspecified), compared to 14% of pre-HIFU and 17% of pre-RP cases [54]. Although a selection bias for more advanced disease is likely present, these findings highlight the potential limitations of post-ablation mpMRI.

Alternatives to multiparametric MRI: Compared to mpMRI, PSMA PET/CT has revealed promising results with equivalent and sometimes greater ability in the detection and localization of cancer in the primary as well as in a salvage setting [55–58].

In the context of local recurrence following RT, PSMA-PET/CT provided a high PPV of 94% (88–97%) and a low NPV of 32% (20–45%) whilst mpMRI had a PPV of 78% (71–85%) and NPV of 58% (30-86%) [51, 59].

In a preclinical model, the sensitivity of ^{68}Ga-PSMA PET/CT scan was found superior to PSA: 75% vs 33% at 1- and 100% vs 83% at 4-week [60]. Similarly, in the salvage FT setting, PSMA PET/CT showed a promising role in complementing mpMRI and may be useful in highlighting lesions not identified by mpMRI. In the FIRE trial, where 37 patients with radio-recurrent PCa were treated with salvage IRE, only 86% of mpMRIs were positive but the remaining 14% were positive on PSMA-PET/CT; conversely, the only PSMA-PET/CT being reported as negative was positive at mpMRI [61]. Others confirmed a high PPV combining these two imaging modalities (97.6%) (Fig. 5) [62].

PSMA PET/MRI is another novel imaging modality offering a radiation-free, higher soft tissue contrast option, with the potential

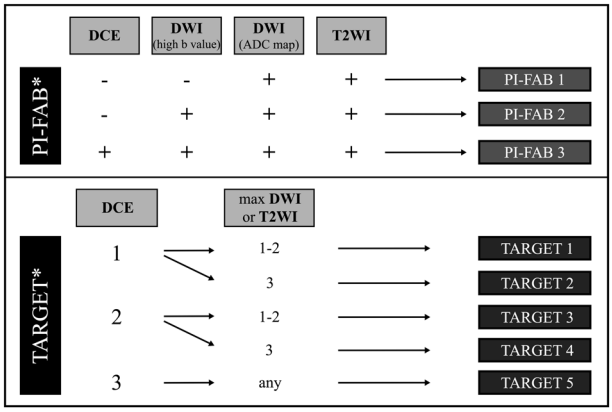

Fig. 4 Prostate Imaging after Focal Ablation (PI-FAB) score and Transatlantic Recommendations for Prostate Gland Evaluation with Magnetic Resonance Imaging After Focal Therapy (TARGET) score. Readapted from Giganti et al. [46] and Light et al. [38]. The PI-FAB score provides a 3-point scale based (in sequential order) on DCE, DWI, and T2W sequences. Each score corresponds to a specific clinical recommendation [46]. The TARGET score provides a 5-point scale including major (DCE) and minor (DWI and T2W) MRI sequences. Each score corresponds to a specific risk category of suspicion of cancer recurrence [38]. In both classification systems, non-suspicious DCE findings result in a low score (PI-FAB 1 or TARGET 1-2). After an equivocal or suspicious DCE finding, the PI-FAB system uses mainly the DWI sequence (high b-value images) to discriminate PI-FAB 2 and 3 while the TARGET system adopts both DWI and T2W sequences. *Both scores are awaiting validation.

for MRI-TRUS fusion [63]. It has been investigated in pilot studies demonstrating some potential to detect PCa recurrence invisible at MRI [64, 65]. Unfortunately, it has high costs and some logistic shortcomings that need to be considered, hampering its widespread adoption in contrast to PET/CT.

Other imaging modalities include CEUS, which has been investigated to monitor disease in the ablated zone as an alternative to mpMRI in the post-FT setting. In a retrospective study of 33 patients, Bacchetta et al. compared the utility of intraoperative CEUS with early post-treatment MRI (within 5-10 days) in patients undergoing partial HIFU: intraoperative CEUS featured a high AUC for detecting csPCa at biopsy than MRI (0.881 vs 0.835) [66]. The ability of CEUS to identify the ablated region contours after FT was also evaluated showing comparable accuracy with mpMRI and high concordance with histopathological findings (RP specimens) [67, 68]. Micro-ultrasound is also another promising modality although still not investigated in a post-FT context.

Prostate biopsy. Due to the suboptimal performance of PSA and mpMRI when compared to prostate biopsy, histological confirmation is recommended in the majority of consensus panels regarding post-FT follow-up [5, 7, 8, 69].

Overall, post-FT biopsies can be performed in the context of a protocol at a pre-defined time ("for protocol" biopsy) or in case of clinical suspicion ("for cause" biopsy –due to suspicious follow-up imaging and/or abnormal PSA or PSA derivatives, and/or digital rectal examination).

Nonetheless, these triggers are not free from limitations and can lead to a fair number of unnecessary biopsies. This inevitably creates discomfort and anxiety and negatively impacts patients' QoL, whose compliance widely varies from 17 to 100% in recent trials [14].

Importantly, FT cohorts using "for protocol" follow-up biopsies [13, 41] generally show inferior success rates compared to "for cause" biopsies [39, 40] as imaging and other clinical tools may miss the presence of csPCa. In two studies adopting a "for cause"

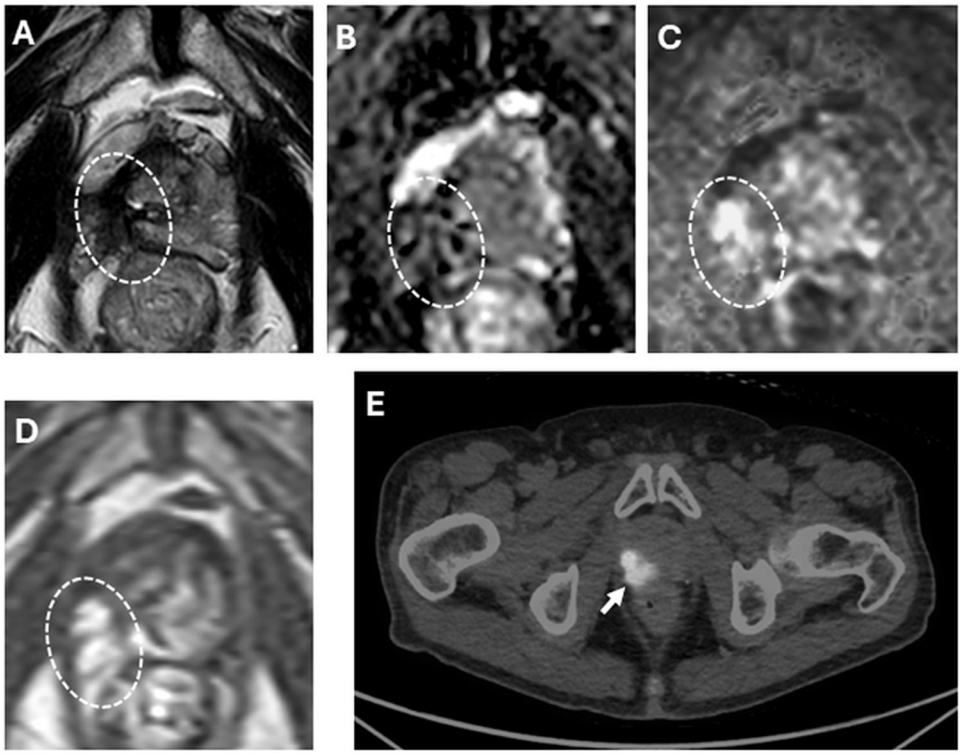

Fig. 5 Multiparametric MRI and PSMA PET/CT showing recurrence 12 months after focal HIFU. Axial T2W MRI (**A**), ADC map (**B**), b1500 DWI MRI (**C**) and DCE MRI (**D**) demonstrate right-sided recurrent lesion (dashed circle), which also demonstrates tracer uptake on 18F-DCFPyL PET/CT (arrow) (**E**).

approach, for instance, only a small proportion of patients (35.5-41%) received post-treatment biopsies after a follow-up of 5 years [39, 40].

Two of the current studies reporting medium-long term follow-up after FT belong to groups adopting different regimens of follow-up biopsy. The "for cause" biopsy cohort revealed a 7-year failure-free survival (no salvage whole-gland or systemic treatment) of 69% after focal HIFU [2], while the "for protocol" group, preferring a planned-control biopsy, reported a 10-year failure-free survival (radical therapy-free or ADT-free) of 51% after focal cryoablation [13].

Another important aspect is whether targeted biopsies of the treated area –with or without suspicion of PCa recurrence– should be complemented by systematic cores, particularly since untreated areas of the prostate remain on AS.

In the treatment-naïve setting, it is well known that the MRI-targeted biopsy should be combined with systematic sampling to detect all csPCa [70]. In the post-FT setting, evidence is again limited. In a phase-II mandatory biopsy-monitored (MRI-targeted plus saturation systematic both pre- and 12-month post-ablation) study with 28 patients undergoing focal cryotherapy, three (10.7%) of the six men having csPCa recurrences were detected only by the systematic sampling [71]. In another biopsy-monitored (MRI-targeted plus template mapping at enrollment and at 12 months) study treating 123 patients with focal IRE, 12.7% of the patients had csPCa OFF at systematic cores [72]. In both studies, a low but non-negligible rate of csPCa OFF was found postoperatively. As such, several consensuses stated that MRI-targeted biopsy of the ablated region plus systematic biopsy of the untreated area should be considered as the preferred biopsy method in the post-FT setting to timely identify patients with persistent IFF and/or OFF [5, 7, 8, 69].

For mpMRI-targeted sampling, 4 cores across the treated area can help account for confounding gland deformity due to fibrosis or remodeling [5]. Indeed, after treatment, the reparative process not only causes scarring and contraction of the ablation site but also distortion and settling of the untreated zone to "fill-in" the space created by that tissue contraction. Thus, targeting the treated zone post-therapy may pose its own unique set of challenges [5]. Concerning systematic biopsy, the 12-core extended sextant template is the most used to interrogate untreated areas [5, 7].

The recommended timing for biopsy is around 12 months after FT [5, 7]. At this time, the inflammatory effects, which might impact the ability of the pathologist to interpret prostate biopsy specimens, are expected to be resolved with the formation of scar tissue [5]. Stromal fibrosis persists for up to 16 months but does not impair pathologists' ability to grade recurrences [73]. Importantly, in biopsies from the treated zone, the pathologist should report findings that confirm that the treated zone has been biopsied, such as the presence of necrosis, hemosiderin deposition, acute and chronic inflammation, glandular atrophy, reactive fibroblasts or stromal fibrosis [5]. If focal RT has been used, it is suggested instead of waiting at least 18 months before proceeding to biopsy [74].

Subsequent biopsies should follow a risk-adapted approach depending on the clinical scenario as endorsed by guidelines for AS and adopted based on institutional standards of care [7].

Longer longitudinal data are required to achieve the optimal schedule and technique for post-ablation prostate biopsy during post-FT surveillance.

Surveillance of functional outcomes and complications

In the post-FT setting, urinary and sexual function should be monitored and compared to baseline using validated questionnaires for study purposes [7, 75] (Supplementary Material 1).

Importantly, the optimal schedule and assessment method to investigate them are affected by the lack of high-level comparative studies and the heterogeneity observed in the design, study populations, and patient-reported outcome measures [22, 76, 77].

Unlike oncologic outcomes that require long-term longitudinal follow-up, functional outcomes typically recover to a new baseline within a year.

According to a recent systematic review on focal HIFU, most of the studies reported outcomes at 3, 6, and 12 months, the time at which complete continence is achieved in 93% to 97% of patients with no further improvement in 2 to 3 years after the procedure. As regards erectile function, patients retain sufficient erections for sexual intercourse usually within 3 to 6 months, with rates remaining stable within the following 2-3 years [78]. Also after IRE and cryotherapy outcomes tend to recover and stabilize at 3-6 months [72]. Interestingly, in an RTC comparing vascular-targeted PDT vs AS, functional outcomes revealed transient deterioration, but the result at month 24 was similar to AS [79]. This pattern of initial "dip" in sexual performance after treatment and then near full recovery has been observed in many FT studies using different devices.

The safety profile of FT is generally high [80]. Since the vast majority of perioperative complications occur within the first 30 days after ablation, patients should be appropriately counseled and given access to hospital facilities if experiencing a complication within this period [80, 81]. An information leaflet explaining in detail the possible post-operative complications should be provided to all patients [82]. Following the first 6 weeks after treatment, patients should be counseled on long-term complications and how to recognize them, but no strict assessment seems required as these occurrences are rare.

Current limitations and future perspectives

The absence of RTCs or other high-quality studies assessing long-term outcomes is the main limitation of surveillance after FT. Today, only a few series provide long-term follow-up after FT [2, 13].

Furthermore, in the absence of worldwide adopted protocols, current FT evidence mainly comes from medium-term results of early adopters with several energies using different ablation schemes and surveillance protocols; all this results in significant heterogeneity hampering a clear conclusion on optimal follow-up schemes. Some of this is to be expected as treatments are customized to the individual patient's cancer and cannot follow a specific treatment template since this is not radical therapy.

Novel tissue, urine, and blood biomarkers might have a similar promising role in the post-FT setting as observed in the AS setting. In men under AS, for instance, SelectMDx showed a moderate ability (AUC 0.714) to discriminate low and very-low-risk PCa patients with pathological progression-free survival at 5 years [83], while the Decipher score, in a study on men with low or favorable intermediate-risk PCa, revealed the potential to identify those at higher risk of GG 3-5 disease at RP [84]. Similarly, the utilization of biomarkers after FT might have the potential to better discriminate those patients who are at higher risk for PCa recurrence needing further investigations from those who can be safely monitored conservatively. However, evidence in this field is currently lacking and future research efforts are awaited.

Novel imaging modalities, such as PSMA PET scan, showed promising findings to improve the diagnostic accuracy to predict PCa recurrence after FT, especially by complementing mpMRI [63]. Increasing the sensitivity and NPV of follow-up imaging would allow more efficient management of the patients treated with FT, with fewer visits and exams.

Finally, while the biopsy is the only way to determine with certainty whether ablation was successful or not, in the case of negative imaging, the persistence of tumor foci may not necessarily impact survival. This is theoretically supported by the high persistence of PCa in men undergone radical cystoprostatectomy for bladder cancer previously treated with RT for PCa. In this setting, almost one in four men has csPCa at final histology. At a median of 77 months, no PCa impact on survival was noted [85].

Hence, while "for protocol" biopsy remains recommended after FT, the impact on survival of a "more stringent" versus "less stringent" follow-up, and of "for protocol" vs "for cause" biopsy, especially with combination of biomarkers and new imaging modalities, remains to be better determined.

Table 1 provides a synthesized overview of the available evidence about surveillance after FT for PCa.

CONCLUSIONS

FT follow-up is a multifaceted process involving clinical, radiological, and histological assessment. Currently, follow-up includes periodic PSA and mpMRI with the majority suggesting a control biopsy to assess treatment success. In light of the low side effects, stringent functional outcomes follow-up may be avoided in the majority of men, particularly after the third month or once functionally recovered.

Table 1. Summary of surveillance after focal therapy for prostate cancer.

PSA and PSA derivatives	PSA remains useful, and some PSA derivatives are promising and should be considered when following patients after FT, to potentially trigger earlier imaging and/or biopsy. Nonetheless, FT surveillance should not rely on biomarkers alone. Early PSA kinetics after FT can be erratic and challenging to interpret but tends to stabilize at 12 months, providing the 1-year time point as the first good opportunity to assess mpMRI and PSA together.
Multiparametric MRI	After focal ablation, a 9-12-month mpMRI is an important tool to monitor ablation appropriateness and verify the absence of disease. Suspicious mpMRI findings should be targeted and biopsied. Whether or not the identification of persistent disease in the presence of a negative mpMRI has an impact on survival remains unknown and additional research endeavors are necessary to establish evidence-based recommendations.
Follow-up biopsy	The first post-ablation biopsy is critical to judge the success of the treatment and should be mandatorily performed as part of the focal therapy protocol. The optimal time is around 1 year. The biopsy should be targeted on mpMRI findings and include the sampling of both treated and untreated areas. After the primary "per protocol" negative biopsy, a "for cause" biopsy strategy is generally suggested, based on mpMRI and PSA results. Nonetheless, in the absence of triggers leading to a "for cause" biopsy, a second, late "per-protocol" biopsy should be included in the post-ablation protocol.
Functional outcomes and complications	Functional outcomes should be evaluated at 3, 6, and 12 months, when typically recover to a new baseline. Since the vast majority of perioperative complications occur within the first post-ablation month, patients should be carefully followed during this period.

Studies should be carried out to produce standardized protocols evaluating the impact of different follow-up strategies and ideal timings as well as the implementation of biomarkers and new imaging modalities.

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AUTHOR CONTRIBUTIONS

Study concept and design: Marra, Marquis, Polascik. Acquisition of data and reviewing journal articles: Marra, Marquis. Analysis and interpretation of data: All authors. Manuscript Draft: Marra, Marquis. Creating tables and images: All authors. Critical revision/editing of the manuscript: All authors. Supervision: Polascik.

COMPETING INTERESTS

The authors declare no competing interests.

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