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TOPIC PAPER

Surveillance after prostate focal therapy

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Abstract

Introduction Long-term outcomes from large cohorts are not yet available upon which to base recommended follow-up protocols after prostate focal therapy. This is an updated summary of a 2015 SIU-ICUD review of the best available current evidence and expert consensus on guidelines for surveillance after prostate focal therapy.

Methods We performed a systematic search of the PubMed, Cochrane and Embase databases to identify studies where primary prostate focal therapy was performed to treat prostate cancer.

Results Multiparametric magnetic resonance imaging (mpMRI) should be performed at 3–6 months, 12–24 months and at 5 years after focal therapy. Targeted biopsy of the treated zone should be performed at 3–6 months and fusion biopsy of any suspicious lesion seen on mpMRI. Additionally, a systematic biopsy should be performed at 12–24 months and again at 5 years. In histological diagnosis, characteristic changes of each treatment modality should be noted and in indeterminate situations various immunohistochemical molecular markers can be helpful. Small volume 3 + 3 (Prognostic grade group [PGG] 1) or very small volume (< 0.2 cc or < 7 mm diameter) 3 + 4 (PGG 2) are acceptable in the treated zone at longitudinal follow-up. Significant volumes of 3 + 4 (PGG 2) or more within the treated zone should be treated. Any clinically significant cancer subsequently arising within the non-treated zone should be treated and handled in the same way as any de novo prostate cancer. Patients should be counseled regarding whole-gland and focal approaches to treating these new foci where appropriate. One or two well-delineated foci of significant cancer can be ablated to keep the patient in the 'active surveillance pool'. More extensive disease should be treated with traditional whole-gland techniques.

Conclusion Focal therapy remains a nascent field largely comprising single center cohorts with little long-term data. Our current post-focal therapy surveillance consensus recommendations represent the synthesis of the best available evidence as well as expert opinion. Further work is necessary to define the most oncologically safe and cost-effective way of following patients after focal therapy.

Keywords Prostate cancer · Focal therapy · mpMRI · Fusion biopsy · Surveillance · Radiation therapy · Prostatectomy · Brachytherapy · Cryotherapy · HIFU · VTP · Irreversible electroporation · Laser ablation

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Introduction

Advancements in diagnostic tools such as prostate mapping biopsies and multiparametric magnetic resonance imaging (mpMRI) have provided clinicians with the ability to identify a specific cancer focus within the prostate. This improved diagnostic approach has created a clinical paradigm where one is able to treat that specific focus while sparing the remainder of the gland to preserve sexual and continence mechanisms. As active surveillance protocols modernize with the increased use of mpMRI and molecular markers, this new approach may better select men for treatment versus observation [1]. Utilizing these new technologies and the recognition that low-risk prostate cancer is unlikely to cause mortality has led to the paradigm shift of treating organ-confined intermediate- or high-grade tumors to "downgrade" the patient back into being an active surveillance candidate.

The shift away from whole-gland treatment leads to traditional markers of therapeutic success becoming less relevant. After a curative radical prostatectomy, one expects an undetectable level of prostate-specific antigen (PSA). After radiation therapy, a significant rise in PSA has been agreed upon as the defining mark of biochemical recurrence. After focal therapy, the PSA level may not significantly change from baseline pre-treatment levels, reflecting the amount of viable prostate epithelia that has been preserved. The assessment of oncological outcome then becomes more onerous, requiring the use of imaging modalities and tissue ascertainment.

As prostate focal therapy remains a nascent field, long-term outcomes from large cohorts are not yet available upon which to base recommended follow-up protocols. Herein, we report an updated summary of a 2015 Société Internationale d'Urologie-International Consultation on Urologic Diseases (SIU-ICUD) review of the best available current evidence and expert consensus on guidelines for surveillance after prostate focal therapy.

Methods

We performed a systematic search of the PubMed, Cochrane and Embase databases to identify studies where primary prostate focal therapy was performed to treat prostate cancer using combinations of the search terms 'prostate cancer' AND ('surveillance' OR 'follow-up') AND ('focal therapy' OR 'focal ablation' OR 'image-guided therapy' OR 'image-guided ablation' OR 'targeted ablation'). Altogether 586 publications were identified, from which all 88 original studies were selected for evaluation, finally yielding 17 studies of interest after exclusion of whole-gland and salvage focal ablation studies. Additionally, existing consensus publications on focal therapy were reviewed. Further relevant evidence was identified from the bibliography of these studies or identified by our expert panel for synthesis in the development of this consensus.

Definition of success/failure: evaluating the treated zone vs. untreated zone

Following the application of focal therapy, there will be a treated segment(s) of the prostate and the remainder of the gland will not have received any intervention. Therefore, to holistically/comprehensively evaluate oncological outcome, we need to divide the definitions of success or failure into the two categories: the treated zone(s) and the untreated zones that remain on surveillance. Failure in the treated zone could be due to ablation failure or targeting failure, while that in the untreated zone could be due to selection failure or de novo cancer [2]. Success can be defined by radiological or biopsy criteria. Generally, the portion of the prostate undergoing treatment should have all aggressive disease eradicated, while the untreated portion should be thoroughly interrogated for aggressive disease, whether with imaging or biopsy and monitored with active surveillance if low-grade disease is present.

In one consensus meeting, Donaldson et al agreed that persistent or recurrent cancer in the treated zone of Gleason score 3 + 3 (Prognostic grade group 1) with a cancer core length ≤ 3 mm post-focal therapy is an acceptable treatment outcome, as long as it represents a decrease from the original cancer burden [3]. The original cancer lesion should be of a higher grade or higher volume than the cancer that remains in the treatment field. The Donaldson consensus panel felt that the remaining lesions of Gleason score 3 + 4 or 4 + 3 (Prognostic grade groups 2 and 3) in the treated zone should be considered failure, regardless of cancer core length [Level 4]. Additionally, the finding of a more substantial volume of Gleason 6 (> 3 mm of core length) does not in itself indicate failure, though, if found on standard transrectal ultrasound biopsy, its presence would be important as a predictor of higher grade cancer and should prompt an MRI/targeted biopsy [Level 3] [4].

Assessing the treated zone

In the treated zone, the definition of success can be described in terms of immediate or technical ablative success versus intermediate to long-term oncological outcomes. Technical success is the operator's assessment that sufficient energy delivery has occurred to the target zone with a suitable margin around the target area, depending on the ablative

technology used. For example, with cryotherapy, at least two freeze–thaw cycles with an ideal nadir temperature of −40 °C is often required to cause complete cell death within the freeze zone [5]. With thermal modalities such as high-intensity focused ultrasound (HIFU) or focal laser ablation (FLA), a temperature of 55 °C for 5 s is lethal to almost all epithelial cells [6, 7]. With in-bore treatment, MR thermometry may help in ascertaining that the target temperature has been reached and an enhanced scan at the end of the procedure can assess treatment coverage [8]. Similarly, immediate evaluation of the treated zone with contrast-enhanced ultrasound (CEUS) microbubble agents can be performed to allow for additional focal ablation of any areas suspicious for residual disease. After irreversible electroporation (IRE), treatment-related changes in the target zone are not apparent on grayscale ultrasound, but may be visualized using CEUS or dynamic contrast-enhanced MRI techniques [9]. If the operator assesses that treatment coverage was inadequate, provisions for repeat or additional therapy may need to be made.

In the intermediate to long term, oncological success is defined histologically with biopsy, and radiologically with mpMRI.[1] These criteria have their pitfalls. As small foci of significant cancer may persist at the margins of the treated zone or exist as skip lesions, longitudinal follow-up with repeated assessments will be necessary to ensure that success is enduring. Based on latest pathological data from the International Society of Urological Pathology (ISUP), from an oncological point of view, we would consider small volume Gleason 3 + 3 (Prognostic grade group 1) or very small volume (< 0.2 cc or < 7 mm in diameter) Gleason 3 + 4 (Prognostic grade group 2) as acceptable within the treated zone at longitudinal follow-up. Significant volume (≥ 0.2 cc or ≥ 7 mm in diameter) of Gleason 3 + 4 (Prognostic grade group 2) within the treated zone would be considered as failure [Grade C].

Appraising the untreated zone

The untreated zone may be monitored for de novo disease alongside the treated zone with radiological means. If there is low-risk disease in the untreated zone, it should be monitored with standard of care active surveillance protocols. The majority of protocols stipulate a systematic re-biopsy within 12–18 months, and thereafter using pre-defined PSA, PSA derivative or radiological triggers [10]. The definition of focal therapy failure in the untreated zone would be the development of any foci of clinically significant cancer requiring further therapy [Grade C]. Those who develop such foci early on (within 12–18 months) likely represent selection failure. Nonetheless, whether de novo or selection failure, these represent failure of focal therapy as a strategy rather than that of the primary ablation itself.

Role of PSA, derivatives and other molecular markers

PSA

PSA being produced by normal prostatic cells does not usually reduce to undetectable levels after non-extirpative therapies. Despite this, robust criteria have been developed to define biochemical recurrence after radiation therapy, and in this setting, PSA nadir levels, times to nadir and subsequent doubling times (PSADT) have been found to be of prognostic value [11–15]. Consequently, these criteria have also been adopted for other non-radiation-based non-extirpative treatments such as cryotherapy or high-intensity-focused ultrasound [16, 17]. After partial gland ablation or true focal therapy with treatment of the index lesion alone, serum PSA levels have been noted to decrease [18]. Nadir PSA or 6-month post-treatment PSA has been found to have poor correlation with residual cancer on biopsy [19]. This may be due to the remaining volume of viable prostate epithelium impairing accurate interpretation of serum PSA levels. Furthermore, the post-treatment serum PSA trend may be affected by age, benign prostatic hypertrophy and other nonmalignant entities [20, 21]. There is currently not enough data describing the course of serum PSA post-focal therapy with long-term prognosis, but expert consensus has been to record post-treatment PSA levels, including density, nadir and other kinetics for future research purposes [22] [Grade C, Level 4].

PSA derivatives

PSA density (PSAD) is pertinent to the post-focal therapy setting as a marked reduction of the treated portion of the gland is routinely observed at follow-up imaging. One study reported PSAD of ≥ 0.1 ng/ml^2 to predict subsequent cancer detection in the untreated zone. Another study showed that PSAD had a, at best, fair ability to predict any residual Gleason 4 cancer at biopsy [19]. While limited by operator dependence in ultrasound-based prostate volume assessment, this is becoming less of an issue with the increased use of MRI for follow-up post-focal therapy. Threshold PSADs based on MRI prostate volume are being developed [23]. The role of other derivatives such as the PSA doubling time or velocity in post-focal therapy surveillance has not been studied. There is currently insufficient evidence defining

[1] By today's standards, mpMRI is the best imaging technique, but radiological assessment may entail other imaging modalities to supplant or complement mpMRI in the future.

the use of PSA derivatives in the post-focal therapy setting. [Grade D, Level 4].

Other molecular markers

Biomarkers beyond PSA have been the subject of intense interest and investigation, particularly in pre-diagnosis or active surveillance applications. However, there is currently little evidence to incorporate these into a post-focal therapy protocol beyond research purposes [Grade D, Level 4].

Role of mpMRI in the post-focal therapy setting

Prostate focal therapy was initially pursued as a hemi-ablation technique, based on biopsy findings of laterality. Multiparametric MRI (mpMRI), which is gaining widespread acceptance in prostate cancer diagnosis, staging and surveillance, has revolutionized the identification of prostate cancer index lesions and their subsequent targeting for confirmatory biopsy and ensuing targeted focal ablation. After focal ablation of an mpMRI-detected lesion, the use of mpMRI for post-treatment surveillance provides the advantage of comparison between the follow-up and pre-ablation treatment zone. Targets can then be assigned for use as in-bore MRI or a TRUS–MRI fusion confirmatory biopsy of the treated zone and/or suspicious lesion. Furthermore, mpMRI is known to detect higher-grade significant prostate cancers and it may play a role in the monitoring of the untreated zone if determined to contain low-grade, low-risk disease initially [Level 3] [24, 25]. At recent expert consensus group meetings, MRI has been recommended at 6- to 12-month intervals after focal treatment of the prostate with one group advising a yearly scan for the first 5 years [Level 4] [22, 26].

mpMRI typically comprises, in addition to the anatomical T1 and T2 sequences, functional imaging such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging. mpMRI has high sensitivity and specificity for the detection of clinically significant prostate cancer and a high negative predictive value with a modest positive predictive value [Level 3] [27]. Thus, a negative mpMRI may be informative, but when there is a suspicious area in the treated zone on mpMRI, histological confirmation is necessary. Technical expertise and specific equipment are necessary to achieve a high-quality mpMRI [28–30].

Few focal therapy series have accumulated long-term follow-up data to inform the intensity or frequency of mpMRI surveillance post-focal treatment. Ahmed et al. reported on a series of 52 men receiving focal HIFU where mpMRI was negative in the treatment zone in 10% of men at 6 months follow-up [18]. Notably, two men had suspicious mpMRI findings in the untreated zone and both were positive for significant disease at biopsy. Expanding on this series, Dickinson found that late post-treatment mpMRI at 6 months (AUC 0.77–0.85) was superior to early mpMRI at < 3 weeks (AUC 0.75–0.76) or PSA nadir, 6-month PSA or density in identifying residual cancer on subsequent biopsy [19]. In 13 men undergoing in-bore MR-guided HIFU, Tay et al. reported that while follow-up mpMRI at 6 and 24 months failed to detect any lesions, clinically significant cancer was detected in three patients at transperineal biopsy [8]. In a longitudinal study using MRSI, local recurrence of prostate cancer after radiation occurred at the same site in eight of nine men as detected by MRSI [31]. While this study reported on men with whole-gland external beam irradiation, the findings relating to the pre- and post-MRI change in dominant cancer focus are instructive for practitioners interested in focal type radiation therapy. Azzouzi et al. reported in a pooled analysis of three phase II trials on vascular-targeted photodynamic therapy that day 7 MRI showed necrosis in the ablated regions, but did not report on the findings of 6-month MRI [32]. Eggener et al. reported on 27 men undergoing MRI-guided focal laser ablation, finding that while follow-up MRI at 12 months was normal, 3 men had clinically significant cancer (1 in the treated zone, 1 in the untreated zone and 1 with cancer in both zones) at follow-up biopsy [33]. After anterior prostatectomy in 17 men, Villers et al. reported no positive mpMRIs at 1 year follow-up, but four positive mpMRIs subsequently which were biopsy proven to be recurrences in the residual peripheral zone of the prostate [34]. In a series of 21 men undergoing focal IRE, Ting et al. found, at 6 months, that one of two men with positive mpMRI in the untreated zone and four of five men with positive mpMRI in the area just adjacent to the treated zone had clinically significant cancer [35]. Long-term mpMRI follow-up data following focal therapy needs to be collected.

Summary and recommendations for the use of mpMRI post-focal therapy

mpMRI is a useful tool in follow-up after focal therapy of the prostate for purposes of monitoring the treated zone as well as the untreated zone. Three-Tesla mpMRI, or 1.5 T with endorectal coil, should be the minimum standards [Grade C] [22]. Until further evidence suggests otherwise, given the developmental nature of focal therapy, mpMRI is recommended at least once 6–12 months after initial treatment [Grade C]. Subsequent serial MR imaging should be performed periodically. The optimal frequency of imaging is not known and should be determined by patient factors and resource availability [Grade D]. Given the long natural history of prostate cancer and the low rate of progression of well-characterized Gleason 6 (Prognostic grade group 1) cancer (about 1% per year), it is likely that repeat imaging

in low-risk patients can be infrequent [Grade D]. A negative mpMRI suggests a low risk of disease recurrence or progression [Grade C]. A positive mpMRI should lead to a targeted biopsy for histologic confirmation [Grade C].

Role of biopsy

Types of biopsy available

Periodic follow-up biopsies are considered to be essential for monitoring after focal therapy. Options available include extended sextant 12-core TRUS biopsy, saturation TRUS biopsy (> 20 cores), transperineal mapping biopsy, in-bore MRI targeted or MRI-TRUS fusion biopsy. These modalities have been investigated in the diagnosis and active surveillance settings, and in general have shown that an increasing yield for clinically significant disease is seen with an increasing number of biopsies performed [Level 3] [36–39]. While MRI fusion biopsy has a higher detection rate for clinically significant disease, it has not detected all clinically significant disease in cohorts undergoing simultaneous systematic biopsy [Level 3] [40].

Timing of biopsy

One expert panel had a consensus that TRUS-guided systematic whole-prostate biopsies and additional targeted (software or cognitive fusion) biopsies should be performed between 6 and 12 months after treatment [Level 4] [41]. This interval was recommended to account for the time taken for resolution of inflammatory effects and formation of scar tissue. It must also be remembered that ablation of a segment of the prostate followed by the reparative process will not only cause 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 of the treated zone post-therapy, depending on when it was assessed, poses its own unique set of challenges. Stromal fibrosis persists up to 16 months follow-up, but does not impair pathologists' ability to grade recurrences [42]. Another expert panel recommended a biopsy of the treated zone in addition to a systematic 12-core TRUS biopsy of the whole prostate (including the untreated zone) at 1 year after treatment and thereafter only when there is suspicion on imaging [Level 4] [22]. A third panel agreed that the optimal time for the first prostate biopsy after focal treatment is at 1 year and that the biopsy should be performed in a targeted manner, as otherwise previously untreated tissue could easily be inadvertently sampled [Level 4] [3]. This panel remained uncertain about whether post-treatment biopsy should also routinely sample the untreated gland.

Triggers for biopsy

Traditional triggers for biopsy in active surveillance settings have been based on time since the diagnostic biopsy and on PSA changes. As mentioned, PSA kinetics are difficult to interpret in the post-focal therapy setting. An expert panel has recommended mpMRI as the only trigger for biopsy of both the treated and untreated zone after a first negative 12-month biopsy [Level 4] [22]. If biopsy is required, this group recommends four to six core-targeted biopsies of the ablation zone to account for fibrosis-related gland deformity and possible misregistration when using software or cognitive fusion.

Donaldson's consensus group agreed that a suspicious area on mpMRI was a trigger for biopsy, but also felt that a rising PSA was a valid trigger [Level 4] [3]. However, given the effect of the remnant prostate on fluctuations in serum PSA, using this as trigger may generate more unnecessary biopsies and thus clinical discretion is advised.

Summary and recommendations for the use of biopsy post-focal therapy

There is currently little longitudinal data in focal therapy series to inform the optimal follow-up biopsy regimen. While a transperineal mapping saturation biopsy may be informative, it often necessitates general anesthesia and a trip to the operating room. mpMRI may detect large and clinically significant lesions in both treated and untreated zones and should be a part of any focal therapy program and trigger a targeted biopsy if a suspicious lesion is detected. By today's standards, targeted biopsy implies either the utilization of MRI–TRUS fusion technology or in-bore MRI guidance. In general, we would recommend four to six cores from the treated zone alone, depending on volume/size of treated zone, at 3–6 months and 12-core systematic plus targeted biopsy of the ablation zone at 12–24 months [Grade C]. Following 24 months, the gland should be biopsied only if there is suspicious change in MRI or PSA/clinical findings [Grade C]. If clinical parameters/PSA are stable, we would also recommend repeat mpMRI at the 5 years mark with possible biopsies of abnormal areas [Grade D]. Biopsy may also be triggered by heightened clinical suspicion based on PSA kinetics, rising PSA, or new mpMRI suspicious finding. These recommendations are summarized in Table 1.

Table 1 Consensus recommendations on follow-up strategy

	MRI with possible fusion biopsy	Systematic biopsy
Treated area	Biopsy at 3–6 months [Grade C] 12–24 months [Grade C] and again at 5 years [Grade D]	None [Grade D]
Untreated area	12–24 months [Grade C] and again at 5 years [Grade D]	12–24 months and again at 5 years [Grade D]

Histological interpretation of post-treatment biopsy

Post-treatment histological changes

After radiation, typical histologic changes include a decreased ratio of tumor glands to stroma, atrophy and squamous-like metaplasia of non-neoplastic glands with or without atypia, stromal fibrosis, arterial luminal narrowing due to myointimal proliferation, foam cells within vessel walls and fibrosis and atrophy of seminal vesicles [43]. Benign prostatic glands show profound histologic changes that may be confused with prostate cancer [44]. In one cohort, routine biopsy after seed implant brachytherapy found that up to 17% of men have a biopsy reported as indeterminate [45]. In another cohort, after external beam irradiation, 17% of men with positive post-treatment biopsy remained clinically disease free at 10 years [46]. In yet another cohort, even among those receiving HDR brachytherapy boost for intermediate-risk prostate cancer, persistent cancer cells on routine 2-year biopsy did not predict which patients would ultimately fail biochemically [47]. These observations have contributed to uncertainty regarding the adoption of post-radiation prostate biopsies as a gold standard for treatment efficacy [48]. Immunohistochemical studies for basal cell-associated markers (p63, high molecular weight cytokeratin and CK5/6), cancer-associated markers (racemase and ERG) and/or cytokeratin stains to detect subtle infiltrating cancer cell play an important role in indeterminate cases and must be employed before an indeterminate diagnosis is rendered.

Whole-mount histology 2 weeks after HIFU treatment shows a spectrum of morphological changes from necrosis to subtle ultrastructural cell damage with all lesions demonstrating loss of cytokeratin 8, signifying severe cellular damage [49]. 6 months after HIFU treatment, necrosis, often accompanied by acute, chronic or granulomatous inflammation, was noted in 72% of the cases with mild to moderate fibrosis in all biopsies [50].

12–24 months post-cryotherapy biopsies have generally found chronic inflammation, myxoid stromal change, stromal hemosiderin and stromal fibrosis [51]. Like HIFU, patients with positive post-treatment biopsy tend to have glands with little or no typical post-therapeutic histological changes, suggesting undertreatment as a cause of disease persistence [51, 52].

Laser ablation induces tissue necrosis by thermal injury and thus the findings are similar to those of HIFU. Lindner et al. described four patients that underwent radical prostatectomy after laser ablation therapy [53]. The ablation zone was characterized by homogeneous areas of coagulation necrosis, surrounded by a small hemorrhagic rim, devoid of vital glandular tissue. Vitality of the residual glands was assessed by the use of cytokeratin 8, which demonstrated an abrupt transition of positive (vital) glandular tissue and negative (ablated) glands. There was a good correlation between MRI and whole-mount H&E histological examination and an even better correlation with the loss of cytokeratin 8 immunohistochemical staining.

Eymerit-Morin et al. described the histopathologic findings in 6-month follow-up biopsies of 53 patients that underwent focal photodynamic therapy [54]. These included sharply demarcated hyaline scars, rare atrophic glands, mild chronic inflammatory infiltrate, hemosiderin deposition and coagulative necrosis. Vascular lesions such as intimal hyaline fibrosis or organized thrombi were not prominent. Seventeen of the 53 patients had residual carcinoma in the treated lobe, all located outside the scarred area, usually close to the capsule. The viable carcinoma glands did not display any therapy-related changes and were easily recognized in most cases with routine histology.

Neal et al. described findings in two patients that underwent radical prostatectomy after IRE [55]. The treatment areas showed extensive necrosis with inflammatory neutrophilic infiltrate, surrounded by an area of reactive fibroblasts and hemorrhage. The adjacent viable ducts displayed squamous metaplasia.

Reporting recommendations for post-focal therapy treatment biopsies

In biopsies from the treated zone, it is important for the pathologist to report findings that confirm that the treated zone has been biopsied (necrosis, hemorrhage, acute and chronic inflammation, stromal edema, glandular atrophy, hemosiderin deposition, reactive fibroblasts, stromal fibrosis).

In the treated zone, diagnostic findings after biopsy finding may include: (1) post-treatment changes and benign prostatic epithelium, no residual carcinoma; (2) HGPIN; (3) atypical small acinar proliferation, suspicious for carcinoma

(a diagnosis usually rendered after examination of multiple levels and or immunohistochemical studies); and (4) prostatic adenocarcinoma. If no treatment-induced changes are apparent, which is usually the case with focal therapy, a Gleason score should be assigned to the finding of prostatic carcinoma in the treated zone. An isolated finding of HGPIN in the treated zone following focal therapy is uncertain, but an isolated focus of HGPIN in this setting is of little clinical significance. As outlined in the introduction, the recently WHO and ISUP recommended prognostic grade groups should be reported in parallel with the Gleason grade.

In core and systematic biopsies outside of the treated zone, handling and reporting should occur in conjunction with established practices.

Molecular markers to help interpret post-treatment histological changes

Immunohistochemistry markers are useful in the microscopic interpretation of treated glands in biopsy specimens [56, 57]. Basal cell markers, such as cytokeratin 34BE12, p63 or cytokeratin 5/6 selectively label basal cells in prostatic glands. These cells are present only in benign glands, and thus their detection is reassuring when the benignity of a group of atypical glands is questioned. The presence of alpha-methylacyl coenzyme A racemase (AMACR), a well-known marker overexpressed in prostate cancer, has been found to facilitate or support decision making in differentiating cancer from benign glands with atypia, and has been shown to be useful in the setting of treated prostates, including post-radiation and post-HIFU [42, 58, 59]. Cytokeratin 8 has been suggested to be a marker of gland viability after HIFU and laser ablation therapy [49, 53].

Several molecular biomarkers have been identified to predict disease progression in the post-irradiation setting. The presence of DNA-ploidy has been identified as a significant predictor of distant metastasis-free survival and cancer-specific survival [60]. The cellular proliferation index derived from MIB-1 labeling is another significant predictor of post-radiation recurrence [61]. In an effort to distinguish between biologically active and inactive 'residual tumors' following prostate irradiation, Crook et al. studied the presence or absence of proliferative cell nuclear antigen (PCNA), finding that a negative PCNA in a positive biopsy predicts an 83–97% chance for eventual resolution of tumor [62].

Summary and recommendations for histology interpretation post-focal therapy

Characteristic changes occur in the prostate following treatment with various energy modalities. Indeterminate histological findings can be sometimes resolved with the use of various immunohistochemical molecular markers, though these should be further evaluated prior to use in routine practice [Grade D]. Our recommendation is to treat definitive cancer on biopsy as a positive finding [Grade D]. Indeterminate findings should be communicated to the patient with the decision on whether to proceed being a shared one.

Clinical management of cancer recurrence or persistence

There have, thus far, been no guidelines defined for the management of patients with failure or recurrence after focal therapy. Further treatment should, logically, be determined by the new disease status, clinically, biochemically, radiologically and histologically, coupled with the patient's comorbidities and quality of life considerations, just as one would for any newly presenting prostate cancer.

In general, findings of high-grade prostate intraepithelial neoplasia and atypical small acinar proliferation are acceptable.

Role of repeat focal therapy

The use of repeat focal therapy remains investigational at this point and caution is recommended in its application. Failure in the treated zone may be due to various factors, including potential problems with disease localization, targeting and energy delivery. Unless one has clearly identified a reversible or correctable factor that encumbered the initial attempt at focal therapy, persisting anatomical or other difficulties may continue to affect the efficacy of a repeat focal therapy. For example, if the treatment failure was due to incomplete coverage, then retreatment may be offered. However, if the issue were due to failure of attaining the required temperature because of a heat sink effect, then retreatment using that particular device would not be recommended. In another example, HIFU may be less effective at the prostatic apex and a recurrence or persistence there could be better salvaged with focal cryotherapy or another ablative technique [63]. In a consensus meeting report, the panel agreed that retreatment rates of $<20\%$ with focal therapy were clinically acceptable [Level 4] [3]. There was agreement that any subsequent whole-gland therapy reflected a failure of focal therapy. A retreatment rate of $<10\%$ with whole-gland therapy was considered to be clinically acceptable.

Choosing the modality of salvage treatment

Following prostate irradiation, re-irradiation with brachytherapy and or image-guided radiotherapy has been found to render up to 50% of patients' biochemical relapse-free [64]. Re-irradiation following radiation-based focal therapies

might be a reasonable extrapolation of these findings, if not limited by dose.

Post-radiation salvage radical prostatectomy has traditionally been observed to have much higher rates of complications, incontinence and erectile dysfunction [65]. There is little data regarding these outcomes following focal therapy with lesion ablation, quadrant ablation, hemi-ablation, etc., but one might expect complication rates to potentially be higher and functional outcomes poorer, depending on the location of the target tissue. The degree of technical difficulty may be dependent on the volume and location of the lesion within the prostate that had been ablated in the focal setting. If additional focal therapy is undertaken, it may be reasonable to switch to a different device or mechanism of action based upon the location of the lesion and the goal of treatment (e.g., to preserve continence/potency when retreating an apical lesion).

Summary and recommendations for salvage therapy post-focal therapy

The cause of cancer persistence or recurrence in the treated zone may be multifactorial. Patients should not be precluded from any of the standard prostate cancer treatment options, including additional focal therapy if clinically appropriate. We would recommend that a finding of Gleason 3 + 3 (Prognostic grade group 1) at a significantly lower volume than pre-treatment is considered acceptable and likely can be monitored [Grade C]. Small volume Gleason score 3 + 4 (Prognostic grade group 2) lesions at a lower volume than pre-treatment may be cautiously monitored depending on the clinical situation or offered further treatment [Grade C]. A Gleason score 3 + 4 (Prognostic grade group 2) lesion of 0.2 cc (or 7 mm in diameter) or greater should be treated [Grade C]. Any Gleason score $\geq$ 4 + 3 (Prognostic grade group 3–5) should be treated [Grade B]. We generally would only recommend salvage focal therapy where the reasons for initial failure can be clearly identified and corrected, and both the physician and patient believe this option is reasonable [Grade D].

Management of the untreated portion of the gland on active surveillance

Role and method of active surveillance

Prostate cancer is a multifocal disease in 60–80% of men [66, 67]. In men with prostate cancer, morphologically normal prostate tissues contain high levels of mutations even though they are distant from the prostate cancer foci [68]. Furthermore, focal therapy series treating the index lesion only have reported detection of clinically significant disease arising in the untreated zone at the 6-month biopsy [18]. It remains unclear at present whether occurrence of cancer in the untreated zone is due to disease progression as a result of field change, or previously undetected small foci of cancer. Nonetheless, the data provide evidence supporting active surveillance of the untreated zone.

Multiple active surveillance protocols have been published. The majority of series include clinical assessment with digital rectal examination, PSA/PSA kinetics and re-biopsy at 12–18 months, followed by time or for cause trigger-based biopsies [10]. Modern protocols have started to include mpMRI and there may be a role for other potential molecular markers [1]. Since patients treated with focal therapy also have areas of untreated tissue, patients will be under a monitoring program likely encompassing the utilization of both mpMRI and prostate biopsy, which goes hand in hand with contemporary active surveillance practices.

Summary and recommendation for monitoring of the untreated gland post-focal therapy

Detection of significant cancer in the untreated zone following focal therapy should be handled in the same way as any de novo prostate cancer. Patients should be counseled regarding whole-gland and focal approaches to treating these new foci where appropriate. One or two well-delineated foci of significant cancer can be ablated to keep the patient in the 'active surveillance pool' [Grade D]. More extensive disease should be treated with traditional whole-gland techniques.

Conclusion

Focal therapy remains a nascent field largely comprising single center cohorts with little long-term data. Our current post-focal therapy surveillance consensus recommendations (summarized in Table 2) represent the synthesis of the best available evidence as well as expert opinion. Further work is necessary to define the most oncologically safe and cost-effective way of following patients after focal therapy.

Table 2 Summary of recommendations

	Recommendations	Grade
Definitions of failure	Significant volume (≥ 0.2 cc or ≥ 7 mm in diameter) of Gleason 3 + 4 (PGG 2) within the treated zone is considered failure	C
	The development of any foci of clinically significant cancer requiring further therapy is considered focal therapy failure (or failure of the focal therapy strategy as a whole) in the untreated zone	C
PSA	There is currently insufficient evidence defining the use of PSA or PSA derivatives in the post-focal therapy setting	D
Other biomarkers	There is currently little evidence to incorporate these into a post-focal therapy protocol beyond research purposes	D
mpMRI	mpMRI should be performed at 3- or 1.5-T with endorectal coil	C
	mpMRI is recommended at least once 6–12 months after initial treatment	C
	The optimal frequency of imaging is not known, and periodic imaging should be determined by patient factors and resource availability	D
	Less frequent repeat imaging is necessary in patients with Gleason 3 + 3 (PGG1) cancer	D
	A negative mpMRI suggests a low risk of disease recurrence or progression	C
	A positive mpMRI should lead to a targeted biopsy for histologic confirmation	C
Biopsy	Follow-up should comprise 4–6 core biopsies from the treated zone alone at 3–6 months and 12 core systematic plus targeted biopsy of the ablation zone at 12–24 months	C
	Following 24 months, the gland should be biopsied only if there is suspicious change in MRI or PSA/clinical findings	C
	If clinical parameters/PSA are stable, mpMRI should be repeated at the 5 years mark with possible biopsies of abnormal areas	D
Interpretation of histology	Resolve indeterminate histology through the use of immunohistochemical markers	D
	Definitive cancer on biopsy should be treated as a positive finding	D
Cancer recurrence in the treated zone/ salvage therapy	A finding of Gleason 3 + 3 (PGG 1) at a significantly lower volume than pre-treatment is considered acceptable and likely can be monitored	C
	Small volume Gleason score 3 + 4 (PGG 2) lesions at a lower volume than pre-treatment may be cautiously monitored depending on the clinical situation or offered further treatment	C
	A Gleason score 3 + 4 (PGG 2) lesion of 0.2 cc (or 7 mm in diameter) or greater should be treated	C
	Any Gleason score ≥ 4+3 (PGG 3-5) should be treated	B
	Salvage focal therapy should only be considered when the reasons for initial failure can be clearly identified and corrected	D
Cancer occurrence in the untreated zone	One or two well-delineated foci of significant cancer can be ablated to keep the patient in the 'active surveillance pool'	D

PGG Prognostic grade group

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Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest to disclose.

Human and animal participants right No human subjects or animals were involved in this study

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