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Multimodal Imaging in Focal Therapy Planning and Assessment in Primary Prostate Cancer

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Abstract

Purpose—There is increasing interest in focal therapy (male lumpectomy) of localized low-intermediate risk prostate cancer. Focal therapy is typically associated with low morbidity and provides the possibility of retreatment. Imaging is pivotal in stratification of men with localized prostate cancer for active surveillance, focal therapy or radical intervention. This article provides a concise review of focal therapy and the evolving role of imaging in this clinical setting.

Methods—We performed a narrative and critical literature review by searching PubMed/Medline database from January 1997 to January 2017 for articles in the English language and the use of search keywords “focal therapy”, “prostate cancer”, and “imaging”.

Results—Most imaging studies are based on multiparametric magnetic resonance imaging. Transrectal ultrasound is inadequate independently but multiparametric ultrasound may provide new prospects. Positron emission tomography with radiotracers targeted to various underlying tumor biological features may provide unprecedented new opportunities. Multimodal Imaging appears most useful in localization of intraprostatic dominant index lesions amenable to focal therapy, in early assessment of therapeutic efficacy and potential need for additional focal treatments or transition to whole-gland therapy, and in predicting short-term and long-term outcomes.

Conclusion—Multimodal imaging is anticipated to play an increasing role in the focal therapy planning and assessment of low-intermediate risk prostate cancer and thereby moving this form of treatment option forward in the clinic.

Keywords

Focal therapy; prostate; cancer; imaging

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Introduction

Focal therapy (male lumpectomy) has been advocated as a viable gland-preserving treatment strategy in men with low-to-intermediate risk localized prostate cancer, as a middle ground option between active surveillance and whole-gland therapy [1-7]. It is defined as targeted lesion-based treatment strategy in appropriate patient population with the goal to eradicate all identified significant tumor sites [8]. Focal therapy is typically associated with minimal morbidity and provides the possibility of retreatment [9]. The transition between active surveillance, focal therapy, and whole-gland radical therapy is still under active debate.

Imaging has been indicated as a pivotal parameter for many decision points in the process of focal therapy of localized prostate cancer. These include appropriate patient and focal therapy selections, accurate assessment of treatment efficacy and potential need for focal retreatment or radical therapy. We performed a narrative and critical literature review by searching PubMed/Medline database from January 1997 to January 2017 for articles in the English language and the use of search keywords “focal therapy”, “prostate cancer”, and “imaging”. We summarize the current experience with focal therapy of localized prostate cancer and present the current state of affairs with role of imaging in this clinical setting. Relevant imaging modalities that we focus on include ultrasound (US), magnetic resonance imaging (MRI), and positron emission tomography (PET). We also discuss the evidence gaps for imaging that will need further investigations.

Focal Therapy of Localized Prostate Cancer

It has been advocated that active surveillance may be considered for men with low-volume Gleason 6 tumor, while in men with larger unifocal Gleason score 6 or 3+4 lesion, and PSA <10-15 ng/ml, focal therapy may be a viable option. In patients with multifocal small Gleason 6 tumors but with a larger index lesion, focal therapy may also be considered. In men with high-grade, large volume disease or younger age with multifocal high-volume low-grade tumors, whole-gland therapy may be appropriate [10].

In a consensus statement that was published in European Urology in 2015, the following expert opinions were presented [11]:

- Patients with intermediate risk, unifocal or multifocal, can be eligible for focal therapy
- MRI-targeted or template-mapping biopsy should be used for treatment planning
- Treatment margins should be 5 mm from the known tumor
- Indolent cancer foci can be left untreated in view of treatment of the dominant index lesion (defined as the tumor focus that likely drives the overall disease natural history)
- Histologic outcome by targeted biopsy at 1 year
- Residual disease in the treated area of 3 mm with Gleason 3+3 do not need further treatment

- Focal retreatment rates of >20% may be considered failure of focal therapy and whole-gland therapy may be considered.

In another multidisciplinary international consensus report on clinical trial design for focal therapy of primary prostate cancer, the inclusion criteria have been described as patients with PSA<15 ng/ml, clinical stage T1c-T2a, Gleason score 3+3 or 3+4, life expectancy of > 10 years and any prostate volume, with good primary outcome defined as negative biopsies at 12 months after focal therapy [12].

However, many challenging issues remain with optimal patient selection, potential under-treatment of significant multifocal disease, over-treatment of low-grade disease, choice of appropriate post-therapy monitoring and best outcome parameters for prognostic assessment [13-17]. In one investigation of post prostatectomy pathological findings, only a small number of patients with pT2a would have been eligible for focal therapy, however, accurate selection of these patients was challenging [18]. Improved imaging methods can play a pivotal role in all these decision points [19, 20].

Postema et al have indicated a minimum of 5 years of follow up after focal therapy which may include PSA monitoring, imaging such as multiparametric US (transrectal greyscale echography, Doppler sonography, shear-wave elastography, contrast-enhanced ultrasonography) or multiparametric MRI (mpMRI: T2-weighted, diffusion weighted imaging, dynamic contrast-enhanced, with use of pelvic phased array and endorectal coil), and entire gland or targeted treated zone biopsies [21-26]. Additional important nononcological outcomes are urinary function (e.g. urinary retention, infection or stricture), erectile function and overall quality of life [27].

In a systematic review of 18 studies and 2288 patients, outcomes of focal therapy appeared to be relatively similar to those with whole gland therapy but with fewer side effects, although the authors suggested that prospective randomized trials would be needed to corroborate these findings [28]. Valerio and colleagues reported on another systematic review of 2350 cases across 30 investigations and found that most studies were retrospective although prospective registered studies were increasing [29]. Focal therapy was mostly directed toward low-intermediate prostate cancer with imaging, particularly mpMRI, used in majority of cases. In primary cancer setting, absence of clinically significant cancer after focal therapy at the time of follow-up ranged from 83% to 100%. The pad-free continence ranged from 95% to 100% and sufficient erectile function ranged from 54% to 100%. Another prospective development study published in Lancet Oncology in 2012 concluded that focal therapy of unifocal and multifocal prostate cancer lesions leads to reasonable rate of early (6 months) absence of clinically significant residual cancer and acceptable rate of genitourinary adverse events [30]. Methods of focal therapy may include high-intensity focused ultrasound (HIFU), laser interstitial thermotherapy (phototherapy), cryotherapy, and irreversible electroporation [31-36].

High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) has been used for treatment of localized primary and recurrent prostate cancer. The advantages of the technique include minimally invasive

procedure, low morbidity, and possibility of retreatments as needed. Disadvantages have included nonstandard therapy protocols, positive post-treatment biopsies and lack of long-term follow-up data [37-39]. A single center study involving 25 patients showed that HIFU is potentially effective in cancer control with biochemical-free survival of 88% [40]. In one prospective multicentric investigation of 111 patients with prostate cancer (68% low-risk, 32% intermediate risk), HIFU-hemiablation resulted in 95% absence of clinically significant cancer at 1 year following treatment and was associated with low morbidity and preserved quality of life [41]. Others have reported similar data [42]. Palermo et al reported the following adverse events, urinary retention in 1-9%, urethral structure in 4-14%, urinary incontinence in 1-15%, erectile dysfunction in 13-53% and rectourethral fistulae in 0-3% of patients [43]. A multicenter prospective investigation has also been designed as a medium-term (36 months) follow-up trial (The INDEX study) for assessment of biopsy outcomes to focal HIFU therapy in men with low-intermediate prostate cancer (PSA<15 ng/ml, Gleason <7, T2cN0M0)[44].

Laser Therapy

Preclinical and pilot clinical trials have shown that focal laser ablation procedures produce precise reproducible tumor ablation zones with minimal injury to surrounding tissue, is well tolerated, and compatible with MR imaging for near real-time monitoring of therapy effect [45, 46]. In a phase I trial in 9 patients, procedure duration was about 2.5-4 hours with mean laser ablation duration of 4.3 minutes. Immediate contrast-enhanced post-treatment MRI showed hypovascular defect in all except one patient. MRI-guided biopsy at 6 months post-therapy showed no cancer in 78% of patients. The authors concluded that transperineal MRI-guided focal laser ablation is feasible, safe and effective [47].

Cryoablation

Cryoablation of focal lesions or the total gland has been shown to be feasible and associated with good cancer control and no major adverse events [48, 49]. In an investigation by Gangi and colleagues, MRI-guided cryoablation was feasible in 10 of 11 patients with localized prostate cancer [50]. The “ice-ball” was clearly visualized in all cases as a signal-void area. Mean hospitalization was 5 days and complications included cases of rectourethral fistula, urinary infection, dysuria, and scrotal pain. In another study with a 3.7 year of follow-up after focal cryotherapy, complete continence and erectile potency were reported in 100% and 86% of patients, respectively [51].

Electroporation

Irreversible electroporation uses brief intense electric pulses delivered by paired electrodes in targeted region, which leads to irreversible disruption of cellular membrane integrity but generally sparing the surrounding connective tissues. The cellular effect depends on tissue conductivity, current intensity, and duration of delivered pulses [52]. The technique may be guided by imaging or under direct vision during surgery. Studies have shown that the technique has a low toxicity profile with acceptable genitourinary outcomes [53].

Ting and colleagues reported on the safety and short-term functional and oncological outcomes of focal irreversible electroporation in patients with low-intermediate risk prostate

cancer [54]. In this study of 25 men who completed the treatment protocol, 76% of patients were free of cancer on biopsy at 8 months. Another group of investigators found that mpMRI and contrast enhanced ultrasound were appropriate for assessing the effects of focal irreversible electroporation therapy in the prostate gland [55].

Imaging in Focal Therapy

The vast majority of literature on imaging in the clinical setting of focal therapy of primary prostate cancer is on the use of multiparametric MRI. There is relative paucity of high-level evidence on multiparametric US and positron emission tomography. However, some recent reports have demonstrated the feasibility of PET-directed, ultrasound-guided biopsy systems [56-58]. Pilot imaging studies such as those with optical coherence tomography have also been reported [59].

Multiparametric MRI

Transrectal ultrasound cannot in general localize the cancer site(s), although more advanced multiparametric techniques may add diagnostic value [60-62]. Multiparametric MRI (mpMRI) is increasingly employed in the evaluation of patients with suspected prostate cancer and in image-guided focal therapy of the detected tumors [63, 64]. A comprehensive description of technique is beyond the scope of this article, and the interested reader is referred to many excellent review articles that have published in the literature [65, 66]. However, a consensus report recommended 3T-imaging device with or without endorectal coil or 1.5T with endorectal coil to be employed and images interpreted by an experienced radiologist with structured and standardized reporting [63]. In general, it appears that sensitivity of index tumor detection increases with tumor size and grade in view typically higher cellular density and microvessel density [67-72].

MR-guided biopsy and focal therapy techniques may include image fusion with transrectal ultrasound, use of an in-bore transrectal calibrated guidance device, or use of in-bore direct transperineal grid template [73-80]. Shoji reported that prostate cancers detected by targeted biopsies with real-time mpMRI and transrectal ultrasound demonstrate significantly higher grades and longer length compared with those detected by standard “blind” systematic biopsies [81]. MRI may also be combined with template-guided mapping biopsy for the applying hemi-ablative focal therapy [82]. In this study of 50 patients, 21 patients had unilateral lobe disease on this combined method and only 2 of the 21 patients had significant bilateral disease at prostatectomy.

mpMRI has been used in monitoring response to focal therapy of localized prostate cancer [83]. Patients with localized prostate cancer (T1c-T3a, Gleason grade 4+3, PSA 20 ng/ml) were treated with focal HIFU and followed with various PSA parameters and mpMRI performed at 3 weeks (early) and 6 months (late) post therapy. Depending on definition of significant disease, the sensitivity and specificity of mpMRI were 0.68-0.91 and 0.52-0.55 for early mpMRI and 0.63-0.80 and 0.67-0.73 for late mpMRI, respectively. mpMRI performed better than PSA measurements in the detection of residual tumor after therapy. Similar data for real-time MRI-guided focused ultrasound has been reported demonstrating the feasibility and low morbidity of this technique in focal therapy of localized low-risk

prostate cancer [84]. Le Nobin and colleagues found that a 9 mm treatment margin around the MRI visible lesion is needed to consistently ensure treatment of entire histological tumor volume during focal therapy [85]. The miss rate by MRI in this study was an average of 14.8% of tumor volume. In general, it appears that what is present at histology may be either overestimated or underestimated on MRI [86, 87].

Fused MRI and transrectal US imaging has been used for focal cryotherapy of intra-prostate lesions with post-therapy mpMRI suggesting no residual disease in the treated areas [88]. Earlier studies had shown that ultrasonography was not reliable for detection of residual tumor after cryoablation [89]. In an investigation of 27 men with localized prostate cancer (stage T1c-T2a, PSA < 15 ng/ml, Gleason 6 in 85% and Gleason 7 in 15%), MRI was used to guide focal laser ablation of these lesions. The end point of no cancer on 3-month ablation zone biopsy was noted in 96% of patients. At 12-month biopsy cancer was identified in 37% of patients including in the ablation zones in 11% of these positive biopsy patients. The authors concluded that MRI visible lesions might be amenable to focal laser ablation with reasonable short-term outcomes [90]. Lepor and colleagues assessed the early outcomes of MRI-guided focal laser ablation of 25 men with prostate cancer (clinical stage T1c-T2a, PSA < 10 ng/ml, Gleason score < 8, and suspicious cancer regions visible on MRI)[91]. The results were quite encouraging with no urinary symptoms, excellent cancer control, and significant decline in serum PSA levels in a 3-month period. Dynamic contrast enhanced MRI (1.5 T) performed 1 week after photodynamic focal ablation therapy was noted to be useful in predicting recurrent disease at 6-month follow up with 100% sensitivity and 60% specificity. The overall accuracy of DCE-MRI was similar regardless of analysis basis (patient, prostate half, or sextant). Changes in PSA level were not predictive [92].

An interesting investigation evaluated treatment efficacy and target accuracy of MR-guided transurethral ultrasound therapy of prostate lesions in comparison to post-prostatectomy whole mount histological section [93]. The histologic mean treatment accuracy was -0.4 ± 1.7 mm. Moreover, 3D target volumes of 4 to 20 cc and with radii up to 35 mm from urethra were treated successfully. The authors concluded in this small pilot study of 5 men that MR imaging-guided transurethral ultrasound therapy is feasible. A similar study has reported results with MR imaging-guided focal laser ablation followed by radical prostatectomy [94]. The ablation zone was best delineated by T1-weighted contrast-enhanced images with significant volume correlation to whole-mount histology section ($r=0.94$, $p=0.018$). Ahmed et al performed a single center study of 56 men with localized prostate cancer (12.5% low risk, 83.9% intermediate-risk, 3.6% high risk) who underwent focal therapy of index lesion and were followed prospectively [95]. At one year, nearly 81% of patients had histological absence of clinically significant cancer. The genitourinary side effects were low. Authors suggested further investigations comparing cancer control outcomes to radical therapy.

While mpMRI has been found to be useful in localization of tumor sites and assessment of response to focal therapy, it is recognized that routine clinical use of mpMRI will require further work in standardization of image acquisition and interpretation to enhance reproducibility and reliability of the technique in this clinical setting [96, 97]. Additional work in real-time 3D fusion of images from multiple modalities can improve diagnostic and guidance accuracy. It is also recognized that mpMRI may occasionally miss extracapsular

tumor extension in view of its low sensitivity (but high specificity)[98]. Deep machine learning, advanced pattern recognition and feature extraction algorithms may also enhance the identification and localization of aggressive tumors amenable to focal therapy [99, 100]. However use of these techniques in the clinic will need additional investigation and validation.

PET/CT and PET/MRI

There is a paucity of evidence on the specific use of PET in focal therapy of localized prostate cancer. This may be in part due to the fact that most PET studies with various radiotracers focus on either biochemical recurrence or castrate-resistant metastatic phases of the disease [101, 102]. PET with radiotracers targeted to metabolites (e.g., glucose, fatty acids, amino acids), antigens (e.g., prostate-specific membrane antigen or PSMA, prostate-specific stem cell antigen), receptors (e.g., androgen receptor, gastrin-releasing peptide receptor) have not demonstrated sufficient specificity for identifying and characterizing primary prostate cancer, a requirement which is essential for focal therapy of prostate cancer [103]. Moreover, the limited relevant data that is available is with PET/CT and none specifically with simultaneous PET/MRI in this specific clinical setting. Nevertheless further investigations with various radiotracers with PET/CT and PET/MRI may provide sufficiently specific findings for consideration for focal prostate cancer treatment in the management algorithm [104].

^{18}F -fluorodeoxyglucose (FDG) is the most common PET radiotracer used in PET. Evaluation of the prostate gland is challenging because of overlap of FDG uptake in normal, benign, and malignant tissues. The multifocal distribution of cancer deposits mixed with noncancerous cells and the proximity of the gland to the urinary bladder are also limiting factors. Therefore, generally, FDG PET has no significant role in the localization of primary prostate cancer [105].

Mean et al. evaluated the potential utility of PET with the lipogenesis radiotracer, ^{11}C -acetate, for detection of localized primary prostate cancer that might be amenable to focal therapy [106]. The findings on PET/CT were correlated with MRI and histopathology after prostatectomy. ^{11}C -acetate uptake peaked 3-5 minutes after injection and reached plateau at about 10 minutes. While the average maximum SUV of tumors (4.4 ± 2.05) was significantly higher than that for normal prostate tissue (2.1 ± 0.94) but it was not significantly different from that of benign prostatic hyperplasia (4.8 ± 2.01). The authors concluded that ^{11}C -acetate might not have utility as an independent modality for evaluation of localized prostate cancer, although it might be useful for monitoring focal therapy in view of anatomic-based imaging limitations in that clinical setting.

Radiolabeled choline (with ^{11}C or ^{18}F) is another widely used lipogenesis PET radiotracer. An investigation of simultaneous ^{18}F -fluorocholine PET/MRI in men with intermediate to high-risk primary prostate cancer showed that both SUV derived from PET and apparent diffusion coefficient (ADC) derived from diffusion-weighted imaging differed significantly between tumor and normal tissue. No significant correlation was found between SUV and ADC suggesting that these two parameters measure different biomarkers [107]. However, in

general given the nonspecificity of choline for cancer, its role in primary cancer localization and characterization is generally limited.

¹⁸F-fluciclovine is a synthetic L-leucine analog that was approved by the Food and Drug Administration on May 27, 2016, for the indication “PET imaging in men with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment” and is now commercialized as Axumin™ (Blue Erath Diagnostics, Oxford, UK). Sorensen and colleagues showed that ¹⁸F-fluciclovine is safe and shows high uptake in prostate cancer deposits with minimal bladder urine activity [108]. Shuster and colleagues from Emory University in Atlanta, GA, showed in a small number of patients who underwent PET imaging prior to prostatectomy that SUVmax was significantly higher in malignant sextants but there was an overlap with non-malignant sextants [109]. However, there was a significant correlation between Gleason score and SUVmax. Nonspecificity was also demonstrated by the group from the National Institutes of Health in that tumor tracer uptake could not be differentiated from that in benign prostatic hyperplasia nodules [110]. However, a recent suggested that Late-window [¹⁸F]Fluciclovine PET imaging (33-38 minutes post tracer injection) might be able to distinguish between prostate tumors and benign tissue and be useful for assessment of tumor aggressiveness [111].

There has been much recent research activity on the potential use of radiolabeled (with ⁶⁸Ga or ¹⁸F) PSMA with most studies focusing on the biochemical recurrence phase of the disease [112]. Few investigations have reported on delineation of intraprostatic tumor load in the primary setting. Zamboglou et al compared ⁶⁸Ga-HBED-CC PSMA (aka PSMA-11) PET/CT and mpMRI for tumor detection in men with primary prostate cancer [113]. In a slice-by-slice analysis with histopathology after prostatectomy, the combination of both PSMA PET/CT and mpMRI information resulted in the highest diagnostic performance. The authors suggested this multimodality imaging could be used for guided biopsy and for focal therapy strategies in primary prostate cancer. Similar findings have been reported for high concordance and improvement in accuracy for detection of primary prostate cancer foci with combined or simultaneous ⁶⁸Ga-PSMA-11 and mpMRI [114, 115]. A recent study of dynamic ⁶⁸Ga-PSMA-11 PET/CT in primary prostate cancer reported a high cancer detection rate of 95.8% with significant moderate correlation between SUVmax and PSA level (r=0.576) and significant but weak correlation between SUVmax and Gleason score (r=0.28) [116]. Clearly these reports are encouraging but further investigations with independent validation will be needed to decipher if ⁶⁸Ga-PSMA PET/MRI may provide the means for accurate localization of the dominant index intraprostatic lesions for targeted focal therapy.

The imaging of cellular proliferation can potentially allow for tumor characterization [117]. We have recently reported on a case report as a part of an ongoing pilot clinical trial of combined clinical 3T mpMRI and a research protocol PET/CT with the cellular proliferation radiotracer ¹⁸F-FMAU (2'-deoxy-2'-[¹⁸F]fluoro-5-methyl-1-B-D arabinofuranosyluracil) for real-time hybrid image-based targeting of the biopsy needle [118]. ¹⁸F-FMAU is a radiolabeled thymidine analog that is preferentially phosphorylated by the mitochondrial thymidine kinase 2 and becomes incorporated into the DNA tracking the thymidine salvage pathway of DNA synthesis. In our case report, mpMRI was equivocal while PET with ¹⁸F-

FMAU was helpful in localizing the nonstandard biopsy sites that on histopathology revealed suspected tumor deposits (Fig. 1). We hypothesized that ^{18}F -FMAU PET may be able to identify aggressive (Gleason score ≥ 7) primary intraprostatic cancers, which may then be amenable to focal therapy. This work is currently ongoing and our findings will be reported when the pilot study is completed.

Conclusion

Focal therapy of localized prostate cancer appears to be getting traction in the clinical arena. This “half-way” treatment strategy between active surveillance and radical therapy may be a suitable option for a number of men with low-intermediate risk. While the technique is being optimized with use of a variety of treatment methods, the experts agree on the important role of imaging that should be played in this clinical setting. This role includes stratification of patients who would most benefit from focal therapy, assessment of therapy efficacy and prediction of short-term and long-term outcomes. In this regard, mpMRI has made some inroads but further investigation in relation to multimodal imaging, particularly PET/MRI, will be needed to realize the full potential of focal therapy of prostate cancer in the clinic.

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Fig. 1.

61 year-old man with high serum PSA level of 10.5 ng/mL and negative prior standard TRUS biopsy. (A) mpMRI evaluation was equivocal, (B) hybrid maximum intensity projection coronal PET/CT with 18F-FMAU demonstrated focally increased tracer localization in left lobe of prostate gland, (C) three-dimensional biopsy mapping trajectories constructed from combined PET/mpMRI/TRUS images were used to direct biopsy to location of PET finding, represented as a yellow sphere, within a volumetric mesh representing the left half of prostate gland. Green and orange poles portray standard biopsy and hybrid imaging directed biopsy sites, respectively. Only the image-directed biopsy site revealed atypical small acinar proliferation suggestive of early malignancy. (Reproduced with permission from refs. 118 and 119).