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Review

Future perspective of focal therapy for localized prostate cancer

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Abstract *Objective:* To summarize the recent literature discussing focal therapy for localized prostate cancer.

Methods: A thorough literature review was performed using PubMed to identify recent studies involving focal therapy for the treatment of localized prostate cancer.

Results: In an effort to decrease the morbidity associated with prostate cancer treatment, many urologists are turning to focal therapy as an alternative treatment option. With this approach, the cancer bearing portion of the prostate is targeted while leaving the benign tissue untouched. Multiparametric magnetic resonance imaging remains the gold standard for visualization during focal therapy, but new imaging modalities such as prostate specific membrane antigen/positron emission tomography and contrast enhanced ultrasound are being investigated. Furthermore, several biomarkers, such as prostate cancer antigen 3 and prostate health index, are used in conjunction with imaging to improve risk stratification prior to focal therapy. Lastly, there are several novel technologies such as nanoparticles and transurethral devices that are under investigation for use in focal therapy.

Conclusion: Focal therapy is proving to be a promising option for the treatment of localized

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prostate cancer. However, further study is needed to determine the true efficacy of these exciting new technologies.

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1. Introduction

Prostate cancer remains one of the most common non-cutaneous malignancies in men [1]. With the introduction of prostate-specific antigen (PSA) screening, there was a great increase in the number of men diagnosed with prostate cancer [2]. While this biomarker detected many aggressive diseases and saved countless lives, it also detected indolent disease [3]. As a result, thousands of men each year were subject to aggressive interventions, including biopsy, surgery or radiation, for a disease that was unlikely to cause death or harm [4].

In an effort to address the morbidity associated with prostate cancer treatment, active surveillance (AS) was introduced [5]. During surveillance, favorable-risk disease is closely monitored rather than being treated upon diagnosis with the goal of pursuing definitive intervention if more aggressive disease manifests. While this has proven to be an effective strategy for low-risk prostate cancer [6], there is still controversy over whether patients with intermediate-risk disease are candidates for AS. Previous studies have shown these patients are not only more likely to progress, but also progress faster [7]. In addition, AS is not morbidity-free, as patients are subject to financial strain, anxiety, and potential side effects of repeat biopsies such as infection and bleeding [8,9].

As surgery may be too aggressive and AS is too conservative, an opportunity for new interventions must be utilized for further care. Focal therapy adopts a minimally to non-invasive approach that targets known cancer area, termed the "index lesion" [10]. This approach is based on the premise that the index lesion drives the prostate cancer biology [11], and most metastatic prostate cancers are monoclonal in origin and derive from the index lesion [12]. Therefore, destroying the index lesion would lead to cancer control. The advent of multiparametric magnetic resonance imaging (mpMRI) facilitates urologists to perform focal therapy, as the cornerstone of this approach relies entirely on accurate localization and treatment of intraprostatic disease [13–17]. One of the most important attributes of successful focal therapy is proper patient selection, which again relies on pre-procedural diagnostic evaluation with mpMRI, biopsies, and biomarkers.

There are several different focal therapy modalities used in practice today [18]. Cryotherapy was the first focal therapy modality introduced and induces apoptosis of cancer cells through rapid freeze/thaw cycles [19]. The next focal therapy modality to be studied was focal laser ablation (FLA) which works by delivering thermal energy to the tumor through small laser fibers, creating a homogeneous area of coagulative necrosis [20]. More recently, another modality explored as a focal therapy option is high-

intensity focused ultrasound (HIFU), which utilizes a transrectal probe to deliver multiple burst of ultrasound energy to targeted regions with a goal of causing prostate cancer tissue coagulation [21]. Focal therapy is not only gaining popularity in Western medicine but is also proving to be a viable treatment option for localized prostate cancer in Asian countries [16]. As these countries continue to increase their utilization of mpMRI and MRI-targeted biopsies, it is likely that urologists will more likely to consider focal therapy as a treatment option for localized disease.

In addition to focal therapy, there are a number of new technologies that are actively being investigated to treat prostate cancer [18,22].

2. Improved selection of candidacy for focal therapy

2.1. Current imaging

In an attempt to minimize focal therapy treatment and selection failure, new imaging technology is being utilized and developed to help aid in appropriate patient selection. As previously mentioned, accurate characterization of disease burden is imperative to treatment success. mpMRI has proven to be a useful tool for patient selection of candidates of focal therapy for several reasons. The adoption of MRI-targeted biopsies has proven to detect more clinically significant disease than the traditional systematic transrectal ultrasound (TRUS) biopsy [23], with the combination of modalities detecting the most clinically significant disease [24]. In a recent meta-analysis, Sathianathan et al. [25] found that mpMRI had a negative predictive value (NPV) of 90.8% for detecting Gleason grade group (GG) 2 disease, and a NPV of 97.1% for detecting GG3 disease. This is important to consider, as identification and treatment of the index lesion is the driving force behind focal therapy. Additionally, a study by Liu et al. [12] demonstrated that most, if not all, metastatic prostate cancers are monoclonal in origin. Bott et al. [26] studied pathology results from 100 consecutive radical prostatectomy specimens and found that there were no cases where the index lesion was found to have insignificant disease and secondary lesions were found to have significant disease. In fact, a study on 135 patients showed that MRI/TRUS fusion biopsies accurately (>90%) predicted location and primary Gleason grade of Index tumor as correlated with radical prostatectomy specimens [27]. Considering these data in conjunction with the high NPV and ability of MRI-targeted biopsy to detect clinically significant disease, expert consensus has been reached that mpMRI should be the standard imaging tool to select patients for focal therapy at this time [17].

In addition to patient selection, mpMRI (combined with prostate and cancer mapping biopsies) also assists urologist in determining the appropriate boundaries of treatment for focal therapy [28,29]. While other ablation templates (quadrant, "hockey stick", subtotal and hemi-ablation) do not require imaging to target a specific focus of cancer, they do rely on MRI for identifying anatomic boundaries in order to avoid unintended organ damage within the pelvis [14].

2.2. Further improvements in imaging

While mpMRI remains the gold standard for focal therapy, novel imaging modalities are being investigated that may have a significant role in improving focal therapy treatment in the future. There is some concern when relying solely on MRI for disease localization as studies have shown this imaging modality may underestimate tumor volume [30]. Therefore, recent efforts aim to incorporate nuclear imaging into treatment planning for focal therapy for improved disease localization. A recent study by Piert et al [31]. aimed to evaluate how accurate mpMRI and ¹⁸F-choline positron emission tomography and computed tomography (PET/CT) were in tumor segmentation in prostate cancer, and found that the combination of the two imaging modalities decreased the mean underestimated tumor volume. ⁶⁸Ga-labeled prostate specific membrane antigen (PSMA) is another nuclear label that is being investigated for PET/CT. In a cohort of men with equivocal MRI results or contraindication for mpMRI, Lopci et al [32]. found that ⁶⁸Ga-PSMA PET/CT was able to detect cancer in 55% of patients. In addition, the uptake value was significantly higher in GG2 cancers compared with GG1. While these results are encouraging, further study is required to determine the added benefit of PET/CT in treatment planning.

Other new imaging modalities that may be useful in focal therapy are 7 tesla (T) MRI and contrast-enhanced ultrasound (CEUS). Compared with 1.5 T or 3 T MRI, 7 T MRI has doubled the magnetic field strength and offered remarkable spatial resolution [33]. One study demonstrated the ability to complete imaging studies in less than 2 min [34]. However, increased magnet strength can also amplify artefact during studies. CEUS utilizes microbubble ultrasound enhancing contrast to identify areas of tissue with greater and longer signal enhancement, thereby identifying regions of cancer [35,36]. In systematic review by van Hove et al. [37], the investigators found that the addition of CEUS to traditional systematic biopsy led to an absolute and relative improvement in the detection of prostate cancer. While these novel modalities have showed an improvement in prostate imaging, more research needs to be done in this area to determine their value in focal therapy patient selection and treatment planning.

2.3. Role of biomarkers

While biomarkers are currently used to help guide treatment in prostate cancer, their specific use in focal therapy is yet to be determined. Traditionally, PSA is used to

determine prostate cancer prognosis, but currently several other biomarkers exist that help refine the risk stratification for prostate cancer. The prostate health index (PHI) is a mathematical formula that combines total PSA, free PSA, and [-2] proPSA to determine the probability of prostate cancer in men with an elevated PSA [38]. Urinary biomarkers also exist such as prostate cancer antigen 3 (PCA3) (formerly known as differential display code [DDC] 3), which is a prostate-specific mRNA that is found to be overexpressed in 95% of prostate cancer tissue [39,40]. Sarcosine, an N-methyl derivative of the amino acid glycine that can also be detected in urine, has been found to be highly elevated in patients with evidence of prostate cancer progression and metastasis [41]. A third urinary biomarker, SelectMDx®, evaluates HOXC6 and DLX1 mRNA levels to determine the risk clinically significant disease (\geq GG2) prior to biopsy [42].

Several studies have been conducted to better understand these biomarkers. Canitello et al. [43] evaluated 156 patients who underwent radical prostatectomy and aimed to determine the ability of PHI and PCA3 to predict adverse pathologic features. The investigators found that the addition of PHI to their baseline model improved the area under the receiver operating curve (AUC) for predicting tumor volume >0.5 mL by 7.9% (89.3% vs. 97.2%, $p<0.05$), while PCA3 did not. For patients with GG1 disease, PHI also showed to improve the AUCs for predicting upgrading to \geq GG2 on final pathology (AUC:83.1 vs. 89.0). Despite not being able to predict tumor volume and GG on final pathology, PCA3 has shown to be useful in predicting multifocality of disease [44]. In another study comparing the value of PCA3, PHI, and Sarcosine, Ferro et al. [45] evaluated 78 patients who underwent radical prostatectomy after having biopsy-proven cancer. When comparing the AUC of the biomarkers for predicting adverse pathology, the investigators found that PHI was an accurate predictor of high-stage, high-grade, and high-volume disease. Sarcosine demonstrated a comparable AUC for predicting T3 stage, where PCA3 showed an inferior AUC in all categories. PHI and PCA3 have also been tested in AS populations. When retrospectively analyzing 188 patients who underwent radical prostatectomy despite being eligible for AS according to Epstein [46] or Prostate Cancer Research International: Active Surveillance (PRIAS) criteria [47], Canitello et al. [48] found that PHI outperformed PCA3 in predicting clinically insignificant disease.

SelectMDx® has also shown great promise in improving the prostate cancer pathway. In a study evaluating the test's efficacy as a triage tool prior to biopsy, Van Neste et al. [42] found that SelectMDx had a 98% negative predictive value for predicting \geq GG2 on biopsy. When SelectMDx® is used to select against biopsy in patients with a low-risk of clinically significant disease, Govers et al. [49] found that this biomarker may reduce healthcare costs while improving long-term quality-adjusted life years.

The results from these studies may have important implications for focal therapy in the future. Having additional tests to confirm tumor volume, GG and multifocality prior to focal therapy will help guide urologists and patients in decision-making and management strategies prior to

treatment. Using these tools in tandem with imaging will improve patient selection for focal therapy.

3. New technology

3.1. Gold-silica nanoshells (GSNs)

Currently, nanoparticle technology is in the spotlight for various cancer treatments, however recently it has come to the forefront of focal therapy treatment of prostate cancer. "Nanoparticles" can capture light intensity in a process known as collective electronic excitation [50]. The nanoparticles are composed of a gold shell surrounding a silica core and long wavelengths of light are absorbed and focused in shorter wavelengths resulting in stronger energy currents that are aimed directly at tumor tissue [50]. For prostate cancer, the utility for this therapy is the sparing of surrounding tissue with focal therapy due to its potential to provide a conformal ablation restricted to where cancer is present and where nanoparticles would aggregate based on perfusion characteristics of the tumor. The relatively poor deposition of nanoparticles in non-target tissue can avoid thermal ablation in these areas consequently preserving erectile function (neurovascular bundle) and urinary incontinence (external urethral sphincter).

After success with animal models [51], recent studies cited the feasibility of nanoparticles for the treatment of prostate cancer in humans. In a study conducted by Rastinehad and colleagues [50], 15 men who were diagnosed with low- or intermediate-risk prostate cancer underwent treatment of GSN infusion and high-precision laser ablation. At 12 months follow-up, all patients had evidence of coagulative necrosis and 88% (14/16) of individuals were not found to have residual cancer on biopsy. Although this study demonstrated promising results on repeat biopsy, further long-term follow-up is necessary to ensure disease-free survival.

3.2. Transurethral ultrasound ablation (TULSA)

Another novel therapy developed for the treatment of prostate cancer is the magnetic resonance imaging guided transurethral ultrasound ablation (MRI-guided TULSA). With this treatment, therapeutic ultrasound is delivered to the gland through the urethra [52]. This leads to ablation of prostatic tissue for both benign and malignant tissue by thermal coagulation. This approach serves to give a real-time quantitative thermometry image to inform feedback control on the ultrasound as well as localizing the prostate cancer with higher accuracy [53]. With this high level of spatial precision, healthy prostatic tissue could be spared of unnecessary ablation, resulting in less morbidity. It can overcome some limitations of treatment distance during transrectal high intensity focused ultrasound ablation of anterior cancers.

There have been several animal trials conducted with TULSA in order to better understand its efficacy. Partanen et al. [54] treated three canines using a prototype of the MRI-guided TULSA system. Upon pathological review, the investigators found that the lesions treated with TULSA were nonviable. Another animal study demonstrated that a

catheter-based approach may improve accuracy due to a modified device curvature, temperature sensitivity, and rate of ablation [55].

This treatment approach has been tested in several phase I clinical trials. In one trial, 21 men were treated with TULSA and the investigators found that the mean treatment time of the whole gland ablation around the capsule was 36 min [56]. After one-month follow-up, the median PSA decreased by 87% (5.8 ng/mL vs. 0.8 ng/mL), total cancer core length on biopsy was reduced by 61%. In another study, Bonekamp et al. [57] found that after 12 months follow-up, the prostate volume was reduced by 88.8% when compared with baseline (43.0 mL vs. 4.8 mL). Upon imaging of the prostate, a contrast-enhanced MRI non-perfused volume showed only 64% of the ablation site, as opposed to 88% when the authors utilized the delayed thermal ablation volumes. While these data are encouraging, further studies in humans with longer follow-up are needed to better understand the oncologic outcomes of TULSA.

3.3. Bipolar radiofrequency ablation (RFA)

RFA is another modality that recently used and tested for focal therapy of prostate cancer. The RFA utilizes radio waves to perform thermal ablation [58]. With this treatment, medium to high frequency currents create frictional heating between ions through kinetic energy, with target treatment temperature of 50°C as this is when radio waves start to destroy tissue through cell membrane damage and protein denaturation [59]. In most procedures, this is performed in a urinary catheter with a monopolar needle or bipolar needles to ablate the tumor.

There have been several animal studies demonstrating the efficacy of RFA for prostate cancer [59,60], with the first human study being completed in 1998 [61]. Aydin et al. [62] recently published their results from a pilot study of 10 men who underwent bipolar RFA for the treatment of their prostate cancer. All patients had T1c disease with Gleason score ≤ 7 . After 6 months follow-up, only one patient was noted to have Grade 3 gross hematuria, and two out of four patients with baseline healthy sexual function were noted to have erectile dysfunction following treatment. No patients reported incontinence or any episodes of urinary infection. While this study showed the feasibility and safety of bipolar RFA, there is a great need for oncologic outcomes to better understand if this modality can successfully treat prostate cancer.

3.4. Targeted cell-perforating agents

Topsalysin is a prodrug that is targeted for cancer therapy. It is a modified form proaerolysin which has a prostate specific protease cleavage site. When it is injected into the prostate, topsalysin has a delayed effect as it causes the production of aerolysin which then oligomerized to form heptamers that can form large membrane channels and induce lysis of PSA expressing prostate cells [63]. Its usability and its selective nature of therapeutic effect make it a ideal candidate to cause precise disruption of membrane integrity of cancerous cells.

Currently, topsalysin is in phase II trials and has shown promise in their phase I and phase II studies (NCT02499848). The greatest limitation to a PSA-based approach is that there is an androgen component that needs to be monitored since androgen decrease is seen in topsalysin administration in a short-term phase. This limits the activation of topsalysin. Additionally, even and predictable distribution of local injections in the prostate can be a challenge, though the prospect of a tissue-specific approach has remarkable potential (Table 1).

3.5. Microwave therapy

Microwave coagulation therapy is a modality that has had success with kidney and liver cancer ablation [64], but is still in preliminary testing for prostate cancer. Under MRI-guidance, needles are placed in the gland and microwave activation amplifies heat onto a specific site. The microwave is set to 30 W or 60 W and the irradiation takes place for 30 s, causing destruction of malignant tissue [65].

Preliminary results of the microwave approach have shown promise. In 2019, Yamada et al. [65] open a phase I clinical trial investigating microwave therapy, with a target enrollment of five participants. Follow-up visits are scheduled 1 week, 1 month, 3 months and 6 months following treatment to measure PSA levels. mpMRI will be performed at 6-month follow-up, with targeted biopsy if there is demonstrated disease persistence or recurrence on imaging. This treatment modality has had success in treating benign prostate hyperplasia (BPH) [66],

suggesting that microwave therapy successfully destroys prostatic tissue.

3.6. Focal radiation therapy

Finally, focal radiation therapy is a new method for treatment of prostate cancer. With the overall goal of prostate cancer procedures to have the endpoint of retaining prostatic and erectile function, focal therapy provides the ability for the prostate to have a specific dose of radiation to predetermined zones to isolate cancer therapy [67]. While initially treating only peripheral zone tumors [68], there is a renewed interest in focal treatment using low-dose rate brachytherapy, high-dose rate brachytherapy, and stereotactic body radiation therapy approaches [69].

Currently, there are a few studies looking into the feasibility of focal therapy with different radiation doses, with the focus primarily on workflow and how doses will target only the prostate without affecting other organs. Fischbach et al. [70] has been currently working on this workflow with nine patients treated so far. Their current findings showed that mean PSA decreased from 8.8 ng/mL to 1.7 ng/mL with a 34-min intervention time. No patients demonstrated signs of infection and no residual prostate cancer was detected in the treated region on follow-up. As this approach to treatment is still in the novel stage, further study is required to determine how effective focal radiation will be for the treatment of prostate cancer.

Table 1 Key studies of various novel technologies that are being investigated as potential treatments for prostate cancer.

Study	Modality	Number of patients	Outcome	Side effect
Rastinehad et al., 2019 [50]	Gold silica nano shells	15	-At 12 months follow-up, 100% of patients had evidence of coagulative necrosis in tumor and 14/16 patients had no cancer on biopsy.	None reported
Chopra et al., 2012 [52]	TULSA	8	-Treatment resulted in a temperature uncertainty was less than 2°C in all patients.	None reported
Chin et al., 2016 [56]	TULSA	30	-Reduction of median PSA to 0.8 ng/mL at 12 months with a 61% reduction in cancer length in positive biopsies.	Hematuria, UTI, acute urinary retention, and epididymitis
Bonekamp et al., 2019 [57]	TULSA	30	-Median prostate volume reduction was 88.8% which was best seen by delayed thermal ablation volume.	None reported
Zlotta et al., 1998 [61]	Bipolar RFA	15	-All patients showed evidence of coagulative necrosis with PSA becoming undetectable.	None reported
Ahmed 2009 [10]	Topsalysin	37	-10/37 patients saw clinically significant response to the first dose and 15 patients showed a partial response.	None reported
Yamada et al., 2019 [65]	Microwave	5	-80% of the subjects had a multifocal disease when ablation was performed; study is ongoing.	None reported

PSA, prostate-specific antigen; RFA, radiofrequency ablation; TULSA, transurethral ultrasound ablation; UTI, urinary tract infection.

3.7. Comparison with current focal therapy modalities and traditional whole gland treatment

With regards to oncologic control, GSNs have shown similar efficacy when compared with current focal therapy modalities. After 12 months follow-up, Rastinehad et al. [50] reported that 88% of patients were found to have no cancer on biopsy after treatment with GSNs. These outcomes are comparable to a recent FLA study by Walser et al. [71] which reported that 83% did not require additional treatment for their cancer 12 months after focal therapy. This is also similar to results from a pooled analysis by Albisinni et al. [72] which found an 87% negative biopsy rate at 12 months following treatment with HIFU. In the first United States series investigating the use of HIFU exclusively for focal therapy, Abreu et al. [73] found a 2-year radical treatment free survival of 91%. In a Chinese study investigating the efficacy of cryotherapy, Lian et al. [74] reported a 22% positive biopsy rate at 6–12 months following treatment. It is important to note that the other new technologies are in the preliminary stages of investigation and therefore oncologic data are limited at this time. The urology community will be interested to see how these new technologies develop and how effective they will be at treating localized prostate cancer.

With regards to morbidity, both nanoparticles and focal radiation have proven to be safe as no side effects have been reported in early studies [50,70]. This is comparable to FLA where recent studies have shown that patients experienced no significant changes to their sexual or urinary function [71,75]. RFA has shown to cause hematuria as well as erectile dysfunction following treatment [62]. Erectile dysfunction is also associated with both cryotherapy and HIFU. After initial treatment of localized prostate cancer, Lian et al. [74] reported a potency preservation rate of 77% in their series. In a feasibility study exploring the use of HIFU in Japan, Shoji et al. [76] reported that only 37.5% (6/16) of patients retained erectile function at 24 months following urethral sparing HIFU. In addition, the investigators reported that 93.3% of patients did not develop a urethral stricture following treatment with HIFU. Incontinence is relatively uncommon but can be seen in patients treated with HIFU [18]. In a pooled analysis of patients treated with either focal or hemiablativ HIFU for localized prostate cancer, Albisinni and colleagues [72] found that continence rates ranged from 91% to 100%, but the definition of continence was not homogenous across studies.

4. Conclusion

The literature surrounding the treatment of prostate cancer is rapidly evolving. There has been a push to explore more conservative treatment options for patients with low to intermediate-risk disease in an effort to avoid the morbidities associated with whole gland treatment. The incorporation of mpMRI into the diagnostic pathway facilitated the advancement of focal therapy and allowed for the exploration of novel approaches. The addition of nuclear imaging to mpMRI may improve tumor localization, allowing for more accurate focal therapy. Biomarkers can

be used to assist and augment patient selection for focal therapy. Lastly, several novel technologies exist that are being actively explored and tested as treatment options for prostate cancer. While many of these technologies have shown encouraging results, further studies are needed to better understand their safety and efficacy in prostate cancer treatment.

Author contributions

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Conflicts of interest

The authors declare no conflict of interest.

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