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Collaborative Review – Prostate Cancer

Focal Therapy for Prostate Cancer: Possibilities and Limitations

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Abstract

Context: A significant proportion of patients diagnosed with prostate cancer have well-differentiated, low-volume tumors at minimal risk of impacting their quality of life or longevity. The selection of a treatment strategy, among the multitude of options, has enormous implications for individuals and health care systems.

Objective: Our aim was to review the rationale, patient selection criteria, diagnostic imaging, biopsy schemes, and treatment modalities available for the focal therapy of localized prostate cancer. We gave particular emphasis to the conceptual possibilities and limitations.

Evidence acquisition: A National Center for Biotechnology Information PubMed search (www.pubmed.gov) was performed from 1995 to 2009 using medical subject headings "focal therapy" or "ablative" and "prostate cancer." Additional articles were extracted based on recommendations from an expert panel of authors.

Evidence synthesis: Focal therapy of the prostate in patients with low-risk cancer characteristics is a proposed treatment approach in development that aims to eradicate all known foci of cancer while minimizing damage to adjacent structures necessary for the preservation of urinary, sexual, and bowel function. Conceptually, focal therapy has the potential to minimize treatment-related toxicity without compromising cancer-specific outcome. Limitations include the inability to stage or grade the cancer(s) accurately, suboptimal imaging capabilities, uncertainty regarding the natural history of untreated cancer foci, challenges with posttreatment monitoring, and the lack of quality-of-life data compared with alternative treatment strategies. Early clinical experiences with modest follow-up evaluating a variety of modalities are encouraging but hampered by study design limitations and small sample sizes.

Conclusions: Prostate focal therapy is a promising and emerging treatment strategy for men with a low risk of cancer progression or metastasis. Evaluation in formal prospective clinical trials is essential before this new strategy is accepted in clinical practice. Adequate trials must include appropriate end points, whether absence of cancer on biopsy or reduction in progression of cancer, along with assessments of safety and longitudinal alterations in quality of life.

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1. Introduction

Since the introduction of prostate cancer screening based on prostate-specific antigen (PSA), practice patterns in the United States offer the best natural study on the impact of widespread screening. The incidence of prostate cancer has risen 26%, the proportion of men with metastases at presentation has decreased 75%, and mortality rates have declined 30% [1]. Concomitant with these encouraging trends has been the substantial number of men diagnosed that do not reap a clinical benefit from treatment because they would not have otherwise had knowledge of their cancer during their natural life span. Autopsy recognition of incidental prostate cancer (men in their 30 s, 40 s, 50 s, and 60 s with rates of 29%, 32%, 55%, and 64%, respectively [2]) significantly outnumbers rates of clinically evident cancers, and with annual screening, estimates of "overdetection" are as high as 50% [3] and suggest the number needed to treat to save one life is between 48 and 100 [4,5].

Surgery and irradiation provide excellent long-term oncologic efficacy [6]. Among 11 000 patients treated with radical prostatectomy (RP) at four medical centers between 1987 and 2005, the 15-yr cancer-specific mortality was 4–7% [7]. In similar patients undergoing radiation therapy, the 10-yr cancer-specific mortality rate was 3–6% [8,9]. However, both modalities can lead to long-lasting urinary, sexual, and bowel morbidity in a significant minority of men. Contemporary series of RP have shown median tumor volume to be $\sim$1 cm^3 [10–12], and the chance of a cancer-related death for patients with organ-confined, well-differentiated cancers is basically nil [7,13,14]. For example, among 3756 patients with organ-confined Gleason score $\leq$6 cancers undergoing RP, only 1 patient died from prostate cancer–related causes [7].

Active surveillance is a strategy designed to minimize rates of overtreatment and personalize the need for intervention. Patients with well-differentiated cancers can safely be observed with longer term results confirming the safety of this approach for select patients. The 10-yr cancer-specific survival rates range from 92% to 100% [5,15–17]. Delayed intervention, when deemed necessary, individualizes the need for treatment and results in comparable outcomes to those treated immediately at diagnosis [18,19]. However, observational strategies can lead to significant anxiety [20,21], and physicians are particularly hesitant to recommend this approach for young healthy men with long life expectancies.

A conceptually appealing option to patients uncomfortable with observational strategies yet highly concerned about the risks of whole-gland treatment is to bridge elements of active surveillance with whole-gland therapy. This hybrid approach, termed *focal therapy,* aims to eradicate known cancer foci with the highest likelihood of progressing or metastasizing while attempting to diminish collateral damage to the vital structures essential for maintaining normal urinary and sexual function. Ideally, ablation of all known lesions would favorably alter the natural history of the cancer without impacting health-related quality of life and allow for safe retreatment with focal therapy or whole-gland approaches if necessary.

Our objective was to review the rationale, patient selection criteria, diagnostic imaging, biopsy schemes, and treatment modalities available for focal therapy of localized prostate cancer with specific emphasis on the possibilities and limitations.

2. Evidence acquisition

A National Center for Biotechnology Information PubMed search (www.pubmed.gov) was performed from 1995 to 2009 using medical subject headings "focal therapy" or "ablative" and "prostate cancer." Additional articles were extracted based on recommendations from an expert panel of authors.

3. Evidence synthesis

3.1. *Rationale for focal therapy*

Multiple lines of evidence suggest the index lesion, defined as the largest focus of cancer, is predominantly responsible for total tumor volume, risk of cancer recurrence, and Gleason grade. Among nearly 500 RP specimens evaluated, index tumor volume predicted cancer recurrence as well as total tumor volume [22], and the presence of secondary tumor foci in low-risk patients did not adversely impact recurrence rates [23]. Using whole-mount tumor maps from 100 RPs, only 3% of index tumors contained a primary Gleason grade lower than the overall primary Gleason grade [24]. These detailed series support the concept of targeting an index lesion as the primary and often sole determinant of prognosis.

3.2. *Specifics of focal therapy*

Focal therapy refers to any form of subtotal prostate ablation. Target regions may include biopsy-confirmed cancer with a concordant radiographic lesion, a sextant, hemi-ablation, or three-quarters ablation (one side and a portion of the contralateral). Ideal patients appear to be those with unifocal lesions (Fig. 1a), unilateral lesions, or index lesions accompanied by nonindex lesions with very low-risk characteristics (Fig. 1b). Patients with multifocal bilateral large lesions are not suitable for focal therapy at this time (Fig. 2). Multiple modalities capable of inducing irreversible cytotoxic damage have been proposed: cryotherapy, high-intensity focused ultrasound (HIFU), photodynamic therapy, and laser-induced interstitial thermotherapy.

3.2.1. *Possibilities*

Three major tenets of focal therapy form the basis of its potential advantages compared with other management strategies (Table 1). First, the side-effect profile has the potential to be significantly and consistently more attractive. By strategically restricting the extent of damage to key anatomic structures responsible for treatment-related morbidity, it may lead to a lower incidence or severity of adverse outcomes, but preferably both. Despite this

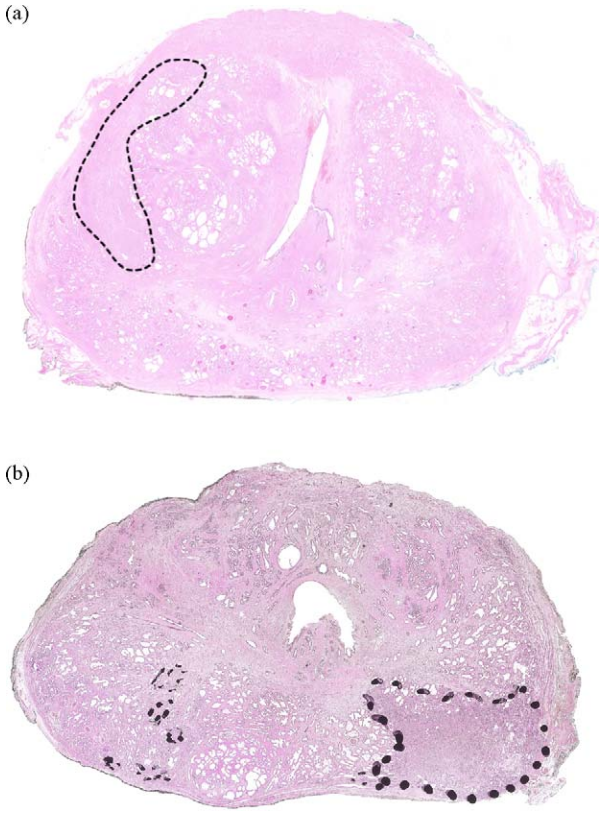

Fig. 1 – Low-power whole-mount radical prostatectomy specimens. (a) Unifocal, organ-confined Gleason 6 cancer; (b) multifocal Gleason 6 cancer with an index lesion and multiple small (<0.5 cm^3), organ-confined nonindex lesions.

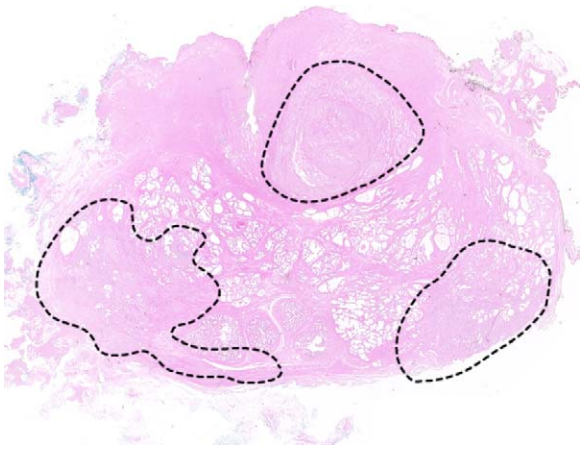

Fig. 2 – Low-power whole-mount radical prostatectomy specimens showing a multifocal prostate cancer not considered suitable for focal therapy.

conceptually rational claim, disturbingly few focal therapy reports have systematically reported quality-of-life outcomes or adverse events using validated tools [25–33].

Second, maintaining the ability to retreat the prostate with focal or whole-gland therapy, if warranted, is an important aspect of the management paradigm. For patients on surveillance, outcomes following delayed RP appear similar to those treated immediately [18,19,34]. Despite these encouraging data, the feasibility, safety, and efficacy of retreatment following focal therapy is not known.

Third, patients eligible for focal therapy are also likely to be candidates for observation-based management, which has excellent cancer-related outcomes in both intermediate-term contemporary series [17,18,35,36] and longer term older series [5,16]. For focal therapy to coexist or supplant observational strategies, studies must establish rates of oncologic success, secondary therapy, and adverse outcomes.

3.2.2. *Limitations*

Along with the substantial promise of focal therapy is much uncertainty (Table 1). The overriding concern is the potential for inadequate cancer control leading to inferior outcomes compared with whole-gland therapies. With inappropriate patient selection, inaccurate mapping of multifocal disease, suboptimal cancer ablation, poor patient compliance, or compromised safety or effectiveness of salvage therapies, the potential for missed curative opportunities exists.

A primary obstacle is suboptimal patient selection because a significant minority of patients are clinically understaged or undergraded, even with contemporary biopsy [37,38] and imaging techniques. Even among the lowest risk patients, including those with a single microfocus of well-differentiated cancer [39,40], rates of extracapsular extension or higher grade cancers at the time of rebiopsy or prostatectomy are approximately 20–30% [39–41].

Second, the inability to visualize prostate cancer reliably limits enthusiasm for focal therapy. Meaningful improvements in identifying tumor location, focality, extent, and differentiation could dramatically improve identification of patients likely to benefit.

Table 1 – Theoretical possibilities and limitations of focal therapy for prostate cancer

Possibilities	Limitations
Ablation of cancer foci with noninferior rates of cancer progression or metastases compared to surgery or radiation	Inadequate cancer ablation
Minimizing risk or severity of treatment-related morbidity	Incomplete tumor characterization due to suboptimal clinical staging, mapping, and imaging
Ability to retreat the prostate with focal or whole-gland interventions	Unknown impact of untreated nonindex lesions
	Posttreatment monitoring of cancer status without validated definitions of clinical failure
	Debatable cost effectiveness

Third, the impact of untreated nonindex lesions is unknown [22–24,42]. Therefore, even if index lesions could be accurately identified and treated, it may not necessarily eradicate the focus of cancer with the highest likelihood of metastasizing, and the long-term impact of untreated nonindex lesions is largely speculative. Gburek et al identified 12 patients with lymph node metastases at prostatectomy where chromosomal anomalies within the metastasis matched the index prostate lesion in only 5 (42%) [43]. Of particular concern is that chromosomal alterations within metastases can be identical to those of nonindex cancers within the prostate [44]. Although it is highly unlikely that patients from these two studies would have been candidates for focal therapy because they already exhibited lymph node metastases, it highlights the fact that nonindex lesions may have metastatic capacity even in the setting of a low-risk cancer.

Fourth, there are significant challenges in determining how to monitor patients following focal therapy. Serum PSA, although inexpensive, convenient, and intuitive, is difficult to interpret in the setting of partially treated prostates that likely harbor untreated nonindex cancers and a significant number of normal or hyperplastic glands. Further, for patients without evidence of prostate cancer, PSA exhibits significant annual and physiological fluctuations [45]. Even in patients with untreated localized prostate cancer electing active surveillance, neither baseline PSA nor PSA kinetics can reliably be used to predict cancer-specific events [46]. Biomarkers and imaging are likely to be suboptimal compared with a prostate biopsy, and, for this reason, routine surveillance biopsies following focal therapy appear to be warranted. However, even with serial biopsies, sizable and high-grade cancers may go undetected [41,47]. Definitions of failure and triggers for retreatment have not been established, although observational phase 2 surveillance studies with variable definitions of failure suggest that patients are at very low risk of developing metastases [17,18,48]. To minimize the risk of treatment failure, an extensive pretreatment biopsy scheme should be used, although the specific extent has yet to be definitively established. At a minimum, posttreatment monitoring should consist of (1) an early and extensive biopsy to establish cancer eradication, (2) routine periodic biopsies to detect cancer progression or newly evident foci, and (3) early and periodic prostate imaging to characterize treatment effects and association with outcome.

Lastly, consideration must be given to the financial impact and implications of the various management strategies. Longitudinal comparisons to active surveillance, surgery, or radiation would be ideal. The price of treatment will widely vary and depend on geography, health care system, mode of ablation, pattern of follow-up, and rates and types of secondary intervention.

3.3. Prostate cancer imaging

Ideally, all cancer foci would be visualized prior to treatment along with tumor extent and histologic grade. If attainable, patients could be appropriately selected for focal therapy, relevant lesions targeted, and accurate posttreatment surveillance instituted.

3.3.1. Magnetic resonance imaging

Multiparametric magnetic resonance imaging (MRI) can assess the anatomic and metabolic characteristics of the prostate and appears to be the most promising imaging tool. Typically performed with an endorectal pelvic phased-array coil, analysis can be done via T2-weighted images, dynamic contrast enhancement (DCE), diffusion-weighted imaging (DWI), and spectroscopy. Despite multiple technological advances, including computer-assisted diagnosis software [49], the staging accuracy of MRI remains suboptimal (sensitivity of 13–95% for extraprostatic extension and 23–80% for seminal vesicle invasion).

Noguiera et al specifically evaluated the role of traditional T2-weighted MRI in patients meeting criteria for active surveillance or focal therapy [39]. Each prostate quadrant was assigned a 5-point score based on the MRI for presence of cancer and an additional 5-point score regarding the suspected presence of extracapsular extension. Assessing 202 patients, 101 (50%) had pathologically indolent cancers. Depending on the prostate quadrant, MRI sensitivity ranged from 2% to 20% with a specificity of 91–95%. MRI-based assessment of extracapsular extension and tumor extent (minimal, moderate, or extensive) each added value in predicting nonindolent cancers compared with standard parameters (area under the curve of 0.62 and 0.53 compared with 0.49), although the improvements were modest. This study suggests standard T2-weighted MRI is inadequate for identifying foci of cancer in low-risk patients but may be useful in excluding patients from focal therapy if the images suggest higher volume or extraprostatic cancers.

Encouraging data from small DWI and DCE series support its continued evaluation. Among 49 patients undergoing prostatectomy following an endorectal MRI with a 1.5-T magnet and each sextant of the prostate assigned a score from 0 to 4 (“definitely no cancer” to “definitely cancer,” respectively), the operating characteristics for detecting tumors >4 mm with a Gleason score ≥ 6 were better with MR-DWI (81% sensitivity and 84% specificity) compared with T2-weighted evaluation (54% and 91%) [50]. Villers et al used enhancement, morphologic features, and T1-T2 DCE concordance to establish a scoring system for each quadrant of the prostate in 24 patients. For tumors >0.5 cm^3, sensitivity was 90% and specificity 88% [51]. Lastly, among 52 patients with a 3-T DCE-MRI prior to prostatectomy with whole-mount pathologic evaluation, the maximum enhancement index was 56% higher in regions of cancer compared with normal peripheral zone tissue, and a combination of quantitative DCE data provided a sensitivity of 89% and a specificity of 90% [52].

3.3.2. Ultrasound

Traditional gray-scale ultrasonography has been the backbone of prostate imaging and biopsies for two decades. Color and power Doppler are proposed strategies to improve the operating characteristics by simultaneously assessing blood flow. Additionally, contrast-enhanced

transrectal ultrasound (CEUS) capitalizes on the intravenous infusion of small encapsulated gas bubbles to image vascular perfusion patterns. Three-dimensional power Doppler CEUS is capable of identifying 68–79% of all tumors >5 mm [53]. Using CEUS-targeted biopsies leads to similar cancer detection rates compared with random biopsies with approximately half the number of biopsy cores [54]. A combination of targeted and random biopsies in 380 men with a PSA between 4 and 10 ng/ml led to a 37% cancer detection rate compared with 27% with either method alone [55] and may also preferentially detect cancers with higher Gleason scores [56]. Halpern et al assessed 60 patients undergoing sextant biopsies and scored the ultrasound images before and after the administration of contrast. Compared with conventional gray-scale imaging, contrast infusion increased the sensitivity from 38% to 65% without a significant decrease in specificity (83–80%) [57].

Elastography is an additional strategy proposed to improve the capabilities of ultrasonography by comparing relative values of signal changes following compression-decompression of the prostate. Elastography with five targeted biopsies was compared with a systematic 10-core biopsy in 230 men with an elevated PSA [58]. Cancer detection rates between the techniques were similar, but elastography yield was more favorable because it required less than half the cores. In 109 men who underwent whole-mount evaluation following prostatectomy and had previous elastography, the sensitivity and specificity for location-specific correlation of tumors were 75% and 77%, respectively [59]. Although elastography is not commonly used, early results suggest it may improve the staging evaluation compared with conventional ultrasonography.

Computer-aided ultrasound of the prostate (HistoScanning; Advanced Medical Diagnostics, Waterloo, Belgium) is a technique that relies on morphologic changes identified via analysis of back-scattered ultrasound data. In a pilot evaluation of 13 patients undergoing radical prostatectomy, there were a total of 12 cancer foci >0.5 cm^3, all of which were correctly identified by computer-aided ultrasound [60]. However, this study did not include evaluation of all patients undergoing the procedure, lacked detailed patient information, and only provides preliminary data supporting further evaluation.

3.4. Biopsy strategies

Prostate biopsies have evolved from a standard sextant approach [61] to more common 12-core strategies. However, standard office-based strategies do not appear to select patients adequately for focal therapy [37,38]. More extensive approaches, beyond 12 cores, appear to enhance information regarding tumor volume, location, focality, stage, and grade [47,62–64]. Among 180 patients with unilateral tumors, an extensive transperineal mapping biopsy (median cores: 50) identified 110 (61%) with newly recognized bilateral tumors and 41 (23%) with Gleason upgrading [63]. Less extensive repeat transrectal biopsies (median cores: 20) in patients with low-risk cancer showed 38% to have a higher Gleason score or more significant tumor volume [47]. The morbidity of transperineal extensive-template biopsies appears to be acceptable with a 7% rate of prolonged catheterization and no significant change in urinary, sexual, or bowel quality of life [65]. The optimal biopsy strategy to identify and localize cancer foci has yet to be determined, but it appears the optimal means of identifying and localizing cancers is by extending the strategy beyond traditional 12-core approaches, with template-based methods and attention to anatomic mapping preferable.

3.5. Patient selection

Inclusion criteria for focal therapy experiences vary widely [25,26,28–33,66,67]. A recently convened panel at the Second International Workshop on Focal Therapy and Imaging in Prostate Cancer constructed a consensus statement on patient selection [27]. Areas of agreement were selection of patients following a transperineal mapping biopsy, inclusion of patients with low-risk cancer features (e.g., Gleason 6, clinical stage ≤T2a), estimated life expectancy >10 yr, that imaging is highly likely to play an important role in the future, and the long-term urinary and sexual effects are unknown.

3.6. Focal therapy modalities

3.6.1. High-intensity focused ultrasound

HIFU relies on the focused conglomeration of ultrasound waves on a specific point in the prostate, leading to elevated temperatures (60–100 °C), protein denaturation, and coagulative necrosis [33]. Distinct margination is visible ultrasonographically between treated and untreated areas. The two systems currently available, Ablatherm (Maple Leaf HIFU, Ancaster, Ontario, Canada) and Sonablate (Focus Surgery, Indianapolis, IN, USA), vary slightly in focal distance, ablation volume, and patient positioning. Large-scale series targeting the entire prostate, primarily in Europe and Asia, with experiences of up to 400 patients, are associated with variable rates of urinary tract infections (UTIs) (2–24%), urethral strictures (4–30%), urinary incontinence (2–14%), impotence (20–60%), and urethrorectal fistula (1–6%) [25,33,66]. Nearly all reports were about whole-gland therapy and limited to prostates <40 cm^3. Oncologic outcomes are particularly difficult to interpret between series or directly to other treatment options because no standardized definition of success or recurrence exists. Variable proportions of patients undergo posttreatment biopsies following whole-gland therapy, and, in those that do, 13–80% have detectable cancer [25,33]. PSA-based outcomes are reported with variable definitions of failure (e.g., PSA nadir plus 2 ng/ml, three successive PSA rises following a nadir >0.5 ng/ml), and no correlation currently exists between post-HIFU PSA outcomes and more meaningful end points such as secondary therapy, metastases, or cancer-specific mortality.

Muto et al studied focal HIFU using the Sonablate system on 29 patients >60 yr of age (median: 72 yr) with T1c–T2a cancers of any Gleason score limited to one side of

the prostate [31]. The treatment zone included bilateral peripheral zones and ipsilateral transition zone, and 7 (24%) received neoadjuvant androgen deprivation. Biopsies were performed 6 and 12 mo following treatment with residual cancer present in 11% and 24%, respectively. No details were given on the location of these residual cancers, how they were subsequently treated, or ultimate outcomes. Urinary function was generally unaffected, and urethral stricture occurred in 4% and UTI in 4%. No data were presented on erectile function. HIFU as a focal therapy modality is also being evaluated in an ongoing registered trial (www.clinicaltrials.gov; Identifier: NCT00770822, NCT00561314).

3.6.2. Cryotherapy

Prostate cell death following cryotherapy occurs from disruption of the cellular membrane and microvascular thrombosis via transperineal needles with success depending on nadir temperature, duration of treatment, number of freeze-thaw cycles, and rate of thawing [68]. Originally associated with high rates of major complications, the advent of third-generation cryoprobes, real-time temperature monitoring, and ultrasound guidance have improved outcomes. Used for decades as whole-gland therapy in the primary or salvage setting, recent series have investigated the potential role of cryoablation as focal therapy, either as hemi-ablation or more targeted focal ablation. Focal therapy series have enrolled up to 100 patients with follow-up ranging from 2 to 6 yr [26,29,32,67]. Incontinence rates following treatment have been low (0–2%) with potency rates from 71% to 90% [26,29,32,67]. Study conditions have been variable with inclusion of patients at significant risk of recurrence, select patients receiving neoadjuvant combined androgen blockade, and poor compliance with posttreatment surveillance biopsies. Clinical experiences continue to accrue patients, and a registered clinical trial is ongoing (www.clinicaltrials.gov; Identifier: NCT0077436).

3.6.3. Laser-induced interstitial thermotherapy

Laser-induced interstitial thermotherapy is a photothermal ablative procedure. Lindner et al evaluated image-guided photothermal therapy in 12 patients with PSA < 10 ng/ml, clinical stage T1c–T2a, Gleason score ≤ 6, $<30\%$ of cores positive, and $<50\%$ of any individual core [30]. Positive biopsies were restricted to one prostate sector and concordant with a visible lesion on MRI. MRI images were coregistered into three-dimensional ultrasound images, and patients underwent transperineal laser placement under ultrasound guidance to ablate the cancerous region. Intravenous microbubbles were also used to monitor real-time treatment effect (Definity; Bristol-Myers Squibb Medical Imaging, Billerica, MA, USA). Side effects were mild and self-limiting. Urinary and sexual function were unaffected, as measured by the International Index of Erectile Function-5 Questionnaire and the International Prostate Symptom Score. Hypoperfused lesions were evident on MRI 7 d after treatment with a median volume of 2.2 cm^3. Among the 12 patients with posttreatment (3–6 mo) biopsies including two targeting the ablated region, 6 (50%) had no evidence of tumor, 2 (17%) had newly recognized contralateral cancers, and 4 (33%) had positive biopsies at the site of ablation. One patient underwent an RP that showed previously unrecognized extraprostatic extension.

3.7. Recommendations for study design

Focal therapy, both conceptually and practically, is in its infancy. Without reliable long-term outcomes available, focal therapy should be considered investigational and studied accordingly under protocols approved by institutional review boards with appropriate informed consent. To provide the necessary data for a reasoned assessment, all focal therapy programs should establish systematic pre- and posttreatment evaluation, well-defined end points, and strict inclusion criteria. Outcomes should include quality of life measured by validated instruments, as well as procedure-related complications with regular review by a data and safety monitoring board. To evaluate the concept and technology, a phase 1 trial would define procedure safety, phase 2 trials would provide initial evidence of effectiveness, and a phase 3 trial would definitively establish meaningful safety and effectiveness. A specific challenge in designing a study is how to assess clinical benefit. Two distinct approaches appear reasonable. First, proof that focal ablation reduces the probability of progression to a significant cancer over time (biopsy-ablation-lack of progression). The major obstacle is agreeing on the definition of a significant cancer and the limitations of recognizing it. The alternative model would be to thoroughly define the characteristics and location of all cancers, ablate them, and repeat the biopsy following treatment to show absence of cancer (biopsy-ablate-biopsy). The current ability to assess cancer outcomes is limited because virtually all studies have median follow-ups of <5 yr [26,28,30–32].

4. Conclusions

Focal therapy for low-risk localized prostate cancer depends on the eradication of known cancers that appear to harbor the greatest potential for cancer progression while preserving healthy tissue to minimize treatment-related toxicity. With extensive prostate mapping schemes and the continued evolution of imaging tools, it is anticipated more patients will have cancer(s) that can be mapped and, preferably, visualized. Significant obstacles remain to optimize patient selection, target index lesions, and establish efficacy. Early clinical experiences with modest follow-up, evaluating a variety of modalities, are encouraging but hampered by design limitations and small sample sizes. Future evaluation should be encouraged within formal prospective clinical trials that include clear eligibility criteria, full documentation of treatment techniques and side effects, longitudinal quality-of-life assessment, and well-defined end points. Before focal therapy can be accepted in clinical practice, the medical community will have to be convinced of the safety and effectiveness of

ablative technologies to eradicate the targeted focus of cancer, reduce the rate of progression to clinically significant cancer compared with alternatives such as active surveillance, and allow safe retreatment with focal ablation or radical therapy when indicated.

Author contributions: Scott Eggener had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Eggener, Salomon, Scardino, De la Rosette, Polascik, Brewster.
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