EDITORIAL

clinical

The state of focal therapy in the treatment of prostate cancer: the university of California collaborative (UC-Squared) consensus statement

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INTRODUCTION

Focal therapy is an emerging management alternative for men with localized prostate cancer, but its optimal use remains controversial. Based on the American Urological Association (AUA) and National Comprehensive Cancer Network (NCCN) guidelines, focal therapy by High Intensity Frequency Ultrasound (HIFU) or other modalities is not routinely recommended for the treatment of patients at any risk level, due to a lack of supporting evidence. This guideline is based on expert opinion [1, 2]. Cryoablation can be considered for the treatment of intermediate risk prostate cancer, but is not recommended for low or high-risk prostate cancer patients. For patients with prostate cancer recurrence after radiation therapy, whole gland cryoablation and HIFU can be considered for salvage treatment per the NCCN guidelines [2]. High-quality evidence in support of focal therapy is limited, but despite this, these techniques are gaining popularity and commonly employed in contemporary practice [3]. Numerous focal therapies have been developed over the years and include but not limited to: Cryoablation [4], HIFU [5], Transurethral Ultrasound Ablation of the Prostate (TULSA™) [6] t, irreversible electroporation (NanoKnife) [7], Photodynamic Therapy, and more recently laser ablation [8, 9].

The current guidelines reflect the accepted standard of care for urologic practices. Although the detailed text of the guidelines do describe focal therapy in passing, they include no direction on the suggested preoperative diagnostic evaluation or post-operative care to help clinicians determine when to offer focal therapy, guidance for patients selecting focal therapy, or expectations for future research.

The recently formed University of California Urologic Collaborative "(UC) [2]" was founded with the goals of synchronizing clinical and research efforts in urologic oncology across the five UC campuses (Davis, Irvine, Los Angeles, San Diego, and San Francisco), and ensuring high quality and safe practices for urology patients. Our Collaborative met with the goal of determining the current state of science and also to determine priority objectives for future research. The Collaborative's first task was to propose several critical questions about the appropriate clinical utility of focal therapy in the treatment of patients with prostate cancer; the intention is to help drive the safe practice of focal therapy and further prompt high quality prospective studies in this space. There was no external entity involved with or supporting the (UC) [2] discussion. The following are a set of five consensus statements on the perceived appropriate use of focal therapy, which balance oncological outcomes, patient safety, and shared decision making (Table 1). These includes guidance on the pre-operative counseling session, candidate selection process, recommended imaging, and post-operative surveillance.

HOW SHOULD PATIENTS BE COUNSELED ON THE USE OF FOCAL THERAPY?

Patients should be counseled that focal therapy is not the standard care of care for the treatment of prostate cancer and there are no randomized trials currently comparing its effectiveness to radiation therapy or surgery (Statement 1). The U.S. Food and Drug Administration has granted 510(k) clearance to Ablatherm Integrated Imaging HIFU for the ablation of prostate tissue but not for the treatment of prostate cancer [10]. Clinicians should discuss with patients that there have been few comparative studies on oncological outcomes, HRQoL outcomes, or morbidity across treatment modalities. Ideally, patients treated with focal therapy should be included in trials or prospective registries (Statement 2).

WHAT ARE THE OPTIMAL CLINICAL SCENARIOS FOR FOCAL THERAPY?

For patients with low risk disease, guidelines now consistently recommend active surveillance as the preferred management strategy [2]. Based on current literature, the 5-year biopsy reclassification-free survival rate is 20–30% [11]. Moreover, metastasis free survival and cancer specific survival are excellent and well over 99% for localized prostate cancer [12]. Thus, current guidelines appropriately recommend against the immediate treatment of patients with low risk prostate cancer.

Despite these recommendations, there is continued interest in treating low risk prostate cancer patients to attempt to effect progression, as well as patient related factors such as anxiety [13]. In this setting focal therapy, along with whole-gland radical treatments are still being used commonly for the treatment of low risk prostate cancer patients [14]. Our Collaborative emphasizes that treatment, including focal therapy, should not be routinely used for low-risk disease, but acknowledge that in unusual cases of low-risk (Gleason 3 + 3) disease (e.g., large lesion on MRI or high genomic risk, with high suspicion for undersampling) immediate treatment may be considered. In most such cases, however, repeat biopsy first to verify pathology is advisable.

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Table 1. Consensus statements on focal therapy.

1. Clinicians must discuss with patients offered focal therapy, that this remains investigational treatment, and that short- and long-term oncological and HRQOL outcomes remain incompletely defined.
2. To as great an extent as possible, patients treated with focal therapy should be included in trials or detailed, prospective registries so that over time we can learn better which men are optimal candidates for this emerging therapy.
3. Patients receiving treatment should have life expectancy at least 10 years, and organ- confined, intermediate risk disease, defined as Gleason 3 + 4 or low-volume 4 + 3, PSA < 10 (or PSA < 20 and PSAD < 0.15) and ≤ cT2c disease. The presence of additional Gleason 6 outside of the target is not a contraindication to treatment.
4. Patients should receive a high-quality prostate MRI prior to biopsy. Radiologists should also be informed of the possibility of focal therapy prior to their interpretation of the imaging. Patients with unfavorable intermediate risk should receive a PSMA PET scan. There should be a minimum of 2 biopsies taken from the target lesion and consideration of sampling of the lesion penumbra to determine treatment margin, a 10–12 core systematic biopsy, and clinically significant disease (GG2) should be visible on MRI. All patients offered focal therapy should have a second (confirmatory or planning) biopsy within 12 months prior to treatment.
5. In addition to regular PSA assessment, patients should have a follow-up MRI and biopsy (systematic and targeted to the ablation zone) at 12 months after treatment.

On the other hand, finding alternatives to whole gland radiation therapy and radical prostatectomy for the treatment of intermediate risk disease is an area of active interest [15]. Perceived benefits include lower impact on health-related quality of life (HRQoL) such as erectile, urinary, and bowel function without compromising oncological outcomes [16]. This has been demonstrated in a recent retrospective and also prospective study [17, 18]. Tremendous heterogeneity in risk exists within the "intermediate risk" group. We have therefore proposed parameters for selection of these patients for treatment (Statement 3).

Suitable criteria for focal therapy in the setting of high or very high-risk prostate cancer remain unclear. Again, actual biological and clinical risk within the "high risk" category varies tremendously: a man with a GG4, pT2c, PSA 22 tumor in 12 of 14 cores faces a very different prognosis than one with a GG1, pT1c, PSA 22 tumor in which the PSA is driven primarily by benign growth but both are classified as "high risk." The latter patient may be a good candidate for focal therapy, whereas the former is not. Generally, however, men with high risk disease are best treated with whole gland surgery or radiation, and current evidence supporting the use of focal therapy for treatment of high-risk disease is limited [19]. Therefore, these patients should not generally be offered treatment outside of the context of a clinical trial or formal prospective cohort study. This consensus statement gives further support for the existing guidelines on this topic [1]a.

Lastly, for patients with recurrence after primary radiation therapy for localized prostate cancer, opportunities for salvage treatment include focal therapy (cryoablation or high intensity frequency ultrasound), radical prostatectomy, irreversible electroporation, salvage radiation therapy, and brachytherapy [20, 21]. There is no accepted standard of care for the treatment of patients with recurrent disease after radiation therapy [2].

HOW SHOULD CLINICIANS CONFIRM IF A PATIENT IS A CANDIDATE FOR FOCAL THERAPY AND DEFINE SUCCESSFUL TREATMENT?

Patients considered for focal therapy should generally have intermediate risk disease (favorable or unfavorable) and meet the criteria outlined in consensus (Statement 3). As noted above, rare patients with low- or high-risk disease might also be considered on an individual basis. Patients should undergo confirmatory MRI-guided prostate biopsy, including both targeted and systematic cores, prior to focal therapy, particularly if the urologist performing the focal therapy did not perform the original biopsy. Additionally, the biopsy should be done within 12 months of the patient receiving focal therapy (Statement 4).

It is recommended that patients undergoing biopsy, should receive an MRI with specifications as outlined in American College of Radiology PI-RADS V2.1 (Statement 2) [22]. Given high rates of inter-observer variation in determining PI-RADS scores, the MRI should be performed, or at least reviewed, by a radiologist with subspecialty prostate expertise, and the treating urologist should personally review the images as well. Clinicians should use fusion technology to perform this biopsy. Alternatively, cognitive fusion can be considered if the urologist has extensive expertise in the interpretation of MRIs and ultrasounds [23].

The authors acknowledge that not all prostate cancer is visible on MRI, and lesion- directed biopsies alone may miss clinically significant prostate cancer in up to 10–30% of cases [24]. Patients with clinically significant prostate cancer found in an MRI invisible lesion, should rarely be considered candidates for focal therapy.

The optimal number of lesion-directed biopsies and the clinical utility of performing biopsies of the margins of the lesion are still under debate. Therefore, the authors agreed that a minimum of two biopsies per lesion is recommended due to intratumor heterogeneity.

Additionally, due to the possibility of MRI invisible disease harboring clinically significant prostate cancer, patients should receive a systematic 10–12 core biopsy of the peripheral zone, consistent with AUA guidelines [1, 25].

Following focal treatment there is no clear recommendation on determining oncological success. In general, a combination of PSA, imaging and repeat biopsy when indicated should be performed. The authors agreed that post-ablation MRI and biopsy should be performed 12 months after treatment to ascertain pathological evidence of treatment response (Statement 5).

WHICH ENDPOINTS SHOULD BE ASSESSED IN STUDIES INVESTIGATING FOCAL THERAPY?

The use of focal therapy in the treatment of prostate cancer should be studied using a wide range of outcomes (Statement 2). These include but not limited to: ablation effectiveness determined by an in-field biopsy rate at 12 months, adverse events, urinary and erectile function using validated questions (UCLA-EPIC, IPSS, IPPS-QOL, IIEF-15), prostate-specific antigen kinetics including PSA nadir and PSA stability, HRQoL validated questionnaires such as EQ-5D. Additional endpoints include clinical recurrence free risk survival, disease specific survival, and overall survival. PSA outcomes are exploratory, and the ASTRO and Phoenix definitions used to define outcomes of radiation therapy should not be used as clinical outcomes in focal therapy research or clinical management.

There is no perfect endpoint for any study; however future prospective studies should include a combination of HRQoL and oncological outcomes.

CONCLUSION

(UC) [2], the University of California Collaborative, is a newly formed group who met with the goal of defining best practices for treatment and research in urologic oncology. In this article, we summarize our conclusions and recommendations about the use of focal therapy in the treatment of localized prostate cancer (Table 1). We acknowledge there will be disagreement with some of the details of these recommendations; however, the growing use of focal therapy calls for the development of consensus statements to guide its increasing utilization. Substantial research needs to be performed to help optimize patient selection, oncological and HRQoL outcomes, as well as standardized of reporting outcomes to facilitate further study of its effectiveness and long-term durability.

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AUTHOR CONTRIBUTIONS

JJ-DL—Design and study conception, draft of manuscript, and editing. MADE—Design and study conception, draft of manuscript, and editing. WB—Editing. KC—Design and study conception, draft of manuscript, and editing. SLW—Design and study conception, draft of manuscript, and editing. TC—Editing. LSM—Editing. HN—Editing. MD—Editing. GG—Editing. CJK—Editing. AB—Design and study conception, draft of manuscript, and editing. MRC—Design and study conception, draft of manuscript, and editing.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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