Prostate International 3 (2015) 35–41

Contents lists available at ScienceDirect

Prostate International

journal homepage: http://p-international.org.

Review Article

Focal therapy for prostate cancer: The current status

Susan Marshall*, Samir Taneja

NYU Langone Medical Center, New York, NY, USA

ARTICLE INFO

Article history:
Received 15 March 2015
Accepted 16 March 2015
Available online 23 March 2015

Keywords:
Ablation
Focal therapy
Fusion prostate biopsy
MRI
MRI-targeted prostate biopsy
Prostate cancer

ABSTRACT

Purpose: In an era of increasing prostate cancer incidence and earlier detection, the assessment of clinical significance of prostate cancer is critical. Minimally invasive therapies are increasingly being investigated in localized prostate cancer.
Methods and results: In this review, we discuss the current status of magnetic resonance imaging targeted fusion prostate biopsy and focal therapy for prostate cancer, its rationale, and techniques.
Conclusion: Focal therapy offers a promising outlook for prostate cancer treatment, with the goal of effectively achieving cancer control while minimizing morbidity. Long term studies are needed.

1. Rationale for focal therapy for prostate cancer

With the widespread use of prostate-specific antigen (PSA) screening and increasing life-expectancy, more men are being diagnosed with localized, low-risk, low-grade prostate cancer.[1] These patients can be managed with definitive therapy, including radical prostatectomy (RP) or radiation therapy (RT). However, these radical therapies are associated with significant complication risks and side effects, which may be unsuitable for or undesired by the patient with low-risk prostate cancer. In an era of increasing prostate cancer incidence and stage migration toward earlier disease, appropriate management of the disease requires assessment of the risk of clinical significance of the disease. Minimally invasive therapies are increasingly being investigated as an alternative.

Prostate cancer is relatively slow growing, with doubling times for local tumors estimated at 2–4 years. Some prostate cancers prove to be so small, low-grade, and noninvasive that they appear to pose little risk to the patient, and are considered indolent. A recent review suggests that 49% of men undergoing RP have pathological features in the RP specimen consistent with an insignificant or indolent cancer (organ-confined cancer < 0.5 mL, no Gleason Grade 4 or 5 component).[2]

Up to 33% of patients on active surveillance (AS) eventually fall out of surveillance and undergo definitive treatment after 2–5 years because of initial understaging or disease progression.[3] Seventy-three percent of patients initially enrolled in AS who undergo RP have a significant cancer on RP specimens.[4] Other downsides of AS include the mental and emotional burden and anxieties associated with untreated cancer. Therefore, AS is an option for only a select group of men.

In order to cure and control localized prostate cancer, the concept of focal therapy has emerged. Focal therapy is the middle ground between AS and radical therapy, offering much less morbidity with cancer control. Focal destruction of cancer, with preservation of the surrounding organ, has already been used widely in the oncological treatment of kidney, liver, breast, and brain.

The concept of focal therapy is relevant for prostate cancer in a number of ways. First of all, there is strong evidence that the vast majority of metastases find their origin in the same prostate cancer cell clone, derived from the same lesion called the index lesion.[5,6] Histopathological features of the index lesion predict the clinical behavior of the entire gland despite multiple synchronous tumors in >90% of patients.[7,8] While prostate cancer is typically multifocal with clonal heterogeneity of prostate cancer within the gland, not all tumors within a single gland have the potential for lethality. Historically, the threshold for clinically significant disease, capable of metastatic progression, has been set at 0.5 mL, with some Gleason grade component $\geq$ 4.[7,8] It has been shown that in >80% patients with an index lesion of cancer, the aggregate volume of secondary tumors is < 0.5 mL.[7,8] Since most metastatic cancers originate from a single clonal cancer cell, it would be reasonable and effective to identify and target this potentially lethal lesion with focal therapy. Thus, selective treatment of clinically significant disease, with acceptance of residual, insignificant disease may

* Corresponding author. NYU Langone Medical Center, 150 East 32nd Street, Floor 2, New York, NY, USA.
E-mail address: susan.marshall@nyumc.org (S. Marshall).

http://dx.doi.org/10.1016/j.prnil.2015.03.007

serve as a meaningful treatment paradigm. To date, limited clinical data exist regarding outcomes of focal therapy.[9]

2. Candidate selection/risk strata

The selection of patients is a critical element of the challenges of focal therapy adoption and use. Patient candidate selection should ultimately be based on the intent of focal therapy. In those patients in whom focal therapy is utilized for cure, the disease should be low risk and low volume in a targetable area of the prostate. The ideal patient would be one with low-stage, low-risk prostate cancer that could be completely eradicated.

Focal therapy can be used with the intent of disease control. A therapy to control cancer would prolong the natural history of prostate cancer and delay the morbidity of radical treatment. In this situation, focal therapy would treat the dominant lesion or index lesion. In doing so, focal therapy could prolong the period of surveillance, and mitigate the uncertainties and anxieties of pure AS.[10]

Lastly, focal therapy could be utilized as a part of a multimodal treatment approach in the high-risk patient who would likely fail single-modality therapy, but avoid the morbidities associated with radical treatment. Use of focal therapy for noncurative intent has yet to be validated and studied.[10]

Up to now, most trials have included only low-risk patients under the premise that men with low-risk disease are at little risk of systemic relapse, and thus, local disease control can be a measure of treatment efficacy.[11] As focal targeting methods develop, there is a stronger impetus to treat men who are at risk of disease-related mortality, as they may be the ones to benefit the most. In treating only low-risk patients, one can argue that the benefit of therapy may never be proven, as these patients would have fared well on surveillance anyway. However, most focal therapy trials include low-risk patients due to the known risk of 30–40% upgrading of surgical pathology from biopsy pathology. At this time, it is not clear if Gleason 7 (3 + 4) with small proportion of 4 has a similar favorable outcome as Gleason 6. Gleason 7 (3 + 4) has an intermediate risk of relapse, and therefore gives focal therapy the opportunity to treat and prevent prostate cancer relapse. The heterogeneity in biological behavior of Gleason 7 tumors has been shown. Gleason score 4 + 3 tumors had an increased risk of progression (compared to Gleason 3 + 4 tumors) independent of stage and margin status, and were predictive of metastatic disease (as opposed to Gleason 3 + 4 tumors).[12] In addition, Gleason 4 + 3 tumors were more strongly associated with extraprostatic extension and upgrading on surgical specimens than Gleason 3 + 4 tumors were.[13] Gleason 7 (4 + 3) tumors have a similar risk of relapse as Gleason 8 (4 + 4) tumors.

Candidate selection relies heavily on accurate patient identification and risk stratification. Risk stratification can be used to assess the chance of unfavorable pathology, poor oncological outcome, biochemical recurrence, and survival. Low-risk category patients have a low risk of short-term cancer mortality. The D'Amico classification is the most common classification used to stratify the risk of biochemical recurrence after radical treatment.[14] The percentage of Gleason 4 tumors is sharply correlated with outcome. Stamey et al suggested that ≤20% of Gleason 4/5 tumors on biopsy (which is correlated to the same percentage of Gleason 4/5 tumor in RP specimens) represents the lower-risk subset of those harboring a Gleason 4 pattern.[15]

3. Limitations of standard systematic biopsy

Transrectal ultrasound (TRUS)-guided biopsy using a 12-core sampling scheme is the standard approach for prostate cancer diagnosis.[16] Performing TRUS biopsy for focal therapy selection is felt to be inadequate due to the risk of underestimating disease risk, volume, and focality.[17] It has been shown that if a 12-core biopsy shows unilateral disease, there is a 75% chance of a tumor on the contralateral side.[18] Focal therapy selection and planning requires accurate assessment of these parameters.

The success of focal therapy clearly depends on the ability to detect the extent and laterality of prostate cancer and then accurately target it. There is no consensus currently on patient selection protocols for focal therapy. The reason for this is twofold. So far, there has been a lack of adequate biopsy techniques that can accurately detect prostate cancer lesions, and also a lack of imaging modalities to complement inadequate biopsies. Detection relies upon reduction of sampling error through the number of samples taken and the location of the samples in the prostate.[19,20] In men with negative biopsies, repeat biopsy is often used up to five or six times before detection – sampling error is overcome through increased sampling. This approach of random sampling leads to three intrinsic errors: (1) underdetection by missing a potentially lethal cancer; (2) overdetection by identifying a small nonlethal cancer; and (3) misclassification by identifying an apparent low-risk cancer in someone with high-risk disease. Even extended TRUS-guided saturation biopsy appears to be inadequate in the proper selection of patients for focal therapy.[21] Transperineal (TP) biopsy with three-dimensional (3D) mapping was thought to improve on cancer localization, as samples are taken every 5 mm throughout the volume of the prostate using a brachytherapy template grid under TRUS guidance. However, >61% of patients diagnosed with unilateral cancer on TP biopsy were found to have bilateral disease, and 27% were upstaged in Gleason score.[22,23] Moreover, TP biopsy has fallen out of favor due to time demands, need for anesthesia, and cost.

Biopsy sampling error may be better addressed through localization of the cancer region by imaging than through simply increasing sampling. To achieve this goal, fusion biopsy has evolved as the standard for accurate maximal fusion of disease foci, according to a consensus panel.[24]

4. MRI-targeted fusion biopsy

The evolution of MRI to multiparametric MRI (MP MRI) is an important innovation for focal therapy in prostate cancer. A typical MP MRI includes T1-weighted sequences with dynamic contrast enhancement (DCE) sequence, T2-weighted sequences, and diffusion-weighted imaging (DWI) sequences performed by torso phased-array coils.[25] MP MRI is the best noninvasive imaging test for the visualization of cancer foci in prostate. While MP-MRI may not detect all foci of disease in the prostate, it appears to better detect clinically significant foci based upon Gleason score and cancer volume.[26] For significant lesions, as defined previously, sensitivity and specificity of MP MRI are up to 90%.[27] In one study, sensitivity, specificity, negative predictive value, and accuracy for peripheral zone cancer detection at biopsy were, respectively, 100, 51.4, 100 and 66.7%.[28] In a series of 83 patients studied by multiparametric imaging (T2 + DWI + DCE) at 1.5 T before biopsy, MRI was associated with a high sensitivity, specificity, and accuracy for detection of prostate cancer of 95%, 74%, and 86%, respectively.[29] MP MRI, as a 3D technique, can determine prostate cancer foci location within the gland and volume/shape of the tumor and can be used to target lesions.

MRI–ultrasound fusion technology has recently allowed targeted biopsies to cancer-suspicious regions noted on MRI. The Artemis spatial tracking and computerized biopsy system functions to record the position of biopsy cores within a 3D template reconstruction of the prostate. Computer software allows fusion of the patient's MRI with real-time ultrasound while performing the Artemis biopsy, allowing targeting of the abnormal region on MRI during Artemis biopsy.