Considerations for patient selection for focal therapy

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Abstract: Focal therapy for prostate cancer is a nascent and emerging field. As such, the patient selection criteria for this new treatment paradigm are evolving in parallel to both the technology on which this approach depends and to our unfolding understanding of the natural history of prostate cancer. Until, and while, prospective trials of focal therapy are being reported, patient selection criteria will be flexible and very dependent on the therapeutic goals. We must carefully define the therapeutic intentions of focal therapy before engaging in the actual process of determining optimal patient selection. The therapeutic intent will define the most appropriate candidate for such therapy. Patient selection encompasses multiple complex issues including the type of prostate biopsy (12 core transrectal *versus* mapping transperineal) to the type of imaging (multiparametric magnetic resonance imaging or enhanced ultrasound) to the specific anatomical location of the disease within the prostate (apex, mid-prostate, base) and a comprehensive assessment of the patient's overall health and life expectancy. It is not as simple as saying a patient with a certain grade or a certain number of cores is or is not appropriate for focal therapy. There are many more considerations for a reasonable and thoughtful approach to this new treatment.

Keywords:
prostatic neoplasms, ablation techniques, focal therapy, transrectal ultrasound, cryoablation, HIFU, MRI, HIFU

Oncologic goals

To date, prostate cancer therapy has been driven by the 'curative intent' goal. In other words, only when all evidence of any prostate cancer is eradicated was the treatment considered successful. As a result, prostate cancer therapy has focused on identifying early stage disease and attacking that disease in a radical and whole gland fashion through radiation, extirpation or ablation. Identification of any cancer, anywhere within the gland allowed for carte blanche treatment of the entire gland and justification of the resultant side effects.

Conversely, focal therapy of prostate cancer has as its aim the eradication of measurable or detectable disease and ultimately, only that cancerous portion of the prostate that has harmful potential. This distinction is subtle in that we are accepting that many patients treated with focal therapy are likely to harbor microtumors that will remain untreated with a focal approach, but will also remain undetected and are believed to not endanger the patient's quality or longevity of life.

Multiple investigators have demonstrated the high prevalence of multifocality and bilaterality of prostate cancer within extirpated specimens removed for unilaterally positive prostate biopsy [Andreoiu and Cheng, 2010; Ward *et al.* 2009; Karavitakis *et al.* 2010, 2012]. Meiers and colleagues reviewed 2988 patients from 12 contemporary radical prostatectomy series and found that the incidence of multifocality ranged from 67% to 87% [Meiers *et al.* 2007]. Similar published studies separated by a decade of stage migration examined the prevalence and impact of synchronous tumors within prostatectomy specimens [Wise *et al.* 2002; Villers *et al.* 1992]. These groups each reported that 80% of these synchronous secondary tumors occupied less than 0.5 ml volume, were dominated by Gleason pattern 3, and had no demonstrable effect on clinical course

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of the disease, as individual tumors or in aggregate, that was not already predicted by the dominant index tumor.

If the oncologic goal of focal therapy is complete eradication of all cancerous foci within the prostate, 20% or less of men with prostate cancer would be adequately treated if performing the various regional template ablations [Ward and Jones, 2010]. However, destruction of the dominant tumor foci may be adequate to alter the clinical course of prostate cancer; the smaller low volume, low grade satellite tumors that go undetected and have no impact on the clinical course of prostate cancer remain. This strategy depends on the dominant tumor theory being correct; namely that the biology of prostate cancer is driven by one dominant tumor that has gained the full compilation of genetic alterations to both grow locally and metastasize. Genetic studies of prostate tumors support this concept of dominant tumor biology, demonstrating that intraprostatic lesions appear to be multiclonal in origin while metastatic lesions appear to be monoclonal in origin [Cheng *et al.* 1998; Liu *et al.* 2009]. However, the concept is important to develop the selection criteria for focal therapy and align the goals of therapy with what we know about prostate cancer multifocality and the danger (or lack of danger) actually posed to the patient by many of the smaller, undetected lesions detected within radical prostatectomy specimens but not by biopsy or imaging.

Selection criteria for focal therapy under this concept therefore depend on identifying men in whom the dominant cancerous region can be encompassed within a template application of destructive energy. The more accurately the region of cancer can be identified and targeted, the less destruction of surrounding normal tissue is required (collateral damage).

Although nondominant small foci of prostate cancer have a very low risk of progression, another concept rarely discussed is that focal treatment could be re-applied to another region of the prostate in the event that an asynchronous and significant focus of prostate cancer develops during the long course of a man's life. The majority of nondominant foci are not of clinical significance (similar to 'autopsy cancers'), and if disease progression of such foci does occur, it could take many years to do so. Many of the technological platforms available for focal therapy permit retreatment with low complication rates. As a result, retreatment of a patient undergoing focal therapy could be considered the same type of oncologic event as a patient undergoing a repeat transurethral resection for superficial bladder cancer or a patient undergoing repeat partial nephrectomy after prior renal-sparing surgery.

Functional goals

The impact of radical therapies for prostate cancer on urinary, bowel and sexual function is well documented and the source of great consternation to patient and physician alike [Chou *et al.* 2011]. The impact of these treatment-related side effects on the quality of a man's life looms so large that they frequently weigh as significantly (if not more significantly) than the oncologic efficacy of a therapy. It is specifically to limit the morbidity of radical prostate cancer therapy that focal therapy of prostate cancer has gained such interest.

After the description by Walsh and Donker of cavernous nerve anatomy [Walsh and Donker, 1982] and the subsequent development of the anatomical radical prostatectomy [Walsh *et al.* 1983], potency rates of 20–95% have been observed when both cavernous nerves have been preserved [Quinlan *et al.* 1991; Kundu *et al.* 2004]. Despite, the success of injection therapy, vacuum constriction devices and penile prosthesis in the treatment of postprostatectomy erectile dysfunction, the importance of return of spontaneous erectile activity, with or without the assistance of oral medication, cannot be overstated.

Recovery of erectile function is directly correlated with the extent and number of neurovascular bundles (NVBs) preserved. After resection of both neurovascular bundles, patients do not recover spontaneous erections. When only one neurovascular bundle is preserved, rates of recovery of spontaneous erections range from 25-53%. [Quinlan *et al.* 1991; Kundu *et al.* 2004; Rabbani *et al.* 2000]. With focal therapy, however, the location of the tumor to be ablated may impact the ability to preserve the microscopic anatomy of the NVB, i.e. a tumor ablated at the apex may have a different impact on the functional outcomes than a tumor ablated at the base of the prostate.

Alsaid and colleagues used computer-aided anatomic 'dissection' (CAAD) to follow the nerve fibers from the level of the seminal vesicles distally

beyond the prostate apex to the penis [Alsiad *et al.* 2011]. The study confirms the concept of anterior fascial and nerve preservation related to the region of the dorsal venous complex. This tissue contains the anterolateral portion of pro-erectile fibers as they swing forward to continue in concert with the dorsal penile sensory nerves. Thus, any treatment of the apex of the prostate has a greater opportunity to induce erectile dysfunction than tissue ablation at the mid or base of the prostate. One of the best illustrated gross anatomic demonstrations of the presumptive pro-erectile nerves adjacent to the apex of the prostate is found in the work of Costello and colleagues [Costello *et al.* 2004]. This study is remarkable for the focal therapist's perspective in the plethora of nerves on the posterior surface of the prostate and prostate-urethral junction (Figure 6 in their report). At this location, a dense collection and decussation of fibers are clearly apparent. This suggests that, when selecting patients for focal therapy, some tumors may be situated in a region of the prostate (e.g. posterior apex) where an increased likelihood of nerve damage is possible. Therefore, patient selection for functional outcomes, and specifically erectile function, may be dependent upon where the tumor is located. Though still the subject of study, this anatomy suggests that focal treatment of apically located tumors may result in greater erectile dysfunction than tumors located in other positions within the prostate. If preservation of erectile function is a major component of the decision to proceed with focal therapy, patients with apically located tumors may not be ideal candidates due to this concentration of pro-erectile fibers in this region.

Consensus statements on patient selection for focal therapy

In 2007 an international panel of urologic oncologists, radiotherapists, medical oncologists, epidemiologist and pathologists all with a particular interest prostate cancer gathered to review many of the current controversies in prostate cancer. The panel was adjourned with a set of selection criteria for men who may be considered for focal therapy of their prostate cancer [Eggener *et al.* 2007]. While this panel provided a broad insight into the overarching themes of prostate cancer detection and treatment in the 21st century, the most significant discussion was concentrated on shifting our 'radical therapy fits all' approach to the prostate cancer patient to a paradigm where the risks of the treatment are balanced to the risks of the disease. Thus, focal therapy for a select group of men was felt to be a rational and sound effort. To proceed in this fashion, the panel reviewed literature related to tumor volume, tumor focality and multifocality, imaging of prostate tumors within the gland, and biopsy strategies in order to provide a consensus starting point for the most appropriate focal therapy candidate. The resulting statement, presented in Table 1, defined the appropriate candidate as one who meets 'low-risk criteria'. This was reasoned by the recognition that there is only a presumed but unproven advantage of focal therapy causing less treatment-related morbidity than more radical therapies. While this is intuitively sensible, the panel agreed that it must be confirmed through trials collecting patient reported quality of life outcomes. Thus, development of a focal therapy strategy has begun but does not necessarily end with patients in whom the treated disease is similar to selection criteria for active surveillance protocols.

In 2009, a second consensus meeting was held with a similar multidisciplinary and international panel of experts (Table 2) [de la Rosette *et al.* 2010]. The objective of focal therapy changed slightly for this panel to the eradication of all measurable disease with the aim of reduction of treatment-related side effects. Recognizing that the first panel limited patient selection criteria to candidates who may also do well with no treatment, the second panel considered the presence of Gleason pattern 4 disease nonexclusionary. This shift was based upon the observation that many men with low-risk features on biopsy are found to have nondominant Gleason 4 disease at radical prostatectomy with very little impact on the clinical course.

However, a more significant outcome of the second consensus meeting was outlining the approach to candidate selection for focal therapy. The second consensus panel agreed that current transrectal ultrasonography biopsy regimens are inadequate for the purposes of candidate selection for focal therapy due to the associated random and systematic error. Transperineal prostate biopsy using a template-guided approach was the agreed upon standard to qualify a patient for focal therapy, though what constitutes acceptable biopsy findings was not defined by the panel [Gravas *et al.* 2012]. There was also an overall agreement that multiparametric functional magnetic resonance imaging (MRI) and new

Table 1. International Task Force on Prostate Cancer and the focal lesion paradigm: proposed clinical, biopsy and imaging criteria for focal therapy patient selection [Eggener *et al.* 2007].

		Reference
Clinical	Clinical stage T1 or T2a	Moore *et al.* [2013]
	PSA <10 ng/ml	Hoeks *et al.* [2012]
	PSA density <0.15 ng/ml/ml	Ukimura *et al.* [2012b]
	PSA velocity <2 ng/ml yearly in the year prior to diagnosis	Hoeks *et al.* [2012]
Biopsy		
	Minimum 12 cores	De Silva *et al.* [2011]
	No Gleason 4 or 5	Moore *et al.* [2013]
	Maximum percentage of cancer in each core (e.g. 20%)	Tsuzuki *et al.* [2005]
	Maximum length of cancer in each core (e.g. 7 mm)	Naya *et al.* [2004]
	Maximum percentage of total cores with cancer (e.g. 33%)	Kestin *et al.* [2002]
Imaging		
	Single lesion with a maximum size (e.g. 12 mm)	
	Maximum length of capsular contact (e.g. 10 mm)	
	No evidence of extraprostateic extension or seminal vesicle invasion	

PSA, prostate-specific antigen.

Table 2. International Workshop on Focal Therapy and Imaging in Prostate & Kidney Cancer Consensus Panel [de la Rosette, 2010].

1. Candidates for focal therapy should ideally undergo transperineal template mapping biopsies, although a state-of-the-art multifunctional MRI with TRUS biopsy at expert centers may be acceptable.
2. Candidates for focal therapy should have a life expectancy of 10 or more years.
3. Patients with previous prostate surgery should be counseled with caution.
4. Patients with previous radiotherapy to the prostate or pelvis should not be treated until more data are available, although the panel accepts that focal salvage therapy may be a possibility in the future.
5. The effects of focal therapy on men with lower urinary tract symptoms are not well known. These men should be counseled with caution.
6. There will be specific attributes that are more related to the energy source than to focal therapy in general. Issues such as prostate size, presence of prostatic calcification, cysts, TUR cavity, access to rectum, and concurrent inflammation of rectal mucosa may need to be taken into consideration when selecting the optimal therapy.
7. Focal therapy should be limited to patients of low to moderate risk.
8. Focal therapy should be limited to men with clinical T2a or less N0M0 disease.
9. Focal therapy should be limited to men with radiologic ≤T2b N0M0 disease.
10. Defining the topography of the cancer is important. Disease that is predominantly apical or anterior in disposition may be technically difficult to manage with existing treatment modalities.
11. The long-term effects of focal therapy on potency/erectile functions are not known. Men should be counseled in this regard before therapy

MRI, magnetic resonance imaging; TRUS, transrectal ultrasound; TUR, transurethral resection.

transrectal ultrasound (TRUS) techniques show promising results in relation to characterizing men with prostate cancer and localizing their tumor, but that the exact role for patient selection needs to be further elucidated through multi-center studies [Hoang *et al.* 2012].

Despite the methodological limitations of both consensus panels, the process itself was helpful in refining some of the conceptual and practical considerations that relate to focal therapy for men with localized prostate cancer.

Patient selection for the real world

The need to reliably identify the prostate tumor and its spatial distribution, then to return to the exact same location to effect tumor ablation is the critical factor for the success of focal therapy. Current biopsy techniques, even the perineal template, saturation biopsy as originally described by Barzell, have all been optimized to detect prostate cancer, not necessarily to exactly locate prostate cancer [Rodríguez-Covarrubias *et al.* 2011]. For the focal therapist, the accuracy of these standard biopsies may not be sufficient to achieve our goals. Huo and colleagues recently undertook a study to determine whether systematic template guided transperineal biopsies accurately locate and sensitively detect prostate cancer [Huo *et al.* 2012]. They retrospectively examined the radical prostatectomy pathology of 414 consecutive patients treated at a single institution between November 2002 and August 2010 who had undergone primary transperineal biopsy. They divided the prostate into eight biopsy regions that could reasonably be considered a target for regional ablation. A minimum of 22 cores was obtained using the brachytherapy template grid and an 18-gauge Tru-Cut® biopsy needle. The average sensitivity and specificity for the detection of cancer in all prostates across all eight biopsy zones was 48% and 84.1%, respectively. There was a statistically significant decrease in the sensitivity of transperineal biopsy in larger prostates. Grading concordance between biopsy and pathology specimens was achieved in 65.7% of patients, although upgrading of Gleason scores occurred in 25.6% of patients and downgrading occurred in 8.8%. The authors concluded that any biopsy scheme will be suboptimal compared with whole gland analysis due to inherent errors in sampling; however, tumors missed on biopsy are often the nondominant, small foci of cancers.

This conclusion supports the work of Ward and colleagues where treatment templates were theoretically applied to extirpated prostates from men with unilaterally positive only 12 core transrectal biopsy [Ward *et al.* 2009]. In this study, a treatment template which included a hemisphere and anterior wing of the prostate ('hockey stick template') would, at least in theory, eradicate all clinically significant tumors. At what cost to functional outcomes this form of three-quarters ablation renders is not known. Thus, while transperineal mapping biopsy strategies may detect more cancers, especially bilaterality, it is not clear that this improves the identification of appropriate patients for focal therapy or improves targeting of significant cancers. Patients after transperineal mapping biopsy experience increased risk for short-term urethral catheterization and hematuria. Additionally, transperineal mapping biopsy requires anesthesia (general or heavy sedation), and added technical and pathology processing expenses that are often not covered by insurance carriers. Therefore, a transperineal mapping or saturation type prostate biopsy is a relatively invasive procedure for a patient believed to have relatively low- or intermediate-risk prostate cancer.

Because the person who performs the biopsy is known to be a statistically significant independent risk factor for the detection of prostate cancer, efforts to eliminate operator bias from the biopsy procedure are also being developed [Lawrentschuk *et al.* 2009; Megwalu *et al.* 2008; Natarajan *et al.* 2011; Ukimura *et al.* 2012a]. With more systematic distribution of biopsy samples and the ability to retarget a specific area of the prostate or to change the target away from an area previously sampled, a better illumination of the contents of the prostate may be gained. Accessories to the biplanar ultrasound are permitting accurate spatial localization of transrectal biopsies [Andriole *et al.* 2007]. The three-dimensional rendering afforded by these tools is even being used to perform coregistration of MRI images that may provide enhanced information on suspicious regions within the prostate [Marks *et al.* 2013; Delongchamps *et al.* 2013; Rud *et al.* 2012].

Three methods of MRI guidance are available for performance of targeted prostate biopsy: cognitive fusion, in which the ultrasound operator simply aims the biopsy needle at the prostate area where the reviewed prior MRI demonstrates a lesion; direct MRI-guided biopsy, performed within an MRI tube by an interventional radiologist; and software coregistration of stored MRI with real-time ultrasound, using a tracking mechanism. Two tracking mechanisms which allow three-dimensional ultrasound rendering and fusion with pre-obtained MRI images have received US Food and Drug Administration approval in the past 5 years: Artemis (Eigen, Grass Valley, CA, USA) and Urostation (Koelis, France). To date, no prospective comparison of the three methods has been made.

Cognitive fusion is simple, quick and requires no additional equipment or specialized training beyond conventional TRUS biopsy and the ability

to read a multiparametric MRI of the prostate. Cognitive fusion was used in some 22 separate studies recently reviewed by Moore and colleagues [Moore *et al.* 2013]. Although data are limited, cognitive fusion does appear to yield improved accuracy over conventional systematic, blind biopsy.

Direct MRI-guided biopsy is performed within the MRI tube. It can be performed freehand or with the use of a guidance system such as the commercially available DynaTRIM MR targeting system (Invivo Corp., Gainesville, FL, USA). A large experience with in-bore biopsy has been published by the Barentsz group at Radboud University in Nijmegen, The Netherlands [Hoeks *et al.* 2012]. The advantages of this method are the limited number of cores taken, the exact localization of the biopsy and the reduced detection of insignificant tumors. The disadvantages of this method include the time and expense required, including the in-bore time and the cost of two MRI sessions necessary to obtain the biopsy specimens. Further, as only suspicious lesions are sampled, tissues with a 'normal' appearance on MRI are not obtained, which is problematic, as any false negative aspects of prostate MRI are not yet known.

The third method for MRI guidance of prostate biopsy is MRI–TRUS fusion. In this method, the operator images the prostate using ultrasound then uses software to digitally overlay a previously performed MRI that has targets delineated by a radiologist. The stereotactic guidance of the system allows the aiming mechanism of the ultrasound to be brought onto the designated target for sampling [Natarajan *et al.* 2011; Ukimura *et al.* 2012b]. This approach has the advantages of lower costs and familiarity of urologists with the biopsy procedure, but requires capital costs in targeting equipment and software while methods to account for variation in the deformation of the prostate for accurate image coregistration are evolving [De Silva *et al.* 2011].

Conclusion

The current treatment choice for men with low- to intermediate-risk prostate cancer lies between active surveillance and radical therapy. A minimally invasive therapy that offers good oncologic results and less morbidity is extremely desirable at the present time. Focal therapy offers that tantalizing potential, but remains an evolving field. The criteria for successful treatment of prostate cancer with focal therapy depend on an open conversation between the focal therapist and the patient during which the goals are clearly defined. The goals will then define who is the appropriate candidate for focal therapy. The exact biopsy and imaging strategies are still being elucidated as are the biopsy criteria regarding tumor volume and grade. While overtreatment of nonthreatening disease (active surveillance candidates) is not the intention of focal therapy, neither is the undertreatment of potentially harmful disease. Herein lies the dilemma for counseling physician and patient alike.

It is inevitable that successful adoption of focal therapy relies on optimal candidate selection and assessment, accurate localization of lesions, evaluation of efficacy, and follow up of the patients. Therefore, significant obstacles remain to be overcome before this new therapeutic strategy is widely accepted in clinical practice.

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