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Conceptual Basis for Focal Therapy in Prostate Cancer

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Abstract

The proportion of men with low- to intermediate-risk prostate cancer is rising with the increasing use of formal and informal prostate-specific antigen screening. The risk-to-benefit ratio of radical therapy is large with many men suffering genitourinary side effects compared with the small degree of cancer control that they derive from surgery or radiotherapy. On the other hand, the current alternative, active surveillance, carries risk of progression as well as some psychological and healthcare burdens. Focal treatment may be an acceptable alternative: in aiming to destroy only the areas of prostate cancer, focal therapy could deliver cancer control while at the same time avoid damage to surrounding structures. This may reduce incontinence, impotence, and rectal toxicity. Improvements in localization of cancer such as template transperineal prostate-mapping biopsies as well as state-of-the-art imaging such as multiparametric MRI and novel ultrasound-based tissue characterization tools have made the delivery of focal therapy possible. Minimally invasive ablative technologies such as cryotherapy, high-intensity focused ultrasound, photodynamic therapy, photothermal therapy, or radiofrequency interstitial tumor ablation can precisely treat to within a few millimeters. Early studies evaluating focal therapy have found a lower side-effect profile with acceptable short- to medium-term cancer control rates. If these promising results are confirmed in future prospective trials, focal therapy could start to challenge the current standard of care.

Introduction

Prostate cancer is the most commonly diagnosed male cancer in the United States. It represents the second leading cause of cancer-related death with 1 man in every 34 dying of the disease.[1] However, once prostate cancer is diagnosed in a man the aim of therapy must be to optimize the risk-to-benefit ratio. At present, a man with prostate cancer has to choose between radical therapy and active surveillance (AS). The difference between these in terms of cancer-related deaths for a prostate-specific antigen (PSA) screened population is unknown, but a number of studies point to this difference being minimal. First, the Scandinavian randomized controlled trial assessing the difference between radical surgery and watchful waiting demonstrated only a 5% absolute risk reduction in mortality rates using surgery over a 10-year period, but this was within a clinically detected population of men rather than a screen-detected population.[2,3] Second, the two PSA screening randomized controlled studies from the United States and Europe showed that the benefits of early detection were negligible or small at most. In other words, although the European screening trial demonstrated a significant decrease in mortality when screening was implemented, there was significant overdiagnosis and overtreatment. The study found that for every one prostate-cancer-related death averted 48 men needed to be diagnosed and treated. The problem is that radical therapy carries on average, a 50% chance of impotence, a 10% chance of urinary incontinence, and a 10% risk of rectal toxicity.[4–6] Combined with the propensity to detect low-risk cancers in younger men as a result of formal and informal screening practices, the overtreatment burden is large.

The challenge of offering a treatment, as opposed to surveillance for those men who will not accept surveillance, is to permit cancer control but with a minimum of treatment-related side effects. Focal therapy proposes to treat only the lesion, so minimizing collateral tissue damage and potentially reduce side effects traditionally associated with radical treatment, while offering ablation of the cancer.[7] In almost all other solid or hollow organ cancers, tissue preservation with surveillance of the remainder of the organ has been a key tenet: wide local excision for breast cancer, partial nephrectomy for

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renal cancer, hemicolectomy for colon cancer, and partial thyroid ectomy for thyroid cancer. In all of these cancers, a form of focal therapy is now a standard option with reduced toxicity and quality-of-life sequelae with proven efficacy.

Materials and Methods

We reviewed articles about focal therapy for prostate cancer using PubMed/Medline between January 1, 2000, and December 1, 2009. The following keywords were used: focal therapy and prostate cancer. Relevant articles were identified. In addition, key articles that formed the background to the rationale of focal therapy, based on personal bibliographies and a manual search of reference lists, were also used even if they fell outside the period of search.

Current Standard of Care

Active surveillance

AS is different in its approach to watchful waiting. AS aims to institute therapy with a curative intent if cancer progression is demonstrated, whereas watchful waiting instigates palliative treatment in case of symptomatic progression. First, with current trends of PSA screening and the lowered PSA threshold for biopsy, 45% to 85% of patients fall in the category of low-risk Prostate Cancer (PCa) (PSA $< 10\,\mu g/L$, Gleason grade $3 + 3$, cT1c–cT2a). Moreover, it is estimated that between 25% and 84% of PCa patients currently being treated would not succumb to their disease should their PCa be left untreated (insignificant disease).[8] Sartor et al report on their review the Kattan' nomogram, that Predicts the probability of cancer death in 10 years in the case of watchful waiting. This includes PSA, stage, Gleason score, biopsy type, percentage of cancer on the biopsy core, age, and neoadjuvant hormones.[9] Criteria for AS attempt to identify low-risk cancer with the following criteria usually used: PSA $< 10\,ng/mL$, PSA doubling time > 3 years, Stage T1c to T2a, Gleason < 7, percentage of positive number of cores, and maximum cancer core length involvement $< 50\%$ of a single biopsy core.[10–15] Detection of progression uses a combination of clinical examination, PSA kinetics such as doubling time or velocity (every 3–6 months), and control biopsies (at year 1 and then every 2–3 years). This regimen is thought to carry no side effects, as there is no treatment until progression. However, AS does involve some deterioration of quality of life all the same, as shown by studies utilizing validated health questionnaires.[8,16–19]

In addition, the psychological burden of living with an untreated cancer may also be a problem. A number of groups have attempted to test this factor, but differing conclusions have been reached. A number of studies have shown higher anxiety levels as a result of surveillance,[20–22] whereas others[23] did not demonstrate this. This may reflect patient-specific and investigator-specific factors. In other words, the degree to which a patient is comfortable with surveillance may reflect the confidence that his clinician has in AS to detect progression before the disease becoming incurable. This is likely but as yet remains unproven.

In addition, there is still no long-term efficacy data concerning cancer control. Medium-term outcome data have demonstrated that, on average, about one quarter of patients progress on biochemical or histological parameters, although the biochemical progression definitions have not been validated. Further, it could be argued that grade progression is not that at all, but simply the ability of further biopsies to overcome the inherent sampling error of diagnostic transrectal ultrasound (TRUS)-guided biopsies in determining burden and grade of cancer. The presence of higher-grade disease and higher burden of disease missed on diagnostic biopsies may also impact indirectly on the biochemical progression rates although this is difficult to ascertain.

On the other hand, this regimen may allow curable cancer to progress into disease with extracapsular extension, or lymph node metastases. For example, Klotz[24] reports a study in which 24 patients underwent a radical prostatectomy in a protocol of AS. Final pathology was pT3a-c in 52%, while 8% were N1 on staging. Some have argued that as we have a limited ability to predict which cancers can be safely observed, there is the potential for undertreating patients and compromising survival—Klotz's[24] latest data will only add to that dissension. Long-term follow-up is required to assess the undertreatment issue.[26]

Radical therapy

Active whole-gland treatments for prostate cancer include radical prostatectomy, external beam radiotherapy, and brachytherapy. Although this is the standard of care for delivering a curative intent for managing prostate cancer, side effects of this approach can be significant because of damage to surrounding structures. These include (1) bladder and bladder neck that lead to reduced bladder capacity, urge incontinence, and bladder neck strictures; (2) rhabdo-sphincter leading to stress incontinence; (3) neurovascular bundles leading to erectile dysfunction; and (4) rectal injury causing diarrhea, pain, and bleeding (particularly after radiotherapy). The side effect profile is shared between all whole-gland approaches although the exact frequency and severity will vary between therapies. Improvements in laparoscopic and robotic surgery as well as intensity-modulated radiation therapy have shown limited success, if any, in reducing toxicity. Particularly, potency and continence rates have not significantly improved,[6,27,28] and one recent study has demonstrated slightly worse outcomes after minimally invasive surgery.[4] It could be argued that living with the side effects of treatment can be worse than living with the disease because very few men die of the disease if on surveillance.

Focal therapy—a middle way

The ability to deliver a therapeutic strategy that treats the cancer while reducing the treatment burden is clearly needed to offer a middle way between the two extremes of care we have outlined in the preceding sections. Over 5 years ago, there was no option available between AS and radical therapy. We could not contemplate treating discrete foci within the gland if we were unable to localize the disease and ablative techniques were in their infancy. Improvements in prostate cancer localization using saturation and template biopsy strategies as well as newer imaging modalities have made the first issue less problematic. Ablative therapies such as high-intensity focused ultrasound (HIFU), cryosurgery, photodynamic therapy (PDT), photothermal therapy, and radiofrequency interstitial tumor ablation at the same time have enabled precision ablation to be delivered to almost millimeter accuracy.

Focal Therapy: An Emergent Concept

Pathology

For the moment, there is no consensus about which criteria should be used to identify the ideal group of patients for focal therapy. Prostate cancer is regarded as a multifocal disease. However, several studies, based on radical prostatectomies specimens, have found a significant proportion of men with either unifocal or unilateral disease. Unilateral disease was found in 16% to 63% of men in some series[29–35] and 13% to 26% with unifocal disease.[9,30,31,36] This raises the prospect that on average one-third of men could be treated with a focal therapy strategy that is targeted to only half of the gland. However, there must be some caution in this proposal. One study seems to demonstrate that unifocal cancer may have a more aggressive behavior than multifocal disease. In a series of 1159 radical prostatectomies, pathological examination found 18.7% versus 10.1% of Gleason 8 to 10 for unifocal and multifocal cancers, respectively; in addition, there was 38.5% and 24.2% biochemical recurrence, respectively. Unifocal cancers had a significantly worse biochemical recurrence-free survival.

The index lesion

Thus, the concept of insignificant and significant foci that exist within the same gland and the concept of the index lesion may be relevant here.[37] It has been demonstrated that a cut-off volume of 0.5 cm^3 (less than a diameter of 9–10 mm) represents significant disease that gives rise to disease progression.[38] Eighty percent of secondary nonindex lesions are less than 0.5 cm^3.[9,33,39,40] Moreover, secondary cancer foci were found to have on average a cumulative volume less of 0.3 cm^3. Ninety percent of extracapsular extension, when present, apparently comes from the index lesion, with this index lesion representing 80% of the total tumor volume.[8,9,41–49] Presence and volume of the secondary cancer foci has no influence on biochemical recurrence after a radical prostatectomy.[9] Focal therapy could permit acceptable cancer control by just treating the index lesion, although this is an area of contention and controversy. The key is in identifying those patients who have significant foci and ensuring those areas that are not treated in focal therapy do not harbor metastatic potential. A systematic review and meta-analysis found that small-volume insignificant tumors on biopsy are those that have one single positive core, less than 3 mm length and without grade 4 or 5.[38,50]

Criteria for population suitable for focal therapy

A number of consensus groups have met to discuss recommendations for focal therapy. In 2006, the first criteria appeared in the Consensus Conference on Focal Treatment: life expectancy > 5 years, stage T1 to T3, PSA < 15 ng/mL, no M1 disease. They considered lymph node disease as a relative contraindication, while in addition stating that PSA density, PSA doubling time, Gleason score, and ploidy status should not be taken into account.[51] These liberal rules for inclusion took a pragmatic approach so that most men who were deemed either localized or could derive benefit from cytoreductive local (focal) therapy with adjuvant systemic therapy could be treated. However, another eminent group, the Focal Lesion TASK Force group, proposed criteria that were more stringent: clinical stage T1–T2a, PSA < 10 ng/mL, PSA density < 0.15 ng/mL, PSA velocity < 2 ng/mL yearly, no Gleason 4 or 5, and no evidence of extraprostatic extension and single lesion.[52] It seems that this is the very same patient population that would be suitable for no treatment because some of the criteria are much more strict than current AS protocols. Sartor et al[9] made another recommendation for patient inclusion by adding criteria for lesion size on imaging. For instance, a single lesion should not exceed the largest dimension of 15 mm in any plane by imaging with capsular contact not to exceed 5 mm on axial images. Further, the regional nodes should not be suspicious for metastatic disease (i.e., they should measure < 7 mm in the short axis and have a smooth border, while there should not be an asymmetric cluster of nodes).

The University College London focal therapy HIFU trials that we are currently conducting use the following criteria for patients eligible for focal therapy: Life expectancy > 5 years, PSA ≤ 15 ng/mL, multiparametric MRI and/or template transperineal biopsies performed before treatment all demonstrating stage T1-2 N0M0, Gleason score ≤ 7, and showing no clinically significant disease elsewhere (either no cancer or cancer with no Gleason pattern 4 and maximum core length involvement on template biopsies of ≤ 3 mm).

Localization of disease—ultrasound

TRUS has a low specificity for prostate cancer. Recently, contrast-enhanced TRUS (CE-TRUS) has appeared. Although it has not been extensively tested, it has been found to provide higher sensitivity for detection of cancer foci. The detection rate of clinically significant prostate cancers was improved in a number of studies.[53–56] It can also be used to guide biopsies.[57] CE-TRUS during therapy appears to provide excellent good measure of the actual treatment effect and whether surrounding structures are damaged. Studies are needed to compare this feedback imaging with CE MRI within 1 to 2 weeks of treatment.[58] Histoscanning has also demonstrated some promise in detection of clinically significant prostate cancer although further validating studies in Europe are currently under way.[59] Elastography may also have good accuracy for lesion localization, with the latest evidence demonstrating a sensitivity of 75% and specificity of 77%. However, like the other two modalities, this needs further validating studies in a well-characterized group of men who do not have cancer to verify its place in the diagnostic armamentarium of prostate cancer.[60]

Localization of disease—MRI

New MRI functional techniques, such as dynamic CE MRI (DCE-MRI), diffusion-weighted MRI (DW-MRI), and MR spectroscopic imaging (MRSI), provide improved accuracy over standard T2-weighted images. This accuracy seems to be cancer volume related as in the new ultrasound modalities.[38] Several studies have shown a better localization and a better detection rate of prostate cancer with these new techniques.

DCE-MRI is considered as the most sensitive sequence for identification and staging of organ-confined peripheral or transition zone cancers. This technique also showed a significant improvement on anterior tumor identification.[38] Sensitivity and specificity of DCE-MRI + T2-MRI are superior to T2-MRI alone.[61–63] These results may be sufficient for its use in guiding treatments.[54,64] Tumor volume is best estimated

on DCE-MRI,[65] and the degree of enhancement may be related to Gleason grade.[66]

DW-MRI adds improved sensitivity to T2-MRI alone.[67,68] It seems to be helpful in detecting small prostate cancers.[62,69–71] However, there is no evidence supporting its sole use over a combination approach with DCE-MRI in a multiparametric imaging protocol.[38] However, the high specificity of DW-MRI is of interest to assess low-risk patients who may be candidates for AS or deferred therapy.[38]

Several studies have found that MRSI adds value to MRI with a higher detection rate than T2-MRI alone, and a higher sensitivity and specificity in low-risk tumor detection.[33] MRSI can also exclude an extensive or aggressive cancer in men with low-risk disease. It is helpful in targeting treatment.[9] However, caution is required with a large multicenter trial in the United States, demonstrating that MRSI has no value in tumor detection over and above that of T2-MRI alone.[72] In addition, the problem can be more technical difficulties compared with T2 alone and the long and steep learning curve with this modality.

In summary, because of these improvements, multiparametric MRI protocols have shown much promise in ruling in clinically significant prostate cancers, with a volume cut-off of 0.5 cm^3, and in ruling out clinically significant lesions in untreated areas of the prostate, in accurate localization of the cancer, and in cancer characterization (intraprostatic location, grade, and extraprostatic extension).[38,53,73,74] Image-guided treatment is now developing, with CE ultrasound[43,58] or MRI.[44–47]

Localization of disease—TRUS biopsy

Prostate biopsies are essential to localize and characterize the cancer until there is strong evidence that multiparametric MRI has sufficient accuracy. TRUS biopsy is not an accurate method to assess unifocality of cancer and to correctly identify men appropriate for focal therapy, whether these are 12-core biopsy or transrectal saturation biopsies.[32,75–77]

Localization of disease—template transperineal biopsy

Transperineal ultrasound-guided mapping biopsies performed using a brachytherapy template, with one core every 5 mm, can be used to provide three-dimensional coordinates of the cancer areas within the prostate. Different studies have shown that prostate-mapping biopsies accurately demonstrate clinically significant prostate cancer with a high degree of sensitivity.[75] Cancer detection rates increase from 29% to 34% for traditional techniques to 47% to 70% for prostate-mapping biopsies,[61,78] particularly in the anterior portion of the gland that is inherently undersampled by the standard transrectal route.[9,75] Crucially, template-mapping biopsies provide accurate information concerning Gleason grade and location.[30,61,75] On simulation models, these biopsies performed every 5 mm could detect 95% of focal cancers.[78] As they do not traverse rectal mucosa the infection rate is significantly lower.[9] Authors and consensus groups alike have concluded that mapping biopsies should be recommended as the primary tool for selection of focal therapy patients.[30] However, one must remember that the extensive fibrosis from template biopsies may pose problems if salvage surgery is required with some authors stating dissection difficulties if a radical prostatectomy is then performed.[9,25,75]

Techniques of focal therapy

Cryotherapy. Data from focal cryotherapy have demonstrated biochemical disease-free rates ranging between 80% and 96%.[30,41,42,79–81] Disease-free survival at 3 years is 84% in one study.[82] All the studies using American Society for Therapeutic Radiation Oncology–Phoenix or the old American Society for Therapeutic Radiation oncology criteria show that primary cryotherapy appears to be comparable, for low-risk patients, as other treatments currently used as standard care. Morbidity seems to be lower after focal cryotherapy when compared with other series evaluating whole-gland cryotherapy.[83,84] Contemporary results for focal cryotherapy show that 90% of men retain potency with little to no incontinence.[82] Comparable rates for whole-gland cryosurgery are 90% or more impotence. In future, the ability to evaluate focal cryotherapy, from large multicenter databases such as the Cryo On-Line Data registry, will be important (see Table 2).

High-intensity focused ultrasound. Two transrectal devices currently exist: the Ablatherm® device (Edap-Technomed, Lyon, France) and the Sonablate® 500 (Focus Surgery, Indianapolis, IN). Side effects from whole-gland HIFU have been reported as incontinence (0.5%–15.4%), urethral stricture (24%), fistula (0%–2%), and impotence (13%–53%).[83] HIFU is promising because it allows precision in targeting lesions and control of the energy, and it seems to have a low morbidity.[85] There has been only one poorly reported and standardized series of focal HIFU[86] in the literature although a number of studies are close to finalization at our center and have been presented in their interim form at the European Congress (2009) and at the Focal Therapy Workshop in Amsterdam (2009) (see Table 1).

Photodynamic therapy. PDT uses a photosensitizing drug that accumulates preferentially in tumor tissue. The drug is then activated by light of a specific wavelength in the tissue or in the vasculature. Tissue oxygen is required for the treatment effect. The activated drugs, associated with oxygen, create tissue damage. This technique is based on a transperineal approach, using a brachytherapy template to insert optical fibers that bring low power laser light.

A few studies are reported. Ahmed et al[83] reviewed seven studies recently. Efficacy with respect to this technique seems to be promising, but in all the studies, there was poor biopsy correlation to treatment with most reporting PSA kinetics. On the other hand, side effects of PDT are better reported. Prospective phase II trials in European multicenter studies and within the United States are currently ongoing. Preliminary results are encouraging, but final results are awaited,[87] with cancer control yet to be confirmed.[88]

Photothermal therapy. This uses interstitial laser fibers inserted under image guidance, usually MRI, to ablate tissue. There has been one series in 12 men that has been reported demonstrating feasibility and low toxicity.[43] Owing to the nature of the study, negative biopsy rates after treatment were 67%, but further larger studies are needed to evaluate this modality further.

Radiofrequency interstitial tumor ablation and brachytherapy. Both of these are performed by the transperineal

Table 1. Focal Therapy High-Intensity Focused Ultrasound Retrospective Series

	Muto et al (2008) (Sonablate 500)	*Barret (2009)* (Ablatherm)*
No.	29	12
Therapy	Hemiablation	Hemiablation
Biopsy	TRUS biopsy	TRUS biopsy
Mean PSA (ng/mL)	5 (range 2–25)	<10
Gleason score	≤ 8	≤ 7
Potency	Not reported	Not reported
Incontinence	Not reported	0%
Disease control	76.5% (biopsy)	58% (10 years)

*Presented at the 2nd International Workshop on Focal Therapy and Imaging in Prostate and Kidney Cancer. June 10–13, 2009. Amsterdam, The Netherlands.

TRUS = transrectal ultrasound; PSA = prostate-specific antigen.

approach, using percutaneous needles inserted under ultrasound guidance. Both could be capable of focal therapy, but there have been no studies to date.

Conclusion

Focal therapy appears to be a logical alternative to radical treatment and AS, potentially combining cancer control and minimal morbidity.[8] The concept of focal therapy is now frequently used in breast or kidney cancer, and increasingly the subject has received much attention from a number of key groups in Europe and North America. The ideal patient group for this new strategy and an accurate method to localize cancer in the prostate is yet to be agreed upon with the optimal ablative technique unknown. As cryotherapy is the better studied focal therapy technique, some consider this modality as the most appropriate technology for early stage localized prostate cancer in appropriately selected patients.[89] However, PDT and HIFU seem to offer better control over the ablative delivery and could deliver very discrete ablation. There is insufficient follow-up concerning focal therapy techniques and certainly no comparative data that can be drawn upon. Feasibility and safety trials are currently in process regarding PDT and HIFU. Efficacy of focal therapy should be assessed by trials with standardized criteria such as negative biopsies, and negative imaging tests, as these examinations have demonstrated their ability to detect tumor both before biopsy and after ablative treatment. Biochemical failure may less significance since untreated tissue that is growing with age remains. Comparative trials using standard care as the optimal comparators (AS and radical therapies) seem to be the most appropriate, considering the uncertainty in standard care, but recruitment to any randomized controlled trial may be difficult to recruit to. The preliminary results of focal therapy demonstrate promise and provide justification to prioritize this research question within the prostate research community within strong, well-managed collaborative groups working toward a common purpose.

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Table 2. Focal Therapy Cryosurgery Series

	Onik 2009 (Endocare)	*Ellis et al 2007 (Endocare)*	*Lambert et al 2007 (Oncura)*	*Bahn et al 2006 (Endocare)*	*Crawford et al 2009 (Endocare)*	*COLD Registry 2009 (Endocare)*
No.	112	60	25	31	100	795
Therapy	Hemi	Hemi	Hemi	Hemi	Focal	"Focal/Partial"
Biopsy	Template	TRUS	TRUS	TRUS + Doppler	Template	TRUS
Mean PSA (ng/mL)	8.3	7.2 ± 4.7	6 (range 1–13)	4.95	5.2 ± 4.1	
Gleason score	≤ 6	≤ 8	≤ 7	≤ 7	≤ 7	≤ 8
Potency	85%	70.6%	70.8%	89%	83%	65%
Incontinence	0%	3.6%	0%	0%	—	2.8%
Follow-up (mean, months)	43.2	15.2	28	70	—	12
Disease control	93% NED	76.7% (biopsy)	88% (>50% nadir reduction)	96% (biopsy) 92% (ASTRO)	97% (biopsy at 12/12)	4.5% (36/295) 25% (36/199) 83% (ASTRO)

ASTRO = American Society for Therapeutic Radiation Oncology; NED = No evidence of disease.

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Abbreviations Used

AS = active surveillance
ASTRO = American Society for Therapeutic Radiation Oncology
CE = contrast-enhanced
COLD = Cryo On-Line Data
DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging
DW-MRI = diffusion-weighted MRI
HIFU = high-intensity focused ultrasound
MRSI = MR spectroscopic imaging
PDT = photodynamic therapy
PSA = prostate-specific antigen
TRUS = transrectal ultrasound