

Avoiding surgery in prostate cancer patients with low-risk disease

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At present, the treatment paradigm for localized prostate cancer (PCa) is to distinguish patients with clinically relevant cancers who require treatment either in the form of traditional radical therapy or a contemporary less aggressive, organ-preserving approach, from the remainder who do not need any intervention at the time of diagnosis. Recent research has proposed a rationale for an active surveillance (AS) strategy with deferred definitive therapy in a select cohort of patients with low-risk PCa; however, this approach requires careful patient selection, regular long-term follow-up and the possibility of altering treatment towards a more aggressive modality. For another select group of patients with unifocal or unilateral PCa, alternative treatment options may include focal therapy or subtotal glandular ablation with cryotherapy, for example, as a more established and proven technique. Other potential minimally invasive procedures that are nonsurgical in nature that can also be utilized in the clinical arena include high-intensity focused ultrasound, or vascular-targeted photodynamic therapy, which is currently undergoing clinical study. However, additional basic science research and large-scale randomized clinical trials with long-term oncologic follow-up and quality of life outcomes are necessary before any conclusions can be made about the sustained efficacy of these minimally invasive options. This perspective article evaluates the current trends for treating localized, low-risk PCa in a nonsurgical fashion, and in particular to discuss focal therapy as a means of targeting the known cancer in select low-risk cases, thus avoiding whole-gland therapy and its inherent potential complications regarding quality of life. Traditional surgical, radiotherapy or hormonal therapeutic modalities are beyond the scope of this perspective article.

Our recent 20-year review of the surgical pathology assessment of radical prostatectomy (RP) specimens from 3676 men treated in a large tertiary medical center showed recent trends in tumor characteristics (pT stage, Gleason Score [GS], percent tumor involvement [PTI] and so on) that has occurred over three eras: 1988–1995, 1996–2000 and 2001–2006 (Mouraviev V, Mayes J, Sun L, Madden J, Moul J, Polascik T: Pathologic stage T2a and T2b prostate cancer in the recent prostate-specific antigen era: implications for unilateral ablative therapy. *Eur. Urol.* Manuscript submitted [2007]). The increasing prevalence of unilateral pT2a and pT2b prostate cancers characterizes a growing proportion of PCa patients electing RP in recent years, supporting data from another large national database [1,3]. These tumors are associated with lower percent tumor PTI and lower GS, and have demonstrated better prostate-specific antigen (PSA)-free survival in the most recent era. At the same time these unilateral tumors could potentially be treated with half-gland therapy (hemi-ablation), a form of focal therapy using modern minimally-invasive methods (Polascik TJ, Mouraviev V: Focal therapy for prostate cancer. *Curr. Opin Urol.* Manuscript accepted to publication [2008]). Traditionally,

PCa has been treated with whole-gland therapy, be it extirpative (radical prostatectomy), or *in situ* therapy (external beam radiotherapy, brachytherapy and cryotherapy, among others). However, the recent trend that a proportion of cancers being diagnosed are unifocal, unilateral or of lower malignant potential ('clinically insignificant') has raised questions as to whether all patients require radical treatment. Is the urologic community ready to modify the traditional treatment paradigm of whole-gland therapy for all PCa patients based upon this recent shift in stage and clinical presentation? Can a select group of patients be treated with less invasive or gland-preserving approaches? The answer seems to be 'not really', since up to 94% of men with low-grade PCa still receive radical treatment [1].

Ultimately, the treatment paradigm of managing localized PCa is to distinguish patients with multifocal, bilateral cancer who require aggressive whole-gland therapy from those with clinically relevant focal cancers who may benefit from either an organ-sparing approach or those who likely do not need any intervention at the time of diagnosis [3,4].

Keywords: cryoablation, focal therapy, HIFU, photodynamic therapy, prostate cancer

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The purpose of this perspective article is to evaluate current trends for the treatment of localized PCa with respect to therapeutic options that do not involve radical surgery or radiotherapy, as potential new frontiers in the treatment armamentarium for this malignancy are becoming increasingly available.

Active surveillance

The first management option for low-risk PCa is a 'do nothing' approach that allows the natural history of the disease to run its course without the possible side effects of an active intervention. The turn of this century witnessed a shift from the traditional 'watchful waiting' strategy towards active surveillance (AS), with selective delayed definitive therapy for those patients who eventually required treatment. While the early results of the Scandinavian Prostate Cancer Group suggested that 'watchful waiting' was reasonable for some patients with 10–15 years of follow-up, not all patients benefited from avoiding treatment [5,6]. Johansson *et al.* showed a decrease in progression-free survival, survival without metastases, and prostate-cancer-specific survival for patients with T1–T2 disease who were followed beyond 15 years as compared with the rates observed up to 15 years [7]. Results from the Connecticut Tumor Registry [8] for residents 75 years or younger diagnosed with clinically localized PCa in 1618 patients who underwent RP, external beam radiation therapy or no initial therapy demonstrated that, at an average follow-up of 13.3 years, 13% of patients had died of PCa. Patients who elected observation had significantly worse cause-specific survival than those who underwent elected RP. These findings suggest that patients undergoing AS may need effective definitive treatment at some point [8].

AS is dependent upon a few critical points: careful selection of patients who have low-risk features according to the D'Amico definition [9], patient age and medical co-morbidity, patient attitude and agreement not to be treated unless necessary. Table 1 presents various definitions of low-risk PCa that may be applicable for AS and other minimally invasive, nonsurgical treatment strategies.

So far, there is no consensus on the optimal AS protocol, with uncertainty regarding the interpretation of PSA kinetics, repeat biopsy results and prostate imaging [10,11]. In addition, the patient agrees to undergo close and frequent monitoring during subsequent follow-up.

Appropriate clinical, radiological and biochemical data must be collected in order to not miss a window of opportunity to undertake more aggressive treatment in a timely fashion if needed that will not result in undertreatment. The physician needs to take the time to properly communicate with the patient to reduce the psychological burden of leaving the cancer untreated.

The literature describes only a few prospective and retrospective Phase II series evaluating the outcome of AS with selective delayed intervention [12,13]. The largest prospective study from Toronto University [12] included 299 patients using the criteria for selective delayed intervention as a PSA doubling time (DT) of less than 3 years, or progression to Gleason 7 (4 + 3) or higher disease. The trial design allowed patients to choose radical intervention at any time. At a median follow-up of 64 months, almost a third of all patients (101 patients) discontinued AS, while 198 had remained on surveillance. The reasons to discontinue AS were the following: 15% due to rapid biochemical progression, 3% due to clinical progression, 4% due to histological progression at follow-up biopsy and 12% due to patient preference. At 8 years, overall survival was 85% and disease-specific survival was 99.3%. Only two of 299 patients have died of PCa, both of whom had a PSA DT of less than 2 years. Both men were treated with RP within 6 months of diagnosis, and metastatic disease developed within 1 year. Both deaths occurred within 5 years of diagnosis.

Recently, a group from John Hopkins [13] updated their experience with AS using a selective population of patients with clinical stage T1c PCa. The study was conducted as a prospective, longitudinal AS protocol. Active treatment was deemed necessary if disease progression was noted on follow-up needle biopsy (Gleason pattern 4 or 5, greater than two biopsy cores with cancer or greater than 50% involvement of any core with cancer). Of 407 men, 239 (59%) remained on AS at a median follow-up of 3.4 years (range 0.43–12.5), 103 (25%) underwent curative intervention at a median of 2.2 years after diagnosis (range 0.96–7.39) and 65 (16%) were either lost to follow-up (12), withdrew from the program (45) or died of causes other than PCa (8). Older age at diagnosis and an earlier date of diagnosis were significantly associated with disease intervention.

Incumbent upon any AS strategy, patient candidacy is a crucial factor to select patients with favorable prognosis to nonintervention in order

Table 1. Definitions of low-risk or ‘clinically insignificant’ prostate cancer.

Author	Prostate-specific antigen	Prostate-specific antigen density	Clinical stage cT	Gleason score	No. of cores positive	Maximum % of cores positives	Extent (mm)	Volume (ml)	Ref.
D’Amico et al. (2007)	<10		T1c-T2	≤6					[8]
Epstein et al. (1998)		0.15		≤6	≤3	<50			[52]
Gardner et al. (1998)				≤6 (w/o any 4)		<5			[53]
Terris et al. (1992)				≤6	1		≤3		[54]
Boccon-Gibod et al. (2005)			T2	≤6				<0.5	[55]
Noguchi et al. (2001)		<0.15			1		<3	<0.5	[56]

w/o: Without.

to minimize the potential need to shift the approach towards more aggressive therapy [14]. One promising tool in this direction may be the development of a nomogram predicting treatment outcome [15]. Finally, only randomized clinical trials comparing different treatment modalities versus AS can control for the many known and unknown confounding factors that can affect long-term outcomes [14]. So far, a high proportion of patients necessitating change from a surveillance strategy towards more definitive therapy is concerning due to insufficient knowledge of tumor biology and factors involving the selection of appropriate candidates.

Scientific background for focal targeted therapy

Today, with the wide application of screening programs and detection of early-stage PCa, focal targeted therapy may assume a more prominent role between the two treatment extremes of radical treatment (RP and so on) and no treatment (AS). It is very important, especially for a relatively young cohort of patients (e.g., in their mid-fifties and sixties who are still potent and willing to preserve bodily functions such as continence and erectile function), to maintain quality of life (QoL) after PCa treatment [3,4,16,17]. During the last decade, several pathologic and clinical studies have been performed to better understand the role and place of organ-preserving ablative technologies, taking into consideration the conceptual promise of using targeted ablation as a 'male lumpectomy' in select, appropriate candidates [18–25].

Eradication of cancer at an early stage offers the best chance for reducing cancer morbidity and mortality. Mouraviev *et al.* analyzed 1184 paraffin-embedded radical prostatectomy specimens from patients with clinically localized PCa treated with surgery [20]. Pathologic assessment paid particular attention to laterality and percentage of tumor involvement (PTI), along with pathologic Gleason score. Completely unilateral cancers were identified in 227 (19.2%) patients. The majority of unilateral tumors (72%) were low volume with a PTI of ≤ 5 . This data demonstrated an even higher rate (39.4%) of clinically significant (Gleason score ≥ 7) tumors among small volume (PTI $\leq 5\%$), unilateral PCa foci than previously appreciated by other groups. This study suggests that perhaps up to 20% of men diagnosed with PCa elected have completely unilateral cancers that would be amenable to focal ablation therapy targeting the involved side of the prostate.

A multidisciplinary report from two institutions [23] recently analyzed 1000 radical prostatectomy specimens from early-stage PCa patients. Only 18% of cancers were unilateral, which is in concert with the data of Mouraviev *et al.* [20]. The largest focus of cancer in all intraprostatic tumors was associated with extracapsular extension (ECE) in more than 90% of cases. Therefore, the clinical implication of this data is that effective ablation of the index lesion may lead to almost complete eradication of the tumor burden that clinically leads to ECE.

Cheng *et al.* [22] found that the majority of small-volume prostate cancers are multifocal, often involving both sides of the prostate. Tumors are located predominantly in the peripheral zone (79%) and the posterior aspect (84%) of the prostate. These data suggest that prostatic carcinogenesis may be attributed to a field effect, supported by recent molecular evidence that multiple prostate cancers arise independently. The finding of frequent multifocality and bilaterality in small-volume PCa is extremely important when considering focal ablative treatment strategies. The fact that these patients have developed multifocal tumors even with a very low total tumor volume suggests that the field effect of carcinogenesis is already in effect and that other tumors may arise in the future if these cancers are left untreated. These authors concluded that small-volume prostate cancers are often multifocal and bilateral, with predilection for the peripheral zone. Of these small-volume cancers, 16% had high Gleason grades that are clinically significant and likely quite aggressive if left untreated.

Another prerequisite for successful implementation of focal targeted therapy in clinical practice is the introduction of high-resolution imaging tools coupled with advances in computerized modeling software. Although some non-invasive techniques such as endorectal or dynamic contrast-enhanced MRI have initially shown promising results in terms of detection of PCa lesions greater than 1 cm in diameter, the reproducibility of these techniques remain to be proven in multi-institutional trials [26–29]. In lieu of PCa-specific imaging, most treating clinicians rely on information obtained by prostate biopsy. For example, Barzell *et al.* [30] used template-guided transperineal, 3-dimensional pathologic mapping to identify clinically significant PCa prior to recommending treatment. These authors carefully selected eight patients for focal cryoablation.

Galosi *et al.* [31] revealed some important features of tumor spread within the gland:

- Separate pathological analysis of each biopsy specimen (or specimens grouped) per anatomical site;
- 12–18 core biopsy mapping that includes peripheral and transition zones, plus target biopsy if necessary;
- Specimen orientation using the pre-embedding or ‘sandwich’ technique with China ink-labeled fragment at one end (i.e., rectal), that has value in determining the distance of the tumor from the inked edge (depth of spread toward peripheral or periurethral tissue) of the core biopsy.

Ultimately, these pathological features detected in the pre-operative biopsy may be useful in planning focal therapy. However, further study is needed.

Application of prostate cryoablation

Primary whole-gland cryoablation

The short- and intermediate-term data of clinical studies using third-generation technology to treat localized PCa demonstrate feasibility and safety of this procedure comparable with RP [32–34]. The high morbidity associated with cryotherapy presented in earlier reports during the previous two decades could be attributable to such factors as the use of first-generation liquid nitrogen-based systems, less refined ultrasound techniques, lack of temperature monitoring and banning of the urethral warming catheter by the US FDA.

Han *et al.* accumulated data on 175 patients treated with whole-gland cryotherapy at several institutions in the USA [35]. A total of 110 patients had a PSA follow-up at 12 months, with 80 (73%) having a PSA level <0.4 ng/ml, while 42 of 65 (76%) low-risk patients also remained without PSA recurrence at 1 year.

Prepelica *et al.* reported on the 6-year results of 65 men for T1–T3 PCa with high-risk features treated with cryosurgery [36]. A Kaplan-Meier analysis showed an 81.7% American Society for Therapeutic Radiology and Oncology (ASTRO)-survival probability with minimal morbidity (only one patient developed incontinence and one patient rectal pain, which subsequently resolved). At the end of study, no patient had demonstrated disease progression, and the overall survival rate was 100%.

Polascik *et al.* reported results on 50 patients with a median follow-up of 18 months [37]. According to the D’Amico risk stratification [38],

36 (72%) patients had low-risk, nine (18%) had intermediate-risk and five (10%) had high-risk PCa. The distribution of the latest PSA for all patients at the time of last follow-up was as follows: less than 0.5 ng/ml in 45 (90%) patients and ≥0.5 ng/ml in five (10%) patients. Two patients had persistent PCa confirmed by prostate biopsy and were treated with salvage cryotherapy or external beam radiotherapy. The overall survival rate was 100%.

Current technology provides a minimal side-effect profile, except for impotence which remains a concerning problem in up to 80–90% of cases [3,33]. The impotence rate has remained high since current thought is to freeze the entire gland, including the neurovascular bundles, in order to completely eradicate all tissue at the periphery of the prostate gland.

Nerve-sparing cryotherapy

A nerve-sparing cryoablation technique to treat PCa was first described by Onik *et al.* in a pilot study of nine patients by performing unilateral ablation of the lobe where the positive biopsy occurred and leaving untreated the contralateral lobe and neurovascular bundle [18]. After a mean follow-up of 3 years, seven of the patients were potent. All patients had a stable PSA level and negative biopsies. However, experimental data with this application showed incomplete ablation in the peripheral prostate tissue [39]. Therefore, nerve-sparing techniques should remain developmental at this stage until additional studies document acceptable cancer control and functional outcomes.

Focal targeted approach using cryotherapy

Rukstalis *et al.* have suggested that prostate parenchyma-sparing cryosurgery may improve outcomes in terms of continence and potency [24]. Despite the multifocal nature of PCa, in an analysis of 112 radical prostatectomy specimens, these investigators assumed that if the largest tumor would be the one detected by biopsy, by restricting treatment to nine of 12 prostate zones, thereby sparing the contralateral neurovascular bundle, cancer control could be accomplished with a 21% risk of significant (i.e., >0.5 ml) residual disease.

Regarding selection of candidates for focal therapy, the criteria are still under development, although preliminary single- and two-institutional trials showed better results can be achieved using the following inclusion criteria: Gleason score of less than 6 or 7 (3 + 4) confined to one

Table 2. Cancer control and complication rates after focal and unilateral cryoablation.

	No. patients	No. Bx cores	Follow-up median months	Cryounit	bDFS (%)	PSA cut-off	Bx-proven recurrence (%)	Potency preserved (%)	Ref.
Unilateral cryoablation									
Lambert et al. (3.5-yr data)	25	12	28	SeedNet™	84	<50%	12%	71	[40]
Bahn et al. (5-yr data)*	31	6–12	70	Cryocare™	93	ASTRO* Negative Bx	8% – untreated lobe 4% – treated lobe 4% – untreated lobe	88.9 total 48.1 – fully recovered 40.8 – medically assisted	[41]
Focal cryoablation of unifocal lesion									
Onik et al. (6-yr data)	21	7–8	50 (mean)	Cryocare™	95	ASTRO*	0 (in one [5%] case cancer was found on MRIS in untreated lobe)	80	[16]

*ASTRO – American Society for Therapeutic Radiology and Oncology definition: three subsequent risings of PSA.

#Results of a two-center clinical trial.

SeedNet™ – Galil Medical, Plymouth Meeting, PA, USA.

Cryocare™ – Endocare, Irvin, CA, USA.

bDFS: Biochemical disease-free survival; Bx: Biopsy; MRIS: MRI spectroscopy.

lobe in one or two contiguous biopsy cores and tumor volume less than 10% in a 12-core biopsy taken via a transrectal approach using either color Doppler ultrasound or a transperineal mapping biopsy via a standard brachytherapy grid [16,40,41].

Table 2 summarizes the first pilot clinical trials of focal prostate cryoablation. Lambert *et al.* [40] presented data on 25 patients who underwent unilateral cryoablation based on a minimum 12-core biopsy suggesting the presence of PCa in one lobe. The criteria for suspicion of biochemical failure were a PSA nadir less than 50%. Of the 25 patients, 21 (84%) demonstrated PSA disease-free survival. Seven patients underwent repeat prostate biopsy, with cancer detected in the contralateral lobe in two patients and in the treated lobe in one patient. Of 24 patients who were potent preoperatively, 17 (71%) were potent postoperatively. All patients preserved their pretreatment urinary function maintaining complete continence.

Bahn *et al.* recently presented the results of a two-institutional trial of 31 patients with clinically organ-confined, unilateral cancer identified by color Doppler ultrasonography, confirmed by targeted and systematic biopsy [41]. The mean age of men was 63 years. All patients, having a strong desire for preservation of sexual function and continence, were treated with unilateral cryoablation. Cancer control data at a mean follow-up of 70 months were acceptable; for example, biochemical disease-free survival using the ASTRO definition of three consecutive PSA increases was maintained in 92.8% of patients with a 96% negative-biopsy rate. The one patient with a positive biopsy in the apex of the contralateral untreated lobe was subsequently retreated with full-gland destruction and remains disease-free. The total potency-preservation rate was 88.9%. There were no cases of incontinence or other complications.

Onik updated his series of 21 patients treated with focal ablation of a unifocal tumor [16]. Using the traditional ASTRO -definition, 20 of 21 patients maintained PSA disease-free survival, despite 10 patients being classified as having moderate- or high-risk disease. Although prostates that were biopsied after treatment remained negative for malignancy, a cancerous lesion in the untreated side was identified in one patient by spectroscopic MRI. Potency was maintained in 17 of 21 patients (80%) without any other complications including incontinence or rectal fistula formation.

One potential advantage of prostate cryoablation as a nonsurgical therapeutic option is that the operator can manipulate the ice ball to extend beyond the prostate capsule on the side involved with unilateral cancer when treating in a focal manner. In contrast, other potential focal treatment techniques such as high-intensity focused ultrasound (HIFU) and vascular targeted photodynamic therapy may be better suited to destroy tumor lesions within the prostate, for example, under the capsule.

Clearly, long-term oncologic efficacy will need to be determined before these approaches become standard. Nevertheless, given all the progress that has been made in the past decade, cryosurgery will likely play an increased role in the future management of PCa.

High-intensity focused ultrasound

High-intensity focused ultrasound another minimally invasive technique for PCa treatment is gaining popularity for whole-gland therapy. Table 3 summarizes the results of large clinical trials using HIFU. Currently two different HIFU units are available on the market for clinical use, for example, Ablatherm[®], (EDAP-TMS, Lyon, France) and Sonablate[®] 500 (Focus surgery, Indianapolis, IN, USA). Oncological efficacy using HIFU demonstrated cancer control ranging from 69–75% with a median follow-up of 22.5 months (range: 13.1–27) [42–46]. In three of these trials the authors demonstrated 5-year disease-free survival rates of 66–78% [43,45,46]. Low-risk features such as a PSA level ≤ 10 ng/ml, a Gleason score ≥ 6 and ≥ 4 positive cores by sextant biopsy may be better selection criteria to achieve a successful result [47]. While prostate volume does not seem to be a major predictor of outcome, large prostates with a volume ≥ 40 cc are more difficult to completely treat due to the limited focal length of existing systems and, usually, the anterior part of the base remains untreated [28]. Therefore, neoadjuvant androgen deprivation may be indicated to decrease prostate volume before treatment. Another alternative is to repeat the procedure as a second treatment following the first session.

Several months following the procedure, the prostate decreases in volume by 40–50% and usually the PSA nadir can be established 3–6 months after HIFU. A PSA nadir ≥ 0.2 ng/ml may be considered a good predictor of favorable outcome [28,46,47]. Complication rates such as incontinence need to be lowered (Table 3) [42–46]. A serious complication such as

Table 3. Results of large clinical series on the efficacy of whole-gland HIFU therapy for treating localized PCa (T1–T2).

Trial	Device	No. patients	Median baseline PSA ng/ml	Median f/u (mos)	Negative Bx (%)	bDFS (%)	Stress incontinence (%)	Impotence (%)	UTI (%)	Fistulas (%)	Ref.
Chaussy <i>et al.</i>	EDAP™	271	8.3	14.8	84.8	82.1 (ASTRO)	15.6	35.9	47.9	0	[42]
Blana <i>et al.</i>	EDAP™	146	11.3	22.5	93.4	84 (PSA < 1) 71.5 at 5 years (PSA < 0.4 or Bx)	0	49.8	0.4	0.5	[43]
Thueroff <i>et al.</i>	EDAP™	402	10.9	13.1	87.2	NA	13.1	NA	13.8	0.5	[44]
Uchida <i>et al.</i>	Sonablate™	63	11.2	23.3	87	78 at 5 years (ASTRO)	0.6	20	6	1	[45]
Poissonnier <i>et al.</i>	EDAP™	227	6.99	27	86	66 at 5 years (ASTRO + Bx)	13	39	2	0	[46]

ASTRO: American Society for Therapeutic Radiology and Oncology; bDFS: Biochemical disease-free survival; Bx: Biopsy; HIFU: High-intensity focused ultrasound; NA: Not available; PCa: Prostate cancer; PSA: Prostate-specific antigen.

rectal–urethral fistula was initially reported in a large series in 0.7–3.2% of patients, associated more frequently with multiple HIFU sessions and in patients having been treated with prostate radiotherapy. The recent introduction of cooling systems and automatic rectal wall recognition systems along with a better understanding of heat diffusion by operators surpassing the ‘learning curve’ of the procedure significantly decreased the frequency of rectal fistula formation. Nearly all patients experience some degree of urinary retention in the postoperative period requiring bladder catheterization. To prevent this complication, some surgeons advocate transurethral resection of the prostate just before HIFU ablation [28,47].

HIFU technology may be potentially applicable for the purpose of focal therapy. To our knowledge, only one pilot trial [48] attempted to focally ablate a PCa lesion in ten patients. All patients subsequently underwent radical prostatectomy with pathological assessment demonstrating residual tumor in seven of ten patients (70%). Contemporary HIFU units may be able to better target a lesion more accurately, but will require data in clinical trials.

Vascular-targeted photodynamic therapy

The first application of vascular-targeted photodynamic (VTP) in humans in a Phase I/II trial [49] showed reproducible and effective cancer control with minimal side effects to treat locally recurrent PCa after radiation therapy. This novel therapy uses a new generation of bacteriochlorophyll-derived photo sensitizer Tookad (WST09) and low-power laser light to activate the intravenously administered agent resulting in thrombosis with subsequent localized tissue necrosis within the prostate [50]. Thus, the activated drug may work selectively to block the blood supply to certain tissues immediately around the tip of the illuminating optical fiber.

Another Phase I/II study using VTP is being conducted to focally treat primary PCa. To date, a total of 27 men have been treated in the study, with 14 having received a two-fiber VPT and 13 men a multifiber VTP. A multifiber VTP is selected to treat with the intent of a focal therapy approach (M Emberton. Unpublished data). This same group developed a new photosensitizer using meso tetra hydroxy phenyl chlorin (mTHPC) for targeted PCa ablation [51]. In a pilot study, six men were treated with this modality through transperineal needles inserted within the PCa lesion (50–100 J per site). The initial results are promising, for example, after eight of ten VTP sessions

the PSA level fell up to 67%. Follow-up MRI scans demonstrated edema and patchy necrosis that resolved over 2 months. Histological assessment of the treated areas after prostate biopsy revealed necrosis and fibrosis at 1–2 months. Forthcoming results of a multicenter Phase II study will hopefully further clarify a potential role of this technique in the treatment of organ-confined PCa.

Future perspective

A major goal of PCa research is the identification and development of pretreatment prognostic indicators based on biopsy tissue, serum and/or urine markers that can predict with better accuracy the likely natural history of a given patient’s tumor. Patients with low risk of disease progression would be candidates for active surveillance alone or focal therapy, whereas those with more aggressive tumor characteristics could receive early, multimodal therapy. Significant advances in better understanding tumor biology and the introduction of novel minimally invasive modalities may be further expected to facilitate the inclusion of minimally invasive treatment for select candidates from radical whole organ-removal (RP) or whole-gland therapy (external beam radiotherapy and cryoablation) towards a more tailored treatment approach favoring subtotal, hemi-gland or truly focal targeted, image-guided therapy of localized PCa. Recent research has confirmed a limited rationale for an AS strategy with deferred definitive therapy in select patients with low-risk PCa features; however, this approach requires careful selection of candidates, regular follow-up and the possibility of shifting the treatment approach towards a more aggressive one if clinically needed. For those patients with unifocal or unilateral PCa lesions who are seeking a more targeted treatment approach with preservation of QoL function, current treatment options now include focal targeted cryoablation, HIFU or VTP. However, further basic science research and the conduction of large-scale randomized clinical trials with long-term follow-up are necessary before any conclusions can be made about the sustained efficacy of these minimally invasive treatment options.

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Executive summary

- A recent shift in pathological stage favoring early detection of low volume, low-risk disease has allowed alternative approaches to avoid radical surgical therapy for some men with clinically localized prostate cancer (PCa).
- Active surveillance may be indicated for select candidates with clinically insignificant or low-risk PCa, but requires very regular and careful follow-up in order to not miss the need to switch treatment strategy towards a more interventional approach in the case of disease progression.
- Focal hemiablation of unilateral lesions or targeted ablation of a unifocal lesion is a conceptually reasonable treatment option in appropriate candidates. Candidacy is based on patients with low-volume, low-grade cancer with pathologic findings of image-guided extended (multicore) prostate biopsies suggesting the absence of cancer in the contralateral lobe. Selection criteria is of paramount importance and needs to be further developed in multicenter trials demonstrating longer follow-up for cancer control.
- Cryoablation applied as focal therapy is a more established technique that has been successfully tested in Phase I/II trials in single and two-institutional trials.
- Short-term results of Phase I/II trials of the clinical application of vascular-targeted photodynamic (VTP) therapy are pending and preliminary data demonstrate a high efficacy of targeted ablation of unifocal lesions for primary treatment of localized PCa and localized radiorecurrent PCa.
- High-intensity focused ultrasound (HIFU) has proven efficacy for whole-gland ablation and potentially can be considered as a treatment option in a focal therapy setting.

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