REVIEW

Focal therapy of prostate cancer

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Purpose of review
The aim of this study was to summarize the latest evidence, as well as the rationale behind using focal therapy for the treatment of prostate cancer. With patients becoming more educated, knowledge of the available evidence is key when discussing treatment.

Recent findings
In older works, the natural history of prostate cancer has been described as being multifocal, driven by one index lesion. This represents the key argument for most experts, why focal therapy is feasible in prostate cancer. Most modalities have similar results. For high-intensity focussed ultrasound (HIFU), a pooled data analysis with a median follow-up of 2.2 years showed a negative biopsy rate of 77% with a salvage therapy free rate of 92%. A matched pair analysis comparing irreversible electroporation with robot-assisted radical prostatectomy showed a better side effect profile for focal therapy in evenly matched groups, yet with worse disease-free survival. Interestingly, the better outcomes concerning continence and erectile function did not translate into better patient-reported outcomes.

Summary
Focal therapy modalities are generally well tolerated and show good results in terms of continence and potency. Long-term follow-up is not available, and inclusion criteria for trials are not yet uniform. Newer technologies, such as photodynamic therapy, are being developed, as well as improvements to older techniques, such as HIFU.

Keywords
focal therapy, index lesion, MRI, prostate cancer

INTRODUCTION

As our knowledge about the natural history of prostate cancer (PCa) grows, so do the options for treatment. The standard treatments for localized PCa, surgery and radiation, are still option of choice for a lot of patients, yet the demand for more precise treatment with fewer side effects is growing constantly. Observation by either active surveillance or watchful waiting has become a more popular strategy, yet is not always optimal. Also, the burden of a tumour diagnosis without any treatment is unbearable for some patents. Although many of those patients should have never been diagnosed with PCa in the first place, and as imaging technology, and biomarkers become more accurate, many of them will not be diagnosed with PCa in the future, there remains a group of small intermediate risk cancers that do require treatment, yet might be overtreated by surgery or radiation.

Focal therapy seems a logical consequence of this. As with many other tumour entities (e.g. breast, kidney, liver), removal of the entire organ is not always necessary to curatively treat the cancer. Although PCa is often considered multifocal in nature, better understanding of the importance of an index lesion has as well as more accurate diagnostics has shown focal therapy to still be a viable treatment approach. Advances in imaging, urine and genetic biomarkers are of great help in this regard.

The available options when deciding for focal therapy are plentiful [1], yet solid data, and long-term follow-up is lacking for most of them. For this reason, the European Association of Urology Guidelines only recommend using focal-therapy within clinical trials. Most of the available options for focal therapy were originally used as whole-gland treatment, thus data for whole-gland treatment exist, yet usually shows significant side effects, which might not occur when deciding for a focal approach. Yet,

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KEY POINTS

- Diagnosis: patients considered for focal therapy should have a prostate-specific antigen of 15 ng/ml or less, clinical stage T1c-T2a, Gleason score 3 + 3 or 3 + 4 (ISUP 1 and 2) and a life expectancy of more than 10 years, as well as a visible index lesion.
- Index lesion is the clinically significant lesion in a patient, that is ideally MRI visible and confirmed by MRI-guided biopsy. For the purpose of focal therapy, it is considered the main driver when it comes to tumour spreading.
- Focal therapy is well tolerated and has lower side effects than radical prostatectomy/radiation therapy. Oncologic outcome is decent, yet large comparative trials with radical prostatectomy/radiation therapy are missing at this time.

again data are scarce and must be evaluated carefully.

It is the aim of this review to show the most recent publications in the field of focal therapy for PCa in hopes to spark interest and future research. There are many potential benefits to a focal therapy, however thorough investigation is needed to ensure adequate oncological outcome.

DIAGNOSIS AND PATIENT SELECTION

When considering a patient for focal therapy proper diagnostics is the key to success. The advantages of using of MRI and MRI-guided biopsy has been proven many times [2,3], and becomes even more important in the context of focal therapy. As a visible lesion is necessary for true focal treatment (not including hemi-ablation), undergoing MRI is almost mandatory. Patients should then undergo MRI-guided biopsy to verify the index lesion as clinically significant cancer. A consensus meeting consisting of experts on focal therapy concluded that patients with a prostate-specific antigen of 15 ng/ml or less, clinical stage T1c-T2a, Gleason score 3 + 3 or 3 + 4 (ISUP 1 and 2) and a life expectancy of more than 10 years should be offered focal therapy as part of a trial [4].

The presence of a multifocal tumour has been shown to not be an absolute contraindication for focal therapy, as tumour spread is believed to be caused by one dominant index lesion [5,6]. In a prospective trial, the outcomes of ablation of the index lesion using high-intensity focussed ultrasound (HIFU) were evaluated. Pad-free incontinence, erections sufficient for intercourse were preserved in 92.0 and 76.9% of patients, respectively. Negative biopsies for clinically significant cancer were obtained in 85.7% of patients at 12 months (48/56), and only 3.6% had clinically significant cancer at rebiopsy in untreated area, which was not detected at baseline [7].

HIGH-INTENSITY FOCUSSED ULTRASOUND

HIFU has been used as whole-gland treatment for a long time, in Europe, and received FDA-approval for ablation of prostate tissue in 2015. Effects of HIFU on human prostate tissue have already been described in 1995 [8] when patients received HIFU prior to radical prostatectomy to analyse tissue changes. It was originally developed as a minimally invasive alternative to radical prostatectomy, as a whole-gland treatment for men with localized PCa. Early results were promising for primary and salvage therapy [9–12], yet large prospective trials comparing HIFU to radical prostatectomy or radiation therapy are missing.

For focal therapy, HIFU is one of the most promising methods being tested. Known side effects such as rectal fistula, which have been known to occur after whole-gland therapy (1.2–2.2%) [10,13], are less common with the focal approach (0–1%), the improvements to the devices and safety precautions, such as rectal cooling [14,15].

In a data analysis by Albisinni *et al.* [16▪▪], seven datasets for focal and hemi-ablation of unilateral PCa were pooled and reported. Three hundred and sixty-six patients were included in this analysis with a median follow-up of 2.2 years. Negative biopsy rate during follow-up was 77% (66–87%) and salvage treatment-free survival (radical prostatectomy, radiation therapy, ADT) was 92% (85–98%). With follow-up being so short, conclusions concerning oncologic outcome are premature at this point. Functional outcomes showed a very low rate of incontinence with continence being defined as pad-free continence in five out of the seven studies included. Even with this very strict definition, continence at 12 months was very high at 96% (91–100%). A potency-rate of 74% (64–84%) at 12 months was also calculated, yet the definitions used in the different studies varied greatly.

The same group also published their matched-pair analysis, comparing 55 patients who underwent hemi-ablation with HIFU to 55 patients undergoing robotic radical prostatectomy [17▪▪]. Within a median follow-up of 36 months, there was no statistically significant difference in salvage therapy, yet patients undergoing HIFU showed a significantly lower rate of de-novo erectile dysfunction (20 vs. 44%, $P = 0.03$) as well as higher continence rates at 1 month (82 vs. 40%, $P = 0.001$).

Ganzer *et al.* [18▪▪] reported the findings of their Phase II clinical trial including 51 patients who underwent hemi-ablation. Follow-up was again short with a mean of 17.4 months. Biopsy at 12 months was positive in 26.5% of patients, with 8.2% showing significant cancer. Ten patients (19.6%) underwent salvage therapy. Of the 30 men being potent preoperatively, 21 maintained potency. Impact of focal therapy on anxiety, depression and quality of life (QoL) was also reported. There were no significant changes in the QoL score used, as well as the anxiety score, which were both normal during the entire follow-up. Yet, the HADS-D (Hospital anxiety and depression scale), used for depression, increased significantly during follow-up from 8.8 at baseline to 10.7 at 3 months ($P = 0.022$). The median then declined during further follow-up, yet remained at 10.1 at 12 months. This is the first study reporting anxiety and depression, which, as one rational behind the use of focal therapy is the reduction of anxiety and depression in some active surveillance patients, shows the need for further investigation of the subject. This also indicates that focal therpy should not be used to reduce anxiety under active Surveillence.

As one of the more frequently used modalities, there is constant optimization of the devices, and some new machines have the option of an in-bore procedure with a transurethral probe and MRI real-time imaging, and heat monitoring. Publications on these new devices will follow soon.

CRYOTHERAPY

Cryotherapy was also originally used as whole-gland treatment, and later adapted to a focal therapy approach [19]. Cryotherapy is administered by using perineal needles, placed under ultrasound guidance to freeze the tissue. The created area of ablation (ice-ball) is monitored in real time with ultrasound as well.

Similar to HIFU, cryotherapy is associated with side effects such as urinary retention, erectile dysfunction and fistula, yet these are again very rare when focal therapy is used.

The Cryo on-line Database (COLD) Registry is a large prospectively maintained database, including patients undergoing Cryotherapy in focal, whole-gland and salvage setting. The use of focal therapy, when compared with whole-gland, has increased significantly over time ($P = 0.01$). The same analysis also showed a BCR-free survival rate of 75.7% at 36 months, which is similar to other focal therapy trials, yet the follow-up in the COLD Registry is longer than for most other published trials on focal therapy. The reported rates of incontinence and new onset erectile dysfunction were 8 and 41.9%, respectively [20]. Also, in cryotherapy, technical advances, such as urethral warmers, have improved the safety profile of the procedure.

ELECTROPORATION

Irreversible electroporation (IRE) uses electrical pulses between electrodes to create pores in the cell membrane, which leads to apoptosis. It is one of the newer methods described for focal therapy of the prostate and, like cryotherapy, requires a transperineal approach for the placement of the electrodes.

IRE has been proven to completely ablate tissue in the chosen field without affecting surround tissue [21]. This is a theoretical advantage, as with thermal ablation techniques, surround tissue gets affected by dispersing heat, thus making complete spearing of neurovascular structures almost impossible.

A recent study by van den Bos *et al.* [22▪] shows promising QoL outcomes, as well as oncological outcomes, comparable to other focal therapy modalities. Overall, 63 patients with clinically significant PCa (high volume Gleason 6, or any Gleason sum 7) who were treated with IRE were analysed. There were no perioperative high-grade adverse events. Also, there was no significant difference in physical, mental, bowel or urinary QoL domains. Sexual QoL did decrease at the 6-month follow-up. Positive rebiopsy rate was 84 and 76% for in-field and whole-gland recurrence, respectively [22▪].

Another study by Scheltema *et al.* [23▪▪] compared IRE with robot-assisted radical prostatectomy (RARP). In this matched-pair analysis, 50 IRE patients were matched to 50 RARP patients by propensity score. Patients with high volume Gleason 6 (ISUP 1) or any Gleason sum of 7 (ISUP 2 and 3) were included. There were no significant differences in the matched groups. IRE was superior to RARP in preserving pad-free continence ($P = 0.01$) as well as erectile function ($P = 0.05$) within the first 12 months. However, analysis of EPIC questionnaires showed no significant difference. Early oncological outcomes show 70.5% of men without significant cancer, although none of the patients in the RARP group experienced biochemical failure within the first 12 months [23▪▪]. This is one of few comparative studies between focal therapy and standard treatments. And, it is the opinion of the authors that with the long follow-up needed for PCa, and the constantly evolving therapies, matched-pair analysis might be the best possible data for newer treatments, especially as these treatments only work for selected patients, who often have specific wishes when considering treatment, and are unwilling to be randomized.

LASER ABLATION

Focal laser ablation (FLA) is another new method of focal therapy. It consists of a laser-fibre being inserted into the tumour and heating up the tissue to cause damage (coagulated necrosis). Both transrectal and transperineal approaches have been used.

Overall, many Phase I trials have been published establishing the safety of FLA. The largest cohort consisted of 12 patients with low-risk cancer and was published by Lindner *et al.* [24] in 2009. In their study continence, erectile function was not affected by therapy, and 67% of patients had a negative biopsy at 6 months. Thermal sensors and real-time contrast-enhanced ultrasound were used to monitor the treatment [24].

A more recent cohort of 11 patients with intermediate risk cancer by Natarajan *et al.* [25▪] also used MRI-ultrasound fusion technology to guide the laser towards the tumour in local anaesthesia. Again, no changes in continence and potency were observed at 6 months. An MRI-ultrasound fusion biopsy performed at 6 months revealed no cancer in 3, microfocal Gleason 3 + 3 and persistent intermediate risk cancer in 4 patients [25▪]. In this case, patients underwent the procedure in local anaesthesia, which is not possible for other thermal ablative techniques such as HIFU. This might be an important advantage in the future, yet at the moment, it is questionable if this is actually desirable, as even small movement of the patient can have an effect on treatment. This might be partially responsible for the relatively low negative biopsy rate at 6 months, and in conjunction with the intermediate-risk population, a general anaesthesia might have shown better results. However, with only very short follow-up, conclusions regarding oncologic outcome should not be dawn at this point.

Another advantage of FLA is the option of real-time MRI treatment and heat monitoring. The largest study published about in-bore FLA was done by Eggener *et al.* [26] in 2016, including 27 low-risk and intermediate-risk patients. The procedure was performed within the MRI unit under conscious sedation and added local anaesthesia. There were no statistically significant differences in I-PSS and sexual health inventory for men at 12 months. At repeat MRI-guided biopsy at 12 months, cancer was present in 37% of patients, 11 of whom were inside the ablation zone [26].

With better technology and understanding to improve outcomes and more data, FLA might become a more widely used method, due its simplicity, which might even allow it to be used in the clinic. This could make it an attractive alternative for practitioners and patients alike.

BRACHY THERAPY

Brachy therapy has long been used as a treatment for low and intermediate-risk PCa. It consists of the implantation of radioactive seeds into the prostate, which then treats the surrounding tissue with radiation.

It is easy to adapt towards a focal approach, wherein seeds are only placed into a lesion [27] or specific area [28,29] of the prostate (hemi-ablation). To this date, there are hardly any data on the oncological outcome of focal brachy therapy however, as the first trial only included 22 patients and does not report oncological outcomes, and the hemi-ablation trial has also not been published in regards to the oncological outcome. Functional outcomes have been compared retrospectively with previous whole-gland cohorts and were improved. International Prostate Symptom Score (IPSS) was lower in focal brachy ($P = 0.04$) and The international index of erectile function (IIEF)-5 was also significantly better ($P = 0.014$) [27]. Yet, with no oncologic outcomes reported at this time, other options for focal therapy seem more promising at this time.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) consists of an intravenous agent, which is subsequently activated by light to generate radical oxygens in the illuminated area, which in turn cause vascular necrosis.

Phase III data are available with 4 years of follow-up reported by Gill *et al.* [30▪▪]. In this randomized controlled trial (RCT), 4013 men with low-risk PCa were randomized to receive either focal therapy with PCM301 (PDT) or active surveillance. PDT was associated with a significantly lower rate of cancer progression [hazard ratio 0.42, 95% confidence interval (95% CI) = 0.29–0.59, $P < 0.001$] and also a lower rate of conversion to radical therapy with 24 vs. 53% at 4 years (hazard ratio 0.31, 95% CI = 0.21–0.46, $P < 0.001$) [30▪▪]. Functional outcomes were reported on the same study after 2 years of follow-up by Azzouzi *et al.* showing no significant difference in IPSS and IIEF-5 after 24 months between the PDT and the active surveillance group ($P = 0.64$). Adverse events were higher in the PDT group, the most common of which were urinary tract infections and perineal pain. The latter occurred in 30 patients undergoing treatment and none for active surveillance [31▪▪].

PDT is exclusive in that it has a phase III RCT showing safety, efficacy and decent oncologic outcome, yet it has only been used for low risk patients, with the active surveillance group showing a very high rate of progression. Also, patients must be

protected from light during the procedure, and avoid direct sunlight for 48 h postoperatively to avoid further side effects. Further trials are currently ongoing including higher-grade tumours.

CONCLUSION

Focal therapy is usually considered to be the ablation of a visible index lesion of clinically significant cancer. In selected patients, focal therapy is well tolerated and efficacious. Side effects, such as erectile dysfunction and incontinence, occur less after focal therapy than after whole-gland treatment. Further trials, or analysis of large retrospective cohorts, are needed before long-term oncologic outcome can be properly assessed and focal therapy can be considered a standard treatment for localized PCa. At this point, however, patients who do fit into the criteria set for focal therapy can and should be offered to partake in a clinical trial involving focal therapy.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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