

## New and established technology in focal ablation of the prostate: a systematic review

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## ABSTRACT

Context: focal therapy of prostate cancer has been proposed as an alternative to whole-gland treatments.

Objective: to summarise the evidence regarding sources of energy employed in focal therapy.

Evidence Acquisition: Embase and Medline (PubMed) were searched from 1996 to 31<sup>st</sup> October 2015 following the PRISMA statement. Ongoing trials were selected from electronic registries.

Evidence Synthesis: thirty-seven articles reporting on 3,230 patients undergoing focal therapy were selected. 13 reported on high intensity focused ultrasound (HIFU), 11 on cryotherapy, three on photodynamic therapy (PDT), four on laser interstitial thermotherapy (LITT), two on brachytherapy, three on irreversible electroporation (IRE), and one on radiofrequency (RFA). HIFU, cryotherapy, PDT and brachytherapy have been assessed in up to stage 2b studies. LITT and IRE have been evaluated in up to stage 2a studies. RFA has been evaluated in one stage 1 study. Median follow-up varied between 4-61 months, and median rate of serious adverse events ranged between 0-10.6%. Pad-free leak-free continence and potency were obtained in 83.3-100% and 81.5-100%, respectively. In series with intention-to-treat, the median rate of significant and insignificant disease at control biopsy varied between 0-13.4% and 5.1-45.9%, respectively. Main limitations are the length of follow-up, the absence of a comparator arm, and study heterogeneity.

Conclusion: focal therapy has been evaluated using seven sources of energy in single-arm retrospective and prospective development studies up to stage 2b. Focal therapy seems to

have minor impact on quality of life and genito-urinary function. Cancer-control is encouraging, although this needs to be verified in high quality comparative effectiveness studies.

Patient summary: seven sources of energy have been employed to selectively ablate discrete areas of prostate cancer. There is high evidence that focal therapy is safe and has low detrimental impact on continence and potency. The oncological outcome has yet to be evaluated against standard of care.

## INTRODUCTION

In the last decade, focal therapy has been evaluated as a novel strategy in selected men harbouring localised prostate cancer. The aim of this tissue-preserving strategy is to maintain the oncological benefit of active treatments, while optimizing genito-urinary function. Focal therapy has as its objective the eradication of clinically significant disease thereby conferring to the individual a transition from a moderate or high-risk status to a lower one. This process aims to preserve as much tissue as is compatible with treating the target volume plus a margin. This approach seeks to protect from injury key structures whose integrity is essential for stable genito-urinary function (neurovascular bundles, urethral sphincter and bladder neck)(1). Further, the bladder and the rectum, two structures that can be impaired by radiation therapy, are fully preserved. Although partial surgery and focal ablation in almost all solid cancers are accepted options in eligible patients, the legitimacy of focal therapy in prostate cancer is debated as this malignancy is multifocal in most cases(2, 3).

While comparative effectiveness research against standard of care options is lacking, the rationale supporting this strategy relies on evidence-based elements. First, the natural history of the disease seems to be linked to the 'index lesion' in the majority of men, and secondary low grade lesions seem to have an indolent behaviour in most if not all cases(4-6). Second, our ability to risk stratify men at a regional level within the prostate has significantly increased. There is growing evidence that the use of multiparametric MRI with targeted and mapping biopsy allows the detection of the index lesion with reliability over 90%(7). Third, these diagnostic tools together are able to rule out clinically significant lesions within discrete areas of the prostate with again accuracy over 90%(7).

Focal therapy has been delivered employing a number of sources of energy: high intensity focused ultrasound (HIFU), cryotherapy, photodynamic therapy (PDT), laser interstitial thermotherapy (LITT), brachytherapy, irreversible electroporation (IRE), and radiofrequency

ablation (RFA). The aim of this systematic review was to summarise the stage of assessment and the evidence available with respect to each of these sources of energy.

## EVIDENCE ACQUISITION

### *Search Strategy and Selection Criteria*

This systematic review was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(8). Embase and Medline (through Pubmed) were searched systematically using medical subject headings including “(<prostate cancer> OR <prostatic neoplasms>) AND (<focal> OR <subtotal> OR <hemiblacion> OR <quadrant>)”. The search was limited to studies reporting focal therapy outcomes between 1996 to October 31st, 2015. Electronic links to related articles and references of selected articles were hand-searched. Additional relevant articles were selected from authors’ bibliography. In addition, ongoing and recruiting registered trials were retrieved from ClinicalTrial.gov and the International Standard Randomised Controlled Trial Number (ISRCTN) registry to assess the current status of evaluation of each source of energy.

Eligible articles included meta-analyses, randomized controlled trials (RCTs) or prospective case series including a control group, prospective development studies and retrospective case-series investigating ablative techniques to treat patients with biopsy-proven prostate cancer in a subtotal manner (focal, quadrant, hemiblacion, dog-leg etc.) in the primary setting. Case reports were excluded, as well as review articles and congress abstracts. Studies related to “whole-gland treatment” or performed in a salvage treatment setting

were excluded while studies involving focal treatment followed by radical prostatectomy were included. The search was limited to human studies and English language. Eligibility was determined by two separate reporters (MV and YC) using the Covidence software ([www.covidence.org](http://www.covidence.org)). Covidence is a web-based software platform designed to ease and improve systematic reviews by facilitating duplicates exclusion and independent selection process from citation screening to data extraction. It also helps with resolution of discrepancies and agreement by consensus. In case of persistent discrepancies after discussion, the senior author (ME) arbitrated. Beside the source of energy used to ablate, at least one of the following main outcome measures had to be reported: oncological outcomes, morbidity or functional outcomes. All studies of interest were obtained as full text articles and scrutinized thoroughly. Relevant data were extracted and documented in a data extraction form developed a priori. In cases of potential duplicated datasets, the study was excluded. If overlapping was partial (< 50% sample size) and over a limited period of time, all studies were fully reported although the risk of duplication was highlighted.

### *Objectives*

The primary objective of this study was to determine the stage of assessment of sources of energy currently used in focal therapy of the prostate. We employed the recommendation from the IDEAL statement which define the stage of assessment according to the design, the sample size, the outcome and the outcome measures used to evaluate a novel surgical procedure(9). Secondary objectives included the definition of the target population, the type of focal therapy delivered, and the assessment of oncological, toxicity and functional

outcome.

#### *Data extraction form*

The following data were extracted from each study: source of energy, study design, stage of assessment, type of ablation, patients' characteristics (age, sample size, preoperative biopsy, preoperative imaging, spatial location of the tumour, PSA, Gleason score and risk stratification), length of follow-up, percentage of patients lost to follow-up, length of hospital stay, disease control outcomes (reason and type of post-focal sampling, presence of residual significant and insignificant disease in the treated and untreated area, transition to secondary and radical treatment, transition to metastatic disease, overall and disease-specific survival), morbidity (serious adverse events, stricture rate, urinary retention rate, urinary infection rate, and recto-urethral fistula rate), and functional outcome (leak-free and pad-free continence, potency preservation, new use of PDE-5 inhibitors and trifecta rate). When available, the patient-reported outcomes measures (PROMs) used were recorded; their variation between beginning and last follow up was also indicated for completeness (deterioration, stability or improvement).

As we could not retrieve raw data, we accepted the definitions used by single studies to risk stratify the population - such threshold for clinically significant disease and risk stratification. When not available, we considered the presence of secondary pattern  $\geq 4$  in control biopsy as clinically significant disease.

### *Statistical analysis*

Continuous variables are given using median, interquartile range (IQR) or overall range according to availability. The mean with standard deviation (SD) was used when the former was not available. Categorical variables are given using frequencies and percentages. To calculate oncological and functional outcomes, decision had to be made with respect to the denominator considered. For determining overall oncological outcomes of every series, only series with intention to treat were considered, although the results of each series were displayed for completeness. Men lost to follow up were excluded from the denominator of all outcomes. In determining the rate of positive biopsy in studies with mandatory post-treatment biopsy, only those men actually undergoing biopsy were part of the denominator. Clinically significant threshold was accepted from each study; if not available, any Gleason pattern 4 was considered as clinically significant disease. Overall biopsy results considered only series with intention to treat, and excluded stage I studies. Functional outcomes were determined as relative rates. For instance, to determine potency, only potent patients prior to focal therapy were part of the denominator. All analyses were performed using SPSS® version 20.0 (Armonk, NY: IBM corporation).

### EVIDENCE SYNTHESIS

Thirty-seven studies were included in the final analysis(10-46) (figure 1). Overall, 13 studies reported on focal HIFU, 11 on focal cryotherapy, three on focal PDT, four on focal LITT, two



on focal brachytherapy, three on focal IRE, and one on focal RFA (figure 2). Across all series, 3,230 patients were treated using any source of energy delivered in a focal manner.

Data extracted from each record are summarised in tables 1-3 in order of the source of energy considered, and of year of publication. In table 1, the design of the study, the eligibility criteria, the ablation strategy and the study population are displayed. In table 2, the type and length of follow-up, the ablation and oncological outcomes are displayed. In table 3, the morbidity, the functional outcomes including outcome measures are displayed.

## HIFU

HIFU is a form of thermal energy that leads to tissue ablation by raising the temperature over 60° using focused high-intensity ultrasound. Tissue ablation is the consequence of two mechanisms: coagulative necrosis due to the extreme temperature, and internal cavitation due to the interaction between water and ultrasounds. Modern devices delivering HIFU to the prostate are transurethral or transrectal, and use in-bore guidance or MR-TRUS fusion, respectively.

Of the 13 series evaluating focal HIFU in 346 men, six were considered stage 1, four stage 2a, and three stage 2b. Two studies were retrospective case series; the others were prospective proof of concept, case series, or development studies. Two series evaluated in-bore transurethral HIFU; the others transrectal focal HIFU. Five series did not clearly report the type of entry biopsy; in the remaining, TRUS standard biopsy, TRUS extended protocols, targeted biopsy and/or template mapping biopsy were performed. MRI was used in 11 series (84.6%). The study population included low, intermediate and high risk patients with median age at 63 years (IQR 62-70) and median PSA at 7.3 ng/ml (IQR 5.8-8.3).

Median follow-up was 12 months (IQR 0-28.5) with 12 series including mandatory sampling and one study including biopsy only 'for cause'. A part from four stage I studies in which men underwent radical prostatectomy early after focal HIFU, the remaining studies employed targeted biopsy, TRUS standard or extended biopsy, and/or template mapping biopsy. In the series with intention to treat, overall presence of significant and insignificant cancer were 0% (IQR 0-13.5%) and 23.3% (IQR 10.4%-38.1%), respectively. However, the first outcome was reported only in five series. Transition to secondary local treatment, overall and disease-specific survival were 7.8% (IQR 3.8-10.3%), 100% (IQR 100-100%) and 100% (IQR 100-100%), respectively. SAE occurred in 1.5% patients (IQR 0-3.2%). Pad-free continence and potency preservation were achieved in 100% (IQR 95-100%) and 88.6% (IQR 78.5-97.5%), respectively. Trifecta rate were reported only in three series with a median at 83.8%.

### Cryotherapy

Cryotherapy is a thermal form of energy relying on extreme cold temperature leading to tissue ablation by a number of mechanisms such as osmotic injury, cytolysis, apoptosis and vascular damage. The procedure is performed through cryo-needles positioned in the target area through the perineum. A given distance is maintained between the needles in order to form a homogeneous ice-ball with no skip lesion in the middle.

Of the 11 series evaluating focal cryotherapy in 1,950 patients, four were considered stage 2a, and seven stage 2b. All studies were retrospective except one prospective case series and one prospective development study. Four series did not clearly report the type of entry biopsy; in the remaining, TRUS standard +/- targeted biopsy, or template mapping biopsy

were performed. The study population included low, intermediate and high risk patients with median age at 66.8 years (IQR 63.8-68.1) and median PSA at 6.3 ng/ml (IQR 5.2-7.2).

Median follow-up was 26 months (IQR 17.6-48.8) with three series including mandatory sampling and eighteen including biopsy only 'for cause'. Control biopsy included TRUS standard +/- targeted biopsy. Overall presence of significant and insignificant cancer were at 5.4% (IQR 1.1-7.3%) and 13% (IQR 4-19.4%), respectively. However, the first outcome was reported only in four series. Transition to secondary local treatment, overall and disease-specific survival were 7.6% (IQR 6.1-13.8%), 100% (IQR 100-100%) and 100% (IQR 100-100%), respectively. SAE occurred in 2.5% patients (IQR NA), although only two series reported these using a standardised classification. Pad-free continence and potency preservation were achieved in 100% (IQR 100-100%) and 81.5% (IQR 69.3-88.2%), respectively. Trifecta rate was reported in no series.

## PDT

PDT ablation relies on the activation of a vascular photosensitiser within the target area, which leads to the formation of reactive oxygen species causing vessels thrombosis, apoptosis and necrosis. In the prostate, laser activating fibers are positioned transperineally, and the photosensitiser is administered intravenously.

Three prospective development studies stage 1 to 2b evaluating focal PDT in 116 patients have been reported in the literature. TRUS standard or template mapping biopsy and MRI were used to identify eligible patients. The study population included low and intermediate risk patients with median age at 63.9 (IQR NA), and median PSA at 6.4 ng/ml (IQR NA).

When reported, median follow-up was homogeneous at 6 months (IQR 6-6) with all three studies including mandatory sampling using TRUS standard biopsy. Presence of significant cancer was reported by none of the studies; insignificant cancer was present in 45.9% (IQR NA). Transition to secondary local treatment was reported only in the stage 1 study, and was at 83.3% (IQR NA). Overall and disease-specific survival were 100% (IQR 100-100%) and 100% (IQR 100-100%), respectively. SAE occurred in 10.6% patients (IQR NA). Pad-free continence rates were not available. Potency preservation was achieved in 88.4% (IQR NA), respectively. Trifecta rate was reported in no study.

#### LITT

LITT is another thermal energy leading to ablation by raising the temperature directly within the target tissue. As opposite to PDT, LITT is a direct thermal energy, and does not employ photosensitizers. The laser fibers are positioned transperineally or transrectally; the number of fibers is dependent by the volume of the target tissue.

Four prospective studies stage 1 to 2a evaluating focal LITT in 50 patients have been reported in the literature. TRUS standard and MRI were systematically used to identify eligible patients. One study included only men with low risk disease, whereas the other studies included also Gleason  $\leq$  4+3 although risk stratification was not clearly reported. Median age was 63.5 (IQR 57.6-66); median PSA was 5.4 ng/ml (IQR 4.5-5.7).

Median follow-up was 4.5 months (IQR 0.8-6) with all series including mandatory sampling after treatment. In the stage 1 study, all men underwent radical prostatectomy, whereas in the other three studies men underwent TRUS standard and/or targeted biopsy. Overall presence of significant and insignificant cancer were at 4.8% (IQR NA) and 22.2% (IQR NA),

respectively. Transition to secondary local treatment, overall and disease-specific survival were 0% (IQR NA), 100% (IQR 100-100%) and 100% (IQR 100-100%), respectively. No SAE were reported in any study. Pad-free continence and potency preservation were achieved in 100% (IQR 100-100%) and 100% (IQR 100-100%), respectively. Trifecta rate was reported in 75% men (IQR NA).

### Brachytherapy

Brachytherapy is an established whole-gland treatment in prostate cancer. Sealed radiating seeds are inserted through the perineum in the prostate. When used as a focal option, brachytherapy is used as a monotherapy with no conjunction of external beam radiation, and only a part of the prostate is planned to receive the radiation dose needed to achieve complete treatment.

Two retrospective stage 2a-b case series evaluating focal brachytherapy in 339 patients have been reported in the literature. Both series used MRI at the outset. One series did not report the type of entry biopsy; in the other, all men underwent TRUS extended biopsy. The study population included low and intermediate risk patients with median age at 62.3 (IQR NA), and median PSA at 6 ng/ml (IQR NA).

One series did not report the length of follow up, while the other had a median follow up at 61 months (IQR 33-88). Both series incorporated TRUS standard biopsy, although in one sampling was mandatory, whereas in the other it was 'for cause'. Overall presence of significant and insignificant cancer were at 1.8% (IQR NA) and 5.1% (IQR NA), respectively. No patient had secondary local treatment (IQR NA). Overall survival was reported by no study, whilst disease-specific survival was at 99.9% (IQR NA). SAE were reported by no series

using a standardised classification. Pad-free continence was reported only by one series and was at 95.2%. Potency preservation and trifecta rate were reported by no series.

## IRE

IRE ablation delivers high voltage low energy electric current within the target tissue. In the prostate, this is achieved by positioning electro-needles through the perineum under TRUS guidance.

One proof of concept stage 1, and two retrospective cases series stage 2a studies evaluating focal IRE in 66 patients have been reported in the literature. TRUS standard, template mapping biopsy and/or targeted were used to identify eligible patients. The study population included low and intermediate risk patients with median age at 65 (IQR NA), and median PSA at 6.1 ng/ml (IQR NA).

Median follow-up was at 6 months (IQR NA) with different follow up strategies and triggers for biopsy. The only stage I study with no intention to treat incorporated mandatory radical prostatectomy after treatment. One stage 2a incorporated mandatory template mapping biopsy after treatment. Overall, presence of significant cancer and insignificant cancer were at 13.4% (IQR NA) and 32.4%. Transition to secondary local treatment was at 11.9%. Overall and disease-specific survival were 100% (IQR 100-100%) and 100% (IQR 100-100%), respectively. SAE occurred in 0% patients (IQR NA). Pad-free continence and potency preservation were achieved in 100% (IQR 100-100%) and 95% (IQR NA), respectively. Trifecta rate was reported in no study.

## RFA

RFA is another thermal procedure delivering medium frequency alternating current in order to generate killing heat within the target area. Similar to all other sources of energy except HIFU in the prostate, it is delivered by inserting specific needles transperineally.

Only one proof of concept stage 1 study evaluating focal RFA prior to radical prostatectomy in 15 men has been reported. No details on the study population were available. None of the other oncological and functional outcome could be extrapolated. Residual tumour was found in all men, although there was no intention to treat in this study.

## DISCUSSION

This systematic review shows that seven sources of energy have been delivered as focal strategies in a clinical setting. HIFU, cryotherapy, PDT and brachytherapy have been assessed in up to stage 2b studies including 346, 1,950, 116 and 339 patients, respectively. LITT and IRE have been evaluated in up to stage 2a studies in 50 and 66 patients, respectively. RFA has been evaluated in one stage 1 study including 15 patients. Overall, this systematic review shows that focal therapy rarely causes significant morbidity and seems to have minor impact on quality of life, although the oncological effectiveness in the long-term needs to be further evaluated.

While this systematic review was comprehensive, there are key aspects that need to be debated prior to discuss further the results. The assessment of novel sources of energy should be distinguished by the evaluation of the strategy itself, namely focal therapy. The success of sources of energy delivered in a focal manner is strictly dependent on our ability to select eligible patients. Although mpMRI has high performance to rule-in and rule-out

clinically significant disease at a regional level, the strategy is not perfect and some relevant cancers might be missed. The issue is even more relevant as the definition of clinically significant disease is debated, and varying the threshold of significance has a substantial impact on the performance of our diagnostic tests(47, 48). Also, the high performance reported in the literature comes from high volume expert centers; reproducibility needs to be verified yet.

Further, no study had a comparator arm represented by a standard treatment approach, and most focused on safety, feasibility, functional outcomes and short- to mid-term outcomes. Therefore, while the results should be considered with respect to the evaluation of these sources of energy within early stage studies, oncological effectiveness of focal therapy is yet to be defined for different reasons. First, if we consider that the aim of focal therapy is to treat only significant disease, some series included a number of men harboring what is currently considered insignificant disease, and there was wide variation in the definition of clinically significant disease. Second, while short- to mid-term oncological outcome, as measured by negative-biopsy rate and/or avoidance of other local treatments, seems encouraging, it should be emphasized that some studies used discordant tools for selecting and following eligible men. For instance, intensive sampling was employed to select suitable patients, but only random systematic sampling was employed to diagnose local recurrence. There is awareness about this limitation in the research community, and recent trials incorporate the same precise diagnostic tools at the outset and in the follow-up. Third, radical prostatectomy series show that although many patients have unmeasurable disease (undetectable PSA) immediately after treatment, depending on the study population, some will recur in the first years, and up to 10% recur after 10 years.



Finally, heterogeneity in study design including target population, risk stratification, type of focal ablation, follow up schedule, as well as outcome measures of morbidity and ablation do not allow to draw reliable comparison between the different sources of energy. For instance, although focal therapy has been lately defined as ablation of the index lesion only by a group of experts, there was intra- and inter-study variability in the ablation strategy with many early series using pragmatic template - such as hemiablation(49).Also, in the case of lesion-only ablation, the location of the tumor has a great impact on functional outcomes, especially the distance from the sphincter and neurovascular bundles is likely to influence continence and potency, respectively.

Focal HIFU and cryotherapy have been the most investigated sources of energy so far in terms of number of studies, stage of assessment and length of follow up. Whilst the evidence regarding focal HIFU relies on a number of prospective studies, most studies investigating focal cryotherapy are retrospective, but it should be noted that these have longer follow-up. Additional studies are ongoing and will further add essential evidence to move forward in the evaluation of these technologies. Two studies, one evaluating focal HIFU and one evaluating focal cryotherapy have fully recruited the expected sample size of 272 and 100 men, respectively, and results will be available in the upcoming months (NCT01194648 and NCT00877682). Both studies incorporate mandatory control biopsy of the treated as well of the untreated area after three years follow up. These studies will verify not only the ablation results of these two modalities in the mid-term, but will also verify the natural course of untreated areas after focal therapy. The multicenter design and the prospective nature with validated outcome measures will also clarify the reproducibility of these procedures and the impact of quality of life, respectively, with longer follow up.

Focal PDT has been offered to patients only within prospective clinical trials, the phase of assessment is 2b, but a phase 3 randomized controlled trial has completed accrual, and results are awaited (NCT01310894). Across 12 European countries, 400 patients with low risk disease were randomized to focal PDT against active surveillance. Absence of residual cancer at two-year control biopsy and treatment failure were the primary end-points. This study represents the first randomized study including a focal therapy arm against a standard arm, represented by active surveillance. Although the results will provide high quality evidence in this setting and will clarify the outcomes of focal PDT within a multicenter trial, further trials will be needed in order to consider focal therapy as a legitimate option. High quality evidence at present shows the study population does not benefit from immediate treatment, and can be safely managed by active surveillance. Future trials will need to incorporate mainly - if not exclusively - men harboring clinically significant disease who are likely to benefit from treatment, and in whom an oncological benefit can be measured.

Focal LITT is in the early stage 2a of assessment. The results seem encouraging with a safe toxicity profile although the short monitoring after treatment up to 6 months points to further assessment needed. This is under the way in three stage 1 to 2a trials with longer monitoring up to three years. Focal brachytherapy is currently recruiting in four stage 2a to 2b prospective studies. While the oncological outcome and toxicity profile of whole-brachytherapy are well defined, the ongoing studies are very important as the available evidence in the focal setting is based exclusively on retrospective data. Focal IRE is another novel source of energy accounting for one stage 1 study and two stage 2a retrospective studies. The procedure seems well tolerated; however, reliable evidence of ablation efficacy is lacking. One stage 2a prospective development study evaluating focal IRE will be soon

reported, and another stage 2b trial supported by the Endourological society will start soon in six European centres. These trials are awaited in order to further evaluate this technology in a rigorous manner. Only one stage 1 study is at present available for RFA, and it is impossible to make any comments about this source of energy in prostate cancer. However, three stage 2a prospective development studies are recruiting men for focal RFA in order to evaluate this technology in a rigorous manner.

The PART trial is a key study to push the evaluation of focal therapy forward. In a multicenter RCT, 100 men will be randomized between radical prostatectomy (control arm) against focal HIFU (interventional arm). The hypothesis is that the effectiveness of treatment would be comparable, although focal therapy will reduce treatment-related toxicity, as measured by validated outcome measures. The main aim is to assess the feasibility of a RCT in this setting with the primary outcome being to recruit over 50% eligible men. In case of positive results, a stage III trial powered to show statistically significant results would be planned.

Delivering a RCT in focal therapy against a standard option will be challenging(50). In the area of prostate cancer, there are few examples of success, and many examples of failures. Many trials in the areas were preemptively closed for two reasons: patients' unwillingness to be randomized in different treatments, and clinicians' lack of equipoise(50). These challenges are very likely to be encountered in a RCT comparing focal therapy to a standard option in light of the different toxicity profiles of the two arms, as well as the debate surrounding the legitimacy of focal therapy among clinicians. If such trial would be revealed unfeasible, an alternative way of randomization should be explored - such as what the researchers have applied within the ProtecT trial - or alternative trial designs should be considered in order to evaluate in a rigorous and timely manner a focal therapy option(51).

## CONCLUSIONS

Seven sources of energy have been delivered in a focal manner in men with localised prostate cancer. HIFU, cryotherapy, PDT and brachytherapy have been investigated in up to stage 2b trials, LITT and IRE in up to stage 2a trials, and RFA in only one stage 1 trial. Focal therapy seems safe and appears to offer good preservation of genito-urinary function. Cancer control in studies with intention to treat is encouraging, although this needs to be verified against standard of care in high quality comparative effectiveness trials.

## LEGENDS

### Figure 1

Preferred reporting items for systematic review and meta-analysis (PRISMA) flowchart.

### Figure 2

Schematic representation of the sources of energy used in actual series: HIFU (a), cryotherapy (b), PDT (c), LITT (d), brachytherapy (e), IRE (f) and RFA (f).

### Table 1

Design, focal therapy strategy and study population of the 37 series included.

### Table 2

Length of follow-up, ablation and oncological results of the 37 series included.

Table 3

Morbidity and functional outcomes of the 37 series included.

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### Conflict of Interest

M. Emberton receive funding from USHIFU, GSK, AngioDynamics and Advanced Medical Diagnostics for clinical trials. M. Emberton is a paid consultant to AngioDynamics, Steba Biotech and SonaCare Medical (previously called USHIFU). He has previously received consultancy payments from Oncura/GE Healthcare and Steba Biotech. None of these sources had any input whatsoever into this article.

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