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New and Established Technology in Focal Ablation of the Prostate: A Systematic Review

Massimo Valerio[a,b,c,†,*], *Yannick Cerantola*[c,†], *Scott E. Eggener*[d], *Herbert Lepor*[e], *Thomas J. Polascik*[f], *Arnauld Villers*[g], *Mark Emberton*[a,b]

[a] *Division of Surgery and Interventional Science, University College London, London, UK;* [b] *Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK;* [c] *Department of Urology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland;* [d] *Section of Urology, University of Chicago, Chicago, IL, USA;* [e] *Department of Urology, New York University School of Medicine, New York, NY, USA;* [f] *Division of Urology, Duke University Medical Center, Durham, NC, USA;* [g] *Department of Urology, Lille University Medical Center, Lille University, France*

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Abstract

Context: Focal therapy of prostate cancer has been proposed as an alternative to whole-gland treatments.
Objective: To summarize the evidence regarding sources of energy employed in focal therapy.
Evidence acquisition: Embase and Medline (PubMed) were searched from 1996 to October 31, 2015 following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. Ongoing trials were selected from electronic registries. The stage of assessment of each source of energy was determined using the Idea, Development, Exploration, Assessment, Long-term study recommendations.
Evidence synthesis: Thirty-seven articles reporting on 3230 patients undergoing focal therapy were selected. Thirteen reported on high-intensity focused ultrasound, 11 on cryotherapy, three on photodynamic therapy, four on laser interstitial thermotherapy, two on brachytherapy, three on irreversible electroporation, and one on radiofrequency. High-intensity focused ultrasound, cryotherapy, photodynamic therapy, and brachytherapy have been assessed in up to Stage 2b studies. Laser interstitial thermotherapy and irreversible electroporation have been evaluated in up to Stage 2a studies. Radiofrequency has been evaluated in one Stage 1 study. Median follow-up varied between 4 mo and 61 mo, and the median rate of serious adverse events ranged between 0% and 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% and 13.4% and 5.1% and 45.9%, respectively. The main limitations were the length of follow-up, the absence of a comparator arm, and study heterogeneity.
Conclusions: 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 a minor impact on quality of life and genito-urinary function. Oncological effectiveness is yet to be defined against standard of care.
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.

† These authors are joint first authors.
* Corresponding author. Division of Surgery and Interventional Science, University College London, 74 Huntley Street, London W1P 7NN, UK. Tel. +44 (0)20 3447 9194; Fax: +44 (0)20 3447 9303.
E-mail address: massimo.valerio.12@ucl.ac.uk (M. Valerio).

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1. Introduction

In the last decade, focal therapy has been evaluated as a novel strategy in selected men harboring localized 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 key structures from injury 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. Firstly, 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 behavior in most if not all cases [4–6]. Secondly, 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 magnetic resonance imaging (MRI) with targeted and mapping biopsy allows the detection of the index lesion with reliability over 90%, at least in expert centers [7]. Thirdly, 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: (1) high-intensity focused ultrasound (HIFU), (2) cryotherapy, (3) photodynamic therapy (PDT), (4) laser interstitial thermotherapy (LITT), (5) brachytherapy, (6) irreversible electroporation (IRE), and (7) radiofrequency ablation (RFA). The aim of this systematic review was to summarize the stage of assessment and the evidence available with respect to each of these sources of energy.

2. Evidence acquisition

2.1. Search strategy and selection criteria

This systematic review was performed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analyses 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 <hemiablation> OR <quadrant>)." The search was limited to studies reporting focal therapy outcomes between 1996 to October 31, 2015. Electronic links to related articles and references of selected articles were hand searched. Additional relevant articles were selected from authors' bibliographies. In addition, ongoing and recruiting registered trials were retrieved from ClinicalTrial.gov and the International Standard Randomized Controlled Trial Number 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, hemi-ablation, 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). Covidence is a web-based software platform designed to ease and improve systematic reviews by facilitating duplicates exclusion and the independent process performed by the reviewers, from 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. Besides the source of energy used to ablate, at least one of the following main outcome measures had to be reported: (1) oncological outcomes, (2) morbidity, or (3) 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.

2.2. 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 Idea, Development, Exploration, Assessment, Long-term study statement which defines 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]. Briefly: (1) Stage 1 (Innovation) refers to the first description of a procedure, (2) Stage 2a (Development) refers to the development phase in which the procedure is carried out by early adopters in well selected patients, but the intervention needs to be refined, (3) Stage 2b (Exploration) refers to the exploration of indications, quality control measures, and reproducibility in larger groups of patients, (4) Stage 3 (Assessment) refers to comparative effectiveness research of the novel procedure against standard of care, (5) Stage 4 (Long-term) refers to the implementation and monitoring of established

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procedures. Secondary objectives included the definition of the target population, the type of focal therapy delivered, and the assessment of oncological, toxicity, and functional outcome.

2.3. Data extraction form

The following data were extracted from each study: (1) source of energy, (2) study design, (3) stage of assessment, (4) type of ablation, (5) patients' characteristics (age, sample size, preoperative biopsy, preoperative imaging, spatial location of the tumor, prostate specific antigen [PSA], Gleason score, and risk stratification), (6) length of follow-up, percentage of patients lost to follow-up, length of hospital stay, disease control outcomes (reason and type of postfocal sampling, presence of residual significant and insignificant disease in the treated and untreated area, probability of transition to secondary and radical treatment, transition to metastatic disease, overall survival, and disease-specific survival), (7) morbidity (serious adverse events, stricture rate, urinary retention rate, urinary infection rate, and recto-urethral fistula rate), and (8) functional outcome (leak-free and pad-free continence, potency preservation, and new use of phosphodiesterase type-5 inhibitors). 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 as the 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.

2.4. Statistical analysis

Continuous variables are given using median, interquartile range (IQR), or overall range according to availability. The mean with standard deviation was used when the former was not available. Categorical variables are given using frequencies and percentages. To calculate oncological and functional outcomes, a decision had to be made with respect to the denominator considered. For determining overall oncological outcomes, 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. To summarize outcomes based on continuous values, we used median and IQR. All analyses were performed using SPSS version 20.0 (IBM Corporation, Armonk, NY, USA).

3. Evidence synthesis

Thirty-seven studies were included in the final analysis (Fig. 1) [10–46]. 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 (Fig. 2). Across all series, 3230 patients were treated using any source of energy delivered in a focal manner.

Data extracted from each record are summarized in Tables 1–3 in order of the source of energy considered, and of the 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. In Table 4, the design of ongoing registered trials investigating focal therapy is displayed.

3.1. 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: (1) coagulative necrosis due to extreme temperature, and (2) 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-transrectal ultrasound (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 of 63 yr (IQR: 62–70 yr) and median PSA of 7.3 ng/ml (IQR: 5.8–8.3 ng/ml).

Median follow-up was 12 mo (IQR: 0–28.5 mo) with 12 series including mandatory sampling and one study including biopsy only *for cause*. Apart from four Stage I studies in which men underwent radical prostatectomy soon 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, the overall presence of significant and insignificant cancer was 0% (IQR: 0–13.5%) and 23.3% (IQR: 10.4%–38.1%), respectively. However, the first outcome was reported only in five series. The probability of transition to secondary local treatment was 7.8% (IQR: 3.8–10.3%); overall and disease-specific survival were 100% (IQR:

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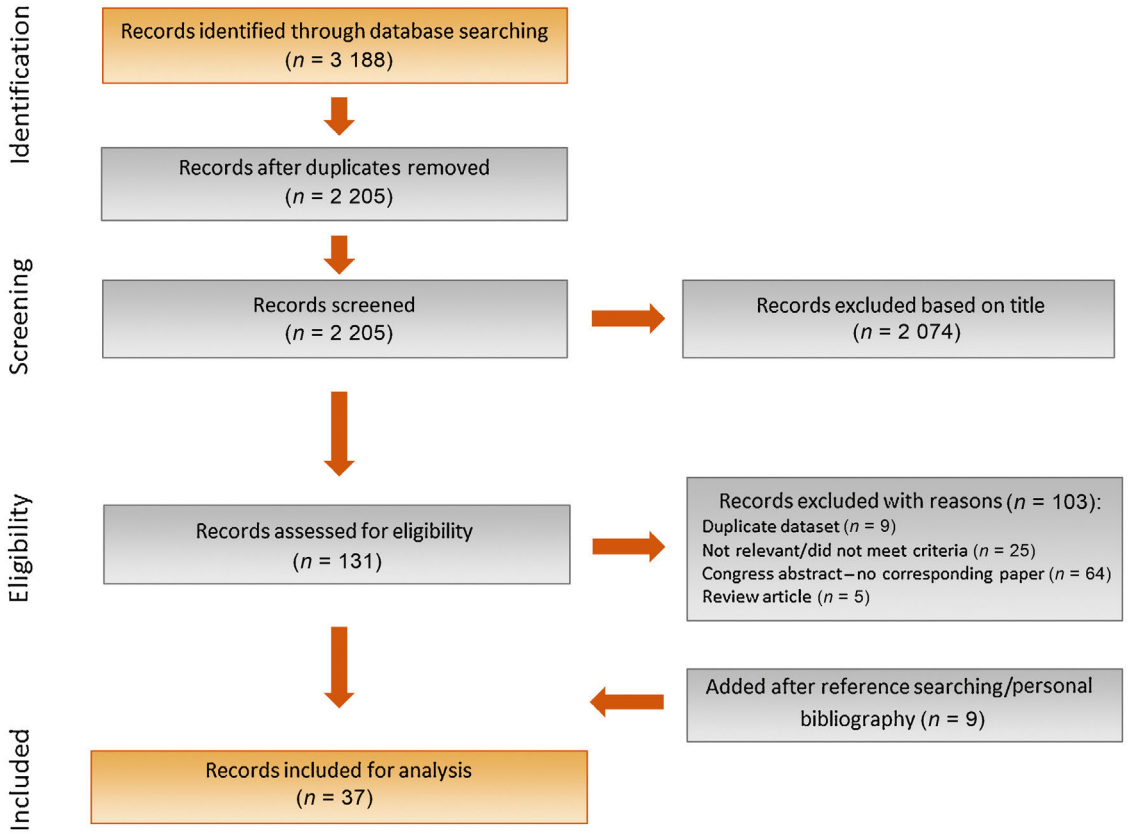

Fig. 1 – Preferred Reporting Items for Systematic Review and Meta-analysis flowchart.

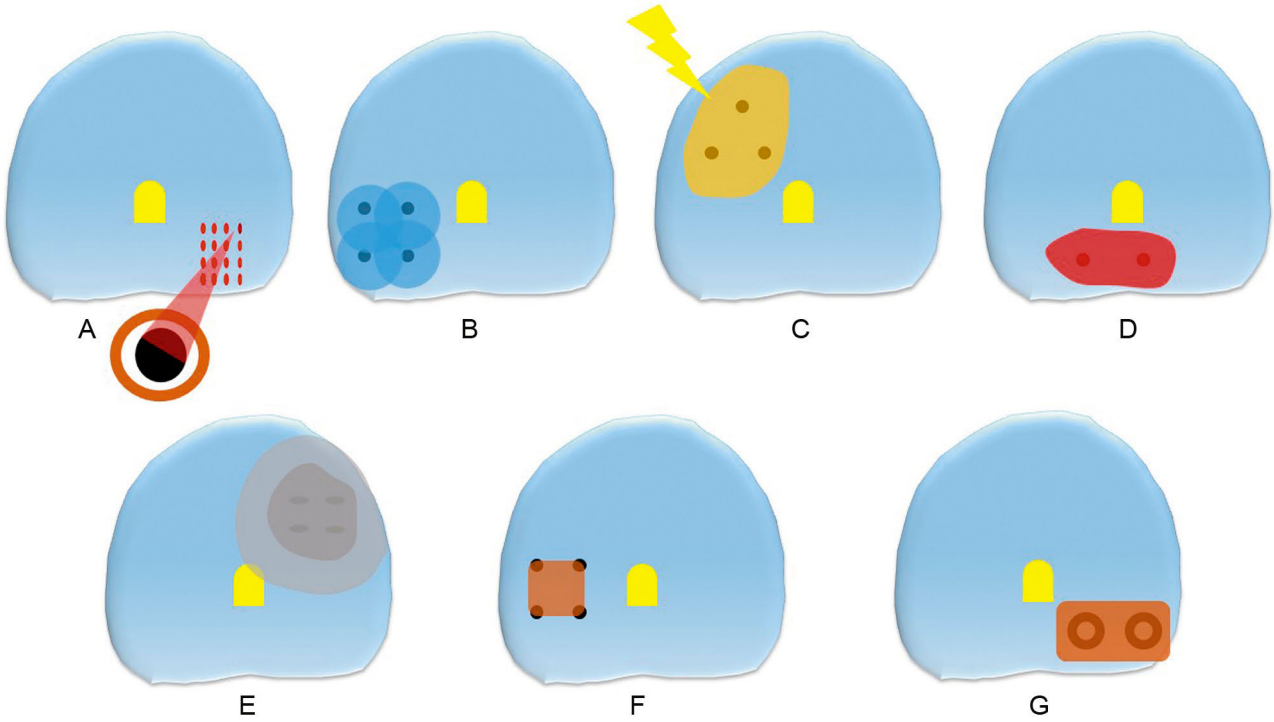

Fig. 2 – Schematic representation of the sources of energy used in actual series: (A) high-intensity focused ultrasound, (B) cryotherapy, (C) photodynamic therapy, (D) laser-induced interstitial thermotherapy, (E) brachytherapy, (F) irreversible electroporation, and (G) radiofrequency ablation.

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Table 1 – Design, focal therapy strategy, and study population of the 37 series included

Ref.	Source of energy	IDEAL stage	Design	Biopsy	Imaging	Location	Type of ablation	No.	Age (yr)	PSA (ng/ml)	Gleason score	Risk stratification
Madersbacher 1995	HIFU	1	Prospective development study	NR	NR	Unifocal or organ-confined	Hemi-ablation or focal ablation with no intention to treat	29	64; 7.2 (mean; SD)	24.5; 18.8 (mean; SD)	NR	NR
Beerlage 1999	HIFU	1	Retrospective case series	TRUS standard	MRI	NR	Hemi-ablation with no intention to treat	14	62; 55–69 (mean; range)	10.8; 3.5–20 (mean; range)	NR	NR
Muto 2008	HIFU	2a	Prospective case series	TRUS extended	MRI	Unilateral	Dog-leg ablation	29	72; 62–80 (median; range)	5.4; 1.8–25.1 (median; range)	6: 55.2% (n = 16); 7: 20.7% (n = 6); 8+: 17.2% (n = 5); unknown: 6.9% (n = 2)	NR
Ahmed 2011	HIFU	2a	Prospective development study	Template mapping	MRI	Unilateral	Hemi-ablation	20	60.4; 5.4 (mean; SD)	7.3; 2.8 (mean; SD)	NR	Low: 25% (5/20); intermediate: 75% (15/20)
El Fegoun 2011	HIFU	2a	Retrospective case series	NR	NR	Unilateral	Hemi-ablation	12	70; 4.8 (mean; SD)	7.3; 2.6–10 (mean; range)	3+3: 83.3% (n = 10); 3+4: 16.7% (n = 2)	NR
Ahmed 2012	HIFU	2b	Prospective development study	Template mapping	MRI	Unifocal or multifocal	Focal ablation	41	63; 58–66 (median; IQR)	6.6; 5.4–7.7 (median; IQR)	3+3: 31.7% (n = 13); 3+4: 58.6% (n = 24); 4+3: 9.8% (n = 4)	Low: 26.8% (n = 11); intermediate: 63.4% (n = 26); high: 9.8% (n = 4)
Chopra 2012	HIFU	1	Proof of concept	NR	MRI	NR	Focal ablation with no intention to treat	8	60; 49–70 (mean; range)	6.2; 2.7–13.1 (median; range)	3+3: 25% (n = 2); 3+4: 50% (n = 4); 4+3: 25% (n = 2)	NR
Dickinson 2013	HIFU	1	Proof of concept	Template mapping	MRI	Unilateral, unifocal, or multifocal	Index lesion ablation or hemi-ablation	26	61; 40–79 (mean; range)	7.7; 1.5–14.2 (mean; range)	3+3: 34.6% (n = 9); 3+4: 65.4% (n = 17)	Low: 11.5% (n = 3); intermediate: 42.3% (n = 11); high: 46.2% (n = 12)
Napoli 2013	MR-HIFU	1	Prospective development study	NR	MRI	Unifocal	Index lesion ablation	5	65.4; 50–75 (median; range)	8.8 (median; IQR and range NR)	3+3: 60% (n = 3); 3+4: 40% (n = 2)	NR
Van Velthoven 2013	HIFU	2a	Prospective development study	NR	MRI	Unifocal	Hemi-ablation	31	71; 55–83 (median; range)	5.3; 0.3–11.0 (median; range)	≤6: 61.3% (n = 19); 7: 32.2% (n = 10); ≥8: 6.5% (n = 2)	Low: 54.8% (n = 17); intermediate: 38.7% (n = 12); high: 6.5% (n = 2)
Ahmed 2015	HIFU	2b	Prospective development study	TRUS standard and/or template mapping	MRI	Unifocal	Index lesion ablation	56	63.9; 5.8 (mean, SD)	7.4; 5.6–9.5 (median, IQR)	NR	Low: 12.5% (n = 7); intermediate: 83.9% (n = 47); high: 3.6% (n = 2)
Feijoo 2015	HIFU	2b	Prospective case series	TRUS extended or template mapping	MRI	Unilateral	Hemi-ablation	71	70.2; 6.8 (mean; SD)	6.1; 1.6–15.5 (median; IQR)	3+3: 86.6% (n = 58); 3+4: 13.4% (n = 9); NR: 4 lost to follow-up	NR
Ghai 2015	MR-HIFU	1	Prospective development study	TRUS extended + targeted	MRI	Unifocal or multifocal	Index lesion ablation	4	63; 56–68 (median; range)	4.7; 0.9–6.7 (median, IQR)	3+3 (100%)	Low: 100% (4/4)
Total	HIFU or MR-HIFU	1–2b	Proof of concept to prospective development studies	Combination (see above)	MRI	Unilateral, unifocal, or multifocal	Combination (see above)	346	63 (IQR 62–70)	7.3 (IQR 5.8–8.3)	3+3 to ≥8	Low, intermediate or high
Bahn 2006	Cryotherapy	2a	Retrospective case series	TRUS standard + targeted	Color-Doppler	Unilateral	Hemi-ablation	31	63; 51–75 (mean; range)	4.9 (mean; IQR NR)	6: 84.3% (n = 23); 7: 25.8% (n = 8)	NR

Table 1 (*Continued*)

Ref.	Source of energy	IDEAL stage	Design	Biopsy	Imaging	Location	Type of ablation	No.	Age (yr)	PSA (ng/ml)	Gleason score	Risk stratification
Ellis 2007	Cryotherapy	2a	Retrospective case series	NR	NR	Unilateral	Dog-leg ablation	60	69 ± 7.8 (mean ± SD)	7.2 ± 4.7 (mean ± SD)	Gleason 6: 78.3%; Gleason 7: 20%; Gleason 8–10 1.7%	Low: 66.7%; intermediate: 23.3%; high: 10%
Onik 2007	Cryotherapy	2a	Retrospective case series	TRUS standard or template mapping	NR	Unilateral	Focal ablation	55	NR	8.3 (mean; IQR NR)	NR	Low: 47.3% (n = 26); intermediate: 36.4% (n = 20); high: 16.4% (n = 9)
Truesdale 2010	Cryotherapy	2b	Retrospective case series	TRUS standard	NR	Unilateral	Hemi-ablation	77	69.5 ± 6.7 (mean ± SD)	6.5 ± 4.9 (mean ± SD)	Gleason 6: 64.9% (n = 50); Gleason 7: 32.5% (n = 25); Gleason 8: 2.6% (n = 2)	Low: 57.1% (n = 44); intermediate: 40.3% (n = 31); high: 2.6% (n = 2)
Bahn 2012[a]	Cryotherapy	2b	Retrospective case series	TRUS standard + targeted	Color-Doppler	Unilateral	Hemi-ablation	73	64; 47–79 (median; range)	5.4; 0.01–20 (median; range)	3+3: 41% (n = 30); 3+4: 34% (n = 25); 4+3: 25% (n = 18)	Low: 33% (n = 24); intermediate: 67% (n = 49)
Ward 2012	Cryotherapy	2b	Retrospective case series	NR	NR	Organ-confined	NR	1160	67.8 ± 7.8 (mean ± SD)	NR	Gleason 6: 73.6%; Gleason 7: 20.9%; Gleason ≥8: 5.6%	Low: 46.8%; intermediate: 40.9%; high: 12.4%
Hale 2013	Cryotherapy	2a	Retrospective case series	Template mapping	NR	Organ-confined	Hemi-ablation or subtotal	26	65; 55–74 (median; range)	NR	3+3: 96.2% (n = 25); 3+4: 3.8% (n = 1)	Low: 88.5% (n = 23); intermediate: 11.5% (n = 3)
Al Barqawi 2014	Cryotherapy	2b	Prospective development study	Template mapping	NR	Organ-confined	Focal ablation	62	60.5 ± 6.8 (mean ± SD)	5.1 ± 2.2 (mean ± SD)	Gleason 3+3 or Gleason 3+4	Low to intermediate risk
Durand 2014	Cryotherapy	2b	Prospective case series	TRUS standard	MRI	Unilateral	Hemi-ablation	48	67; 50–77 (median; IQR)	6.1; 3.1–9.7 (mean; range)	Gleason 3+3: 100%	Low: 100%
Lian 2015	Cryotherapy	2b	Retrospective case series	NR	NR	Unilateral	Hemi-ablation	41	67; 56–76 (median; IQR)	7.1; 2.6–14.1 (median; range)	3+3: 58.5% (n = 24); 3+4: 24.4% (n = 10); 4+3: 17.1% (n = 7)	Low: 56.1% (n = 23); intermediate: 43.9% (n = 18)
Mendez 2015	Cryotherapy	2b	Retrospective case series	NR	NR	NR	NR	317	66.5 ± 6.6 (mean ± SD)	NR	Gleason 3+3: 100%	Low: 100%
Total	Cryotherapy	2a–2b	Retrospective case series to prospective development study	Combination (see above)	MRI or color-Doppler	Unilateral or organ-confined	Combination (see above)	1950	66.8 (IQR 63.8–68.1)	6.3 (IQR 5.2–7.2)	3+3 to ≥8	Low, intermediate or high
Moore 2006	PDT	1	Prospective development study	TRUS standard	MRI	Unilateral	Focal ablation	6	66; 61–71 (mean; range)	1.9–15 (range)	3+3 (100%)	Low: 50%; intermediate: 50%
Azzouzi 2013	PDT	2b	Prospective development study	NR	NR	Organ-confined	Hemi-ablation	68	62.7; 5.5 (mean; SD)[b]	6.4; 2.3 (mean; SD)[b]	3+3: 97.1% (n = 66); 3+4: 2.9% (n = 2)	NR
Moore 2014	PDT	2b	Prospective development study	TRUS standard or template mapping	MRI	Organ-confined	NR	42	63.9; 5.3 (mean; SD)	NR	3+3: 97.6% (n = 41); 3+4: 2.4% (n = 1)	Low: 100%
Total	PDT	1–2b	Prospective development studies	TRUS standard or template mapping	MRI	Unilateral or organ-confined	Focal or hemi-ablation	116	63.9 (IQR NA)	6.4 (IQR NA)	3+3 or 3+4	Low to intermediate risk
Lindner 2009	LITT	2a	Prospective development study	TRUS standard	MRI	Unifocal	Focal ablation	12	56.5; 51–52 (median; range)	5.7 ± 1.1 (mean ± SD)	3+3: 100%	Low: 100%
Lindner 2010	LITT	1	Proof of concept	TRUS standard	MRI	Unifocal	Focal ablation	4	66; 61–73 (median; range)	4.2; 2.9–14.8 (median; range)	3+3: 50% (n = 2); 4+3: 50% (n = 2)	NR
Oto 2013	LITT	2a	Prospective development study	TRUS standard	MRI	Unifocal	Focal ablation	9	61–52–77 (median–range)	5.5 ± 2.6 (mean ± SD)	3+3: 88.9% (n = 8); 3+4: 11.1% (n = 1)	NR

Lepor 2015	LITT	2a	Prospective development study	NR	MRI	Unifocal or multifocal	Focal ablation	25	66; 49–84 (median; range)	5.3; 2–9.4 (median; range)	3+3: 44% (n = 11); 3+4: 52% (n = 13); 4+3: 4% (n = 1)	NR
Total	LITT	1–2a	Proof of concept to prospective development studies	TRUS standard	MRI	Unifocal or multifocal	Focal ablation with or without intention to treat	50	63.5 (IQR 57.6–66)	5.4 (IQR 4.5–5.7)	3+3 to 4+3	Low
Nguyen 2012	Brachytherapy	2b	Retrospective case series	NR	MRI	Organ-confined	Peripheral zone ablation	318	NR	5; 3.8–6.9 (median; IQR)	3+3: 88% (n = 280); 3+4: 12% (n = 38)	Low: 83% (n = 265); intermediate: 17% (n = 53)
Cosset 2013	Brachytherapy	2a	Retrospective case series	TRUS extended	MRI	Unilateral	Focal ablation	21	62.3; 56–75 (mean; range)	6.9; 3.6–13.9 (mean; range)	3+3: 9.5% (n = 2); 3+4: 90.5% (n = 19)	NR
Total	Brachytherapy	2a–2b	Retrospective case series	TRUS extended	MRI	Unilateral or organ-confined	Focal or peripheral zone ablation	339	62.3 (IQR NA)	6 (IQR NA)	3+3 or 3+4	Low to intermediate risk
Valerio 2014	IRE	2a	Retrospective case series	Template mapping and/or targeted	MRI	Organ-confined	Index lesion ablation	34	65 ± 6 (mean ± SD)	6.1; 4.3–7.7 (median; IQR)	3+3: 26% (n = 9); 3+4: 56% (n = 19); 4+3: 15% (n = 5); 4+4: 3% (n = 1)	Low: 26% (n = 9); intermediate: 71% (n = 24); high: 3% (n = 1)
Ting 2015[c]	IRE	2a	Retrospective case series	Template mapping or targeted	MRI	Organ-confined	Index lesion ablation	25	67; 60–71 (median; IQR)	6; 4.3–8.6 (median; IQR)	3+3: 8% (n = 2); 3+4: 60% (n = 15); 4+3: 32% (n = 8)	Low: 8% (n = 2); intermediate: 92% (n = 23)
Van den bos 2015	IRE	1	Proof of concept	TRUS standard	NR	Organ-confined	Focal ablation with no intention to treat	16	60; 44–75 (median; range)	9; 3.6–25 (median; range)	3+3: 50% (n = 8); 3+4: 18.8% (n = 3); 4+3: 18.8% (n = 3); 4+4: 12.5% (n = 2)	NR
Total	IRE	1–2a	Proof of concept to retrospective case series	Combination (see above)	MRI	Organ-confined	Index lesion or focal ablation with no intention to treat	66	65 (IQR NA)	6.1 (IQR NA)	3+3 to 4+4	Low to intermediate risk
Zlotta 1998	RFA	1	Proof of concept	NR	NR	NR	Focal ablation with no intention to treat	15	NR	NR	NR	NR
Total	RFA	1	Proof of concept	NR	NR	NR	Focal ablation with no intention to treat	15	NR	NR	NR	NR

HIFU = *high-intensity focused ultrasound*; IDEAL = Idea, Development, Exploration, Assessment, Long-term study; IRE = irreversible electroporation; IQR = interquartile range; LITT = laser-induced interstitial thermotherapy; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; PDT = *photodynamic therapy*; PSA = prostate-specific antigen; Ref. = Reference; RFA = radiofrequency ablation; SD = standard deviation; TRUS = transrectal ultrasound.

[a] Partial overlap with Bahn et al., 2006.

[b] Data referring to the whole population including bilateral ablation.

[c] Partial overlap with Valerio et al., 2014.

Table 2 – Length of follow-up, ablation, and oncological results of the 37 series included

Ref.	Length follow-up (d)	Lost to follow-up (%)	Length of hospital stay (d)	Postfocal histology	Type of histology	Overall significant cancer (%)	Overall any cancer (%)	Significant cancer treated area (%)	Any cancer treated area (%)	Significant cancer untreated area (%)	Any cancer untreated area (%)	Any secondary local treatment (%)	Secondary focal ablation (%)	Radical treatment (%)	Hormonal treatment (%)	Metastatic disease (%)	Overall survival (%)	Disease-specific survival (%)
Madersbacher 1995	0	NA	NR	Mandatory	Radical prostatectomy	NR	70[a]	NR	70[a]	NR	NR	NA	NA	NA	NA	NA	NR	NR
Beerlage 1999	NR	NR	NR	Mandatory	Radical prostatectomy	NR	92.9[a]	NR	28.6[a]	NR	92.9[a]	NA	NA	NA	NA	NA	100[a]	100[a]
Muto 2008	34; 8–45 (median; range)	NR	1 (median and IQR)	Mandatory	NR	NR	23.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	100	100
Ahmed 2011	12 (median and range)	0	1 (median and IQR)	Mandatory	Targeted	0	10.5)	0	10.5	0	0	5	5	0	0	0	100	100
El Fegoun 2011	127; 90–133 (median; range)	0	NR	Mandatory	TRUS standard	0	8.3	NR	NR	NR	NR	8.3	8.3	NR	33.3	NR	83	100
Ahmed 2012	12 (median and range)	0	1; 1–2 (median; IQR)	Mandatory	Targeted	7.7	23	7.7	23	0	0	10.3	10.3	0	0	0	100	100
Chopra 2012	0	NA	NR	Mandatory	Radical prostatectomy	75[a]	100[a]	NR	NR	NR	NR	NA	NA	NA	NA	NA	100[a]	100[a]
Dickinson 2013	0	NA	NR	Mandatory	Template mapping + targeted	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NR	NR
Napoli 2013	0	NA	NR	Mandatory	Radical prostatectomy	40	100	0	0	40	100	NA	NA	NA	NA	NA	100	100
Van Velthoven 2013	38; 12–61 (median; range)	6.5	4; 2–6 (median; range)	For cause	TRUS standard	NR	10.3	NR	0	NR	10.3	10.3	10.3	0	6.9	0	100	100
Ahmed 2015	12 (median and range)	0	1 (median and IQR)	Mandatory	Targeted	19.2	42.3	15.4	34.6	3.8	7.7	7.2	3.6	3.6	0	0	100	100
Feijoo 2015	12; 6–50 (median; IQR)	6	NR	Mandatory	TRUS standard	NR	25.4	NR	16.4	NR	10.5	NR	NR	NR	NR	NR	NR	NR
Ghai 2015	6 (median and range)	0	NR	Mandatory	TRUS extended + targeted	0	100	0	25	0	100	0	0	0	0	0	100	100
Total HIFU	12 (IQR 0–28.5)	0 (IQR 0–6)	1 (IQR 1–2.5)	Mandatory or for cause	Combination (see above)	0 (IQR 0–13.5)	23.3 (IQR 10.4–38.1)	0 (IQR 0–11.6)	16.4 (IQR 0–25)	0 (IQR 0–21.9)	10.3 (IQR 0–100)	7.8 (IQR 3.8–10.3)	6.7 (IQR 2.7–10.3)	0 (0–1.8)	0 (IQR 0–13.5)	0 (IQR 0–0)	100 (IQR 100–100)	100 (IQR 100–100)
Bahn 2006	70; 2–107 (median; range)	3.2	NR	Mandatory	TRUS standard + targeted	NR	4%	0	0	NR	4	3.3	0	3.3	0	0	100	100
Ellis 2007	12; 3–36 (median; range)	1.7	NR	For cause	NR	NR	23.7	NR	1.7	NR	22	18.6	18.6	0	0	0	100	100
Onik 2007	43.2 (mean; IQR NR)	NR	NR	For cause	TRUS standard	NR	7.3	0	0	NR	7.3	7.3	0	7.3	NR	NR	100	100
Truesdale 2010	24; 0–87 (median; range)	NR	1 (median and range)	For cause	TRUS standard	NR	13	NR	3.9	NR	10.4	NR	NR	NR	NR	NR	100	100
Bahn 2012	44; 12–102 (median; range)	4.1	1 (median and range)	For cause	TRUS standard + targeted	4.3	17.1	1.4	1.4	2.9	15.7	5.7	2.9	1.4	1.4	0	100	100
Ward 2012	21.1 ± 19.7 (mean ± SD)	NR	NR	For cause	NR	NR	3.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hale 2013	19.1; 2–52 (mean; range)	NR	1; 1–2 (median; range)	For cause	TRUS standard	0	7.7	NR	NR	NR	NR	7.7	0	7.7	0	0	100	100
Al Barqawi 2014	28; 26–31 (median; IQR)	0	NR	Mandatory	TRUS standard	NR	19.4	NR	12.9	NR	8.1	11.3	8.1	3.2	0	NR	100	100
Durand 2014	13.2; 7.4–26.5 (median; IQR	0	3.4; 2–32 (median; range)	Mandatory	TRUS standard	6.5	26.1	6.5	13	2.2	15.2	14.6	6.3	6.3	2.1	0	100	100
Lian 2015	63; 12–92 (median; IQR	2.4	NR	For cause	TRUS standard	7.5	17.5	2.5	5	5	12.5	7.5	5	2.5	5	0	100	100
Mendez 2015	NR	NR	NR	For cause	NR	NR	2.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Total cryotherapy	26 (IQR 17.6–48.8)	2.1 (IQR 0–3.4)	1 (IQR 1–2.8)	Mandatory or for cause	TRUS standard +/– targeted	5.4 (IQR 1.1–7.3)	13 (IQR 4–19.4)	1.4 (0–4.5)	2.8 (IQR 0.4–10.9)	2.9 (IQR NA)	11.5 (IQR 7.5–15.6)	7.6 (IQR 6.1–13.8)	4 (IQR 0–7.7)	3.3 (IQR 1.7–7.1)	0% (IQR 0–2.1)	0% (IQR 0–0)	100 (IQR 100–100)	100 (IQR 100–100)
Moore 2006	NR	NR	1–4 (range)	Mandatory	TRUS standard	NR	100	NR	NR	NR	NR	83.3	NR	83.3	0	0	100	100
Azzouzi 2013	6 (median and range)	1.5	NR	Mandatory	TRUS standard	NR	23.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	100	100
Moore 2014	6 (median and range)	11.9	NR	Mandatory	TRUS standard	NR	45.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	100	100

Table 2 (*Continued*)

Ref.	Length follow-up (d)	Lost to follow-up (%)	Length of hospital stay (d)	Postfocal histology	Type of histology	Overall significant cancer (%)	Overall any cancer (%)	Significant cancer treated area (%)	Any cancer treated area (%)	Significant cancer untreated area (%)	Any cancer untreated area (%)	Any secondary local treatment (%)	Secondary focal ablation (%)	Radical treatment (%)	Hormonal treatment (%)	Metastatic disease (%)	Overall survival (%)	Disease-specific survival (%)
Total PDT	6 (IQR 6–6)	6.7 (IQR NA)	NR	Mandatory	TRUS standard	NR	45.9 (IQR NA)	NR	NR	NR	NR	83.3 (IQR NA)	NR	83.3 (IQR NA)	0 (IQR NA)	0 (IQR NA)	100 (IQR 100–100)	100 (IQR 100–100)
Lindner 2009	6 (median and range)	0%	1; 1–2 (median; range)	Mandatory	TRUS standard + targeted	16.7	50	16.7	33.3	0	16.7	8.3	0	8.3	0	0	100	100
Lindner 2010	1 wk (median and range)	0	NR	Mandatory	Radical prostatectomy	NR	NR	0	0	NR	NR	NA	NA	NA	NA	NA	100	100
Oto 2013	6 (median and range)	0	NR	Mandatory	Targeted	0	22.2	0	22.2	0	0	0	0	0	0	0	100	100
Lepor 2015	3 (median and range)	0	NR	Mandatory	Targeted	4.8	4.8	4.8	4.8	0	0	0	0	0	0	0	100	100
Total LITT	4.5 (IQR 0.8–6)	0 (IQR 0–0)	1 (IQR NA)	Mandatory	Combination (see above)	4.8 (IQR NA)	22.2 (IQR NA)	2.4 (IQR 0–13.7)	13.5 (IQR 1.2–30.5)	0 (IQR 0–0)	0 (IQR NA)	0 (IQR NA)	0 (IQR 0–0)	0 (IQR NA)	0 (IQR 0–0)	0 (IQR 0–0)	100 (IQR 100–100)	100 (IQR 100–100)
Nguyen 2012	61; 33–88 (median; IQR)	NR	NR	For cause	TRUS standard	3.5	5.3	NR	NR	NR	NR	NR	NR	NR	NR	0.3	NR	99.7
Cosset 2013	NR	NR	NR	Mandatory	TRUS standard	0	4.8	0	0	0	4.8	0	0	0	0	0	NR	100
Total brachytherapy	61 (IQR NA)	NR	NR	Mandatory or for cause	TRUS standard	1.8 (IQR NA)	5.1 (IQR NA)	0 (IQR NA)	0 (IQR NA)	0 (IQR NA)	4.8 (IQR NA)	0 (IQR NA)	0 (IQR NA)	0 (IQR NA)	0 (IQR NA)	0.2 (IQR NA)	NR	99.9 (IQR NA)
Valerio 2014	6; 1–23 (median; range)	0	1; 1–2 (median; range)	For cause	Targeted	2.9	2.9	2.9	2.9	0	0	11.8	8.8	2.9	0	0	100	100
Ting 2015	7 (median; range NR)	NR	1; 1–5 (median; range)	Mandatory	Template mapping	23.8	61.9	19.0	19.0	4.8	NR	12	8	4	0	0	100	100
Van den bos 2015	1 (median; range NR)	0	NR	Mandatory	Radical prostatectomy	NR	NR	NR	NR	NR	NR	NR	NR	NA	NA	NA	NR	NR
Total IRE	6 (IQR NA)	0 (IQR 0–0)	1 (IQR 1–1)	Mandatory or for cause	Combination (see above)	13.4 (IQR NA)	32.4 (IQR NA)	11 (IQR NA)	11 (IQR NA)	2.4 (IQR NA)	0 (NA)	11.9 (IQR NA)	8.4 (IQR NA)	3.5 (IQR NA)	0 (IQR 0–0)	0 (IQR 0–0)	100 (IQR 100–100)	100 (IQR 100–100)
Zlotta 1998	NR	NR	NR	Mandatory	Radical prostatectomy	NR	100[a]	NR	NR	NR	NR	NR	NA	NA	NA	NA	NR	NR
Total RFA	NR	NR	NR	Mandatory	Radical prostatectomy	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NR	NR

HIFU = *high-intensity focused ultrasound;* IRE = irreversible electroporation; IQR = interquartile range; LITT = laser-induced interstitial thermotherapy; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; PDT = *photodynamic therapy*; PSA = prostate-specific antigen; Ref. = Reference; RFA = radiofrequency ablation; SD = standard deviation; TRUS = transrectal ultrasound.

[a] Not included in cumulative analysis as there was no intention to treat.

Table 3 – Morbidity and functional outcomes of the 37 series included

Ref.	Serious AE, % (scale)	PROM for continence	Leak-free (%)	Pad-free (%)	PROM for erectile function	Potency preservation (%)	Stability	New use of PDE-5 inhibitors (%)	PROM for urinary symptoms	Change	Catheterization time (min)	Stricture rate (%)	Urinary retention rate (%)	UTI rate (%)	PROM for bowel symptoms (%)	Change	Recto-urethral fistula (%)	PROM for quality of life	Change
Madersbacher 1995	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Beerlage 1999	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR	NR
Muto 2008	NR	UCLA-EPIC	NR	NR	NR	NR	NR	NR	IPSS	Stable	19.7; 7.6 (mean; SD)	4	NR	4	NR	NR	NR	NR	NR
Ahmed 2011	NR	UCLA-EPIC	90	95	IIEF-15	95	Stable	NR	IPSS	Stable	NR	5	0	0	NR	NR	0	FACT-P	Stable
El Fegoun 2011	NR	NR	NR	100	NR	NR	NR	NR	IPSS	Stable	NR	0	8.3	16.7	NR	NR	NR	NR	NR
Ahmed 2012	NR	UCLA-EPIC	100	100	IIEF-15	88.6	Deterioration	NR	IPSS	Stable	8.5; 8.0–15.0 (median; IQR)	0	2.4	17.1	NR	NR	2.4 (suspicion)	FACT-P	Deterioration
Chopra 2012	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dickinson 2013	NR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Napoli 2013	0 (Dindo-Clavien)	NR	NR	NR	NR	NR	NR	NR	NR	NR	3 (median and range)	NR	NR	NR	NR	NR	NR	NR	NR
Van Velthoven 2013	3.2 (Dindo-Clavien)	NR	NR	100	NR	80	NR	13.8	NR	NR	2; 2–21 (median; range)	3.4	3.4	10.3	NR	NR	0	NR	NR
Ghai 2015	0 (Dindo-Clavien)	ICS	NR	100	IIEF-5	100	Deterioration	0	IPSS	Stable	6; 0–7 (median; range)	NR	0	0	NR	NR	0	SF-12HS	Stable
Ahmed 2015	NR	UCLA-EPIC	92.6	92.6	IIEF-15	76.9	Deterioration	29.6	IPSS	Stable	9; 7–14 (mdeian; IQR)	7.1	NR	17.9	NR	NR	0	FACT-P	Stable
Feijoo 2015	3 (Dindo-Clavien)	ICS	100	100	IIEF-5	NR	Deterioration	NR	IPSS	Stable	NR	0	9.0	6.0	NR	NR	0	NR	NR
Total HIFU	1.5 (IQR 0–3.2)	UCLA-EPIC or ICS	96.3 (IQR 90.7–100)	100 (IQR 95–100)	IIEF	88.6 (IQR 78.5–97.5)	Deterioration or stable	13.8 (IQR NA)	IPSS	Stable	7.3 (IQR 2.8–11.7)	3.4 (IQR 0–5)	2.9 (IQR 0–8.5)	8.2 (IQR 1–17)	NR	NR	0 (0–0)	FACT-P or SH-12HS	Stable or deterioration
Bahn 2006	NR	NR	100	100	BMSFI	88.9	NR	40.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ellis 2007	NR	NR	96.4	100	NR	70.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR	NR
Onik 2007	NR	NR	NR	NR	NR	86.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Truesdale 2010	NR	NR	NR	100	IIEF	NR	Stable	NR	IPSS	Improvement	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bahn 2012	NR	NR	NR	100	IIEF-5	86	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR	NR
Ward 2012	NR	NR	NR	98.4	NR	58.1	NR	NR	NR	NR	NR	NR	1.1	NR	NR	NR	0.1	NR	NR
Hale 2013	NR	NR	NR	100	SHIM	100	NR	26.9	IPSS	NR	NR	0	3.8	3.8	NR	NR	0	NR	NR
Al Barqawi 2014	0 (NR)	NR	NR	100	SHIM	NR	Stable	NR	IPSS	Improvement	7 (median; IQR NR)	NR	NR	0	NR	NR	0	NR	NR
Durand 2014	4.2 (Dindo-Clavien)	NR	NR	100	IIEF-5	NR	Stable	NR	IPSS	Stable	3.5; 1–34 (median; range)	2.1	14.6	0	NR	NR	2.1	NR	NR
Lian 2015	2.5 (Dindo-Clavien)	NR	NR	100	IIEF-5	76.9	NR	17.1	NR	NR	NR	NR	2.5	NR	NR	NR	0	NR	NR
Mendez 2015	NR	NR	NR	100	NR	68.8	NR	NR	NR	NR	NR	NR	5	NR	NR	NR	0.3	NR	NR
Total cryotherapy	2.5 (IQR NA)	NR	98 (IQR NA)	100 (IQR 100–100)	IIEF, SHIM, or BMFSI	81.5 (IQR 69.3–88.2)	Stable	26.9 (IQR NA)	IPSS	Improvement or stable	5.3 (IQR NA)	1.1 (IQR NA)	3.8 (IQR 1.8–9.8)	0% (IQR NA)	NR	NR	0 (IQR 0–0.3)	NR	NR
Moore 2006	NR	NR	83.3	NR	BMSFI	NR	Stable	NR	IPSS	Stable	1–4 (range)	NR	33.3	16.7	NR	NR	0	NR	NR
Azzouzi 2013	9.3 (CTCAE)[a]	NR	NR	NR	IIEF-5	88.6[a]	Deterioration	NR	IPSS	Improvement	NR	1.2[a]	12.8[a]	14[a]	NR	NR	0	NR	NR
Moore 2013	11.9 (CTCAE)	NR	NR	NR	IIEF-5	88.2	Stable	NR	IPSS	Improvement	NR	NR	5	NR	NR	NR	0	NR	NR
Total PDT	10.6 (IQR NA)	NR	83.3 (IQR NA)	NR	IIEF or BMSFI	88.4 (IQR NA)	Stable or deterioration	NR	IPSS	Improvement or stable	NR	1.2 (IQR NA)	12.8 (IQR NA)	15.4 (IQR NA)	NR	NR	0 (IQR 0–0)	NR	NR
Lindner 2009	0 (NR)	NR	100	100	IIEF-5	100%	Stable	NR	IPSS	Stable	0; 0–1 (median; range)	0	16.7	0	NR	NR	0	NR	NR
Lindner 2010	0 (NR)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Oto 2013	0 (CTCAE)	NR	NR	100	SHIM	100	Stable	NR	IPSS	Stable	NR	NR	NR	NR	NR	NR	0	NR	NR
Lepor 2015	0%(NR)	NR	NR	100	SHIM	NR	Stable	NR	IPSS	Stable	0; 0–3 (median; range)	0	28	0	NR	NR	0	NR	NR
Total LITT	0 (IQR 0–0)	NR	100 (IQR NA)	100 (IQR 100–100)	SHIM or IIEF	100 (IQR 100–100)	Stable	NR	IPSS	Stable	0 (IQR 0–0)	0 (IQR 0–0)	22.4 (IQR NA)	0 (IQR 0–0)	NR	NR	0 (IQR 0–0)	NR	NR

Table 3 (*Continued*)

Ref.	Serious AE, % (scale)	PROM for continence	Leak-free (%)	Pad-free (%)	PROM for erectile function	Potency preservation (%)	Stability	New use of PDE-5 inhibitors (%)	PROM for urinary symptoms	Change	Catheterization time (min)	Stricture rate (%)	Urinary retention rate (%)	UTI rate (%)	PROM for bowel symptoms (%)	Change	Recto-urethral fistula (%)	PROM for quality of life	Change
Nguyen 2012	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cosset 2013	NR	ICS	NR	95.2	IIEF-5	NR	Stable	NR	IPSS	Stable	NR	NR	4.8	NR	NR	NR	0	NR	NR
Total brachytherapy	NR	ICS	NR	95.2 (IQR NA)	IIEF	NR	Stable	NR	IPSS	Stable	NR	NR	4.8 (IQR NA)	NR	NR	NR	0 (IQR NA)	NR	NR
Valerio 2014	0 (CTCAE)	NR	NR	100	NR	95	NR	NR	NR	NR	3; 0–9 (median; range)	0	5.9	14.7	NR	NR	0	NR	NR
Ting 2015	4 (Dindo-Clavien)	UCLA-EPIC	100	100	UCLA-EPIC	NR	Stable	NR	IPSS	Stable	2; 2–5 (median; range)	NR	20	NR	UCLA-EPIC	Stable	0	SF-12HS	Stable
Van den bos 2015	0 (NR)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR	NR
Total IRE	0 (IQR NA)	UCLA-EPIC	100 (IQR NA)	100 (IQR 100–100)	UCLA-EPIC	95 (IQR NA)	Stable	NR	IPSS	Stable	2.5 (IQR NA)	0 (IQR NA)	13 (IQR NA)	14.7 (IQR NA)	UCLA-EPIC	Stable	0 (IQR 0–0)	SF-12HS	Stable
Zlotta 1998	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Total RFA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

BMSFI = Brief Male Sexual. Function Inventory; CTCAE = Common Terminology Criteria for Adverse Events; EPIC = Expanded Prostate *Cancer* Index Composite; FACT-P = Functional Assessment of Cancer Therapy-Prostate; HIFU = *high-intensity focused ultrasound*; ICS = *International Continence Society*; IIEF = International Index of Erectile Function; IRE = irreversible electroporation; IPSS = *International Prostate Symptom Score*; IQR = interquartile range; LITT = laser-induced interstitial thermotherapy; NA = not applicable; NR = not reported; PDT = *photodynamic therapy*; PROM = patient-reported outcomes measures; Ref. = Reference; RFA = radiofrequency ablation; SD = standard deviation; SF-12HS = Short Form-12 Health Survey; SHIM = Sexually Health Inventory for Men; TRUS = transrectal ultrasound; UCLA = University of California, Los Angeles; UTI = urinary tract infection.

[a] Data referring to the whole population including bilateral ablation.

100–100%) and 100% (IQR: 100–100%), respectively. Significant adverse events (SAE) occurred in 1.5% of 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.

3.2. *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 is order to form a homogeneous ice ball with no skip lesion in the middle.

Of the 11 series evaluating focal cryotherapy in 1950 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 of 66.8 yr (IQR: 63.8–68.1 yr) and median PSA of 6.3 ng/ml (IQR: 5.2–7.2 ng/ml).

Median follow-up was 26 mo (IQR: 17.6–48.8 mo) with three series including mandatory sampling and 18 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. The probability of transition to secondary local treatment was 7.6% (IQR: 6.1–13.8%); overall and disease-specific survival were 100% (IQR: 100–100%) and 100% (IQR: 100–100%), respectively. SAE occurred in 2.5% patients (IQR: not applicable [NA]), although only two series reported these using a standardized classification. Pad-free continence and potency preservation were achieved in 100% (IQR: 100–100%) and 81.5% (IQR: 69.3–88.2%), respectively.

3.3. *PDT*

PDT ablation relies on the activation of a vascular photosensitiviser 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 photosensitiviser is administered intravenously.

Three prospective development studies on 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 a median age of 63.9 yr (IQR: NA) and median PSA of 6.4 ng/ml (IQR: NA).

When reported, median follow-up was homogeneous at 6 mo (IQR: 6–6 mo) with all three studies including

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Table 4 – Design of ongoing clinical trials

Registration no.	Name	Source of energy	Sample size (*n*)	Open	Close	City	Stage	Target population risk	Primary outcome	Primary outcome measure	Secondary outcomes	Secondary outcome measures	Follow-up
NCT01226576	Focal MR-Guided Focused Ultrasound Treatment of Localized Low-Intermediate Risk Prostate Cancer: Feasibility Study	HIFU	80	2010	2015	Multicenter	2a	Low-intermediate	Safety at 6 mo Effectiveness at 6 mo	Adverse events Template mapping biopsy	Safety at 24 mo Effectiveness at 24 mo Genito-urinary toxicity & quality of life at 24 mo	Adverse events Template mapping biopsy IPSS, SF12, UCLA-EPIC	2 yr
NCT02016040	Focal Therapy Using HIFU for Localized Prostate Cancer	HIFU	25	2013	2016	Montreal (Canada)	2a	Low-intermediate	Cancer control	MRI targeted biopsy	Safety Genito-urinary toxicity & quality of life Cost	Adverse events Questionnaires NR NR	6 mo
NCT01657942	Focal MR-Guided Focused Ultrasound Treatment of Localized Low and Intermediate Risk Prostate Cancer	HIFU	40	2013	2016	Multicenter	2a	Low-intermediate	Safety	Adverse events	Cancer control	Template mapping biopsy	6 mo
NCT02265159	Intervention Trial Evaluating Focal Therapy Using High Intensity Focused Ultrasound for the Treatment of Prostate Cancer	HIFU	100	2014	2020	Zurich (Switzerland)	2b	Low-intermediate	Cancer control	Template mapping biopsy	Biochemical failure MRI performance Cost Genito-urinary toxicity & quality of life Secondary intervention rate	PSA kinetics Template mapping biopsy NR IPSS, IIEF-15, UCLA-EPIC, FACT-P V4, Memorial Anxiety Scale for Prostate Cancer Transition to other treatments	3 yr
ISRCTN99760303	Partial prostate Ablation versus Radical prosTatectomy	HIFU	100	2015	2017	Oxford (UK)	2b	Intermediate	Feasibility of RCT	Uptake of ≥50% eligible patients	Cancer control Genito-urinary toxicity & quality of life	TRUS biopsy, MRI IPSS, IIEF-15, UCLA-EPIC, EQ-5D-5L, FACT-P V4, The Modified 18-term Memorial Anxiety Scale for Prostate Cancer, Resource Utilization Questionnaire	3 yr
NCT01094665	MRI Targeted Focal Laser Thermal Therapy of Prostate Cancer	LITT	60	2009	2016	Toronto (Canada)	1	Low-intermediate	Safety	NR	Cancer control	TRUS biopsy	4 mo
NCT02243033	Laser Interstitial Thermal Therapy of Prostate Cancer	LITT	100	2010	2016	Indian Wells (USA)	2a	Low-intermediate	Safety	Adverse events	Cancer control Ablation volume Approach efficacy Genito-urinary toxicity & quality of life	MRI targeted biopsy MRI No patients undergoing the procedure IPSS, SHIM, and PHQ-9	1 yr
NCT02200809	MR-guided Focal Laser Ablation of the Prostate	LITT	20	2014	2019	Nijmegen (Netherlands)	2a	Low-intermediate	Cancer control	MRI targeted biopsy	NR	NR	3 yr
NCT02357121	Focal Laser Ablation of Prostate Tissue (FLA)	LITT	12	2015	2016	Los Angeles (USA)	1	Low-intermediate	Safety	Adverse events	Efficacy	MRI	1 yr
NCT02600156	Focal Laser Ablation of Prostate Cancer Tumors	LITT	20	2015	2018	Rochester (USA)	1	Low-intermediate	Feasibility Safety	Target, access, monitor, and ablate tissue Adverse events	Cancer control	MRI	3 yr
NCT01830166	Focal Therapy for Prostate Cancer - A Pilot Study of Focal Low Dose Rate Brachytherapy	Brachytherapy	10	2013	2018	Vancouver (Canada)	2a	Low	Develop treatment plans	NR	Quality of life Cancer control	NR MRI, mapping biopsy	4 yr

Table 4 (*Continued*)

Registration no.	Name	Source of energy	Sample size (*n*)	Open	Close	City	Stage	Target population risk	Primary outcome	Primary outcome measure	Secondary outcomes	Secondary outcome measures	Follow-up
NCT01902680	Phase II Study of Feasibility of Focal Therapy for Prostate Cancer of Good Prognosis With Permanent I125 Localized Implant	Brachytherapy	17	2013	2015	Toulouse (France)	2a	Low	Feasibility	Dosimetry study by CT/MRI	Progression-free survival Cancer control Safety Genito-urinary toxicity & quality of life	Phoenix criteria Targeted biopsy Adverse events IPSS, IIEF, EORTC-QLQ	1 yr
NCT02391051	Focal Brachytherapy in Patients With Selected Low-risk Prostate Cancer - A Phase-II-trial	Brachytherapy	50	2014	2017	Erlangen (Germany)	2a	Low	Safety	Adverse events at 6 wk	Cancer control Genito-urinary toxicity & quality of life at 6 wk	PSA IPSS, IIEF, EORTC-QLQ, ICIQ	6 wk for primary outcome 10 yr overall
NCT02290366	Prospective Evaluation of Focal Brachytherapy Using Cesium-131 For Patients With Low Risk Prostate Cancer	Brachytherapy	100	2014	2020	Pittsburgh (USA)	2b	Low	Disease-free survival	NR	Genito-urinary toxicity & quality of life	NR	5 yr
NCT02303054	MRI-Targeted Focal Ablation of the Prostate in Men With Prostate Cancer	RFA	21	2014	2016	New York (USA)	2a	Low-intermediate	Cancer control	MRU fusion targeted biopsy	Genito-urinary toxicity & quality of life	IPSS, IIEF-15, UCLA-EPIC, SF-12 QoL	6 mo
NCT02328807	Focal Prostate Radio-Frequency Ablation	RFA	30	2014	2016	Tampa (USA)	2a	Low-intermediate	Cancer control	Biopsy (type NR)	Safety Genito-urinary toxicity & quality of life	Adverse events IPSS, IIEF-5, UCLA-EPIC, and RAS	6 mo
NCT02294903	Focal Prostate Radiofrequency Ablation	RFA	20	2015	2016	London (UK)	2a	Low-intermediate	Cancer control	Template mapping biopsy	Safety Genito-urinary toxicity & quality of life	NR NR	6 mo

EPIC = Expanded Prostate *Cancer* Index Composite; FACT-P = Functional Assessment of Cancer Therapy-Prostate; HIFU = *high-intensity focused ultrasound;* IIEF = International Index of Erectile Function; IRE = irreversible electroporation; IPSS = *International Prostate Symptom Score;* LITT = laser-induced interstitial thermotherapy; MRI = magnetic resonance imaging; NR = not reported; PHQ-9 = Patient Health Questionnaire-9; PSA = prostate-specific antigen; QoL = quality of life; RAS = *Relationship Assessment Scale;* RFA = radiofrequency ablation; SF-12HS = Short Form-12 Health Survey; SHIM = Sexually Health Inventory for Men; TRUS = transrectal ultrasound; UCLA = University of California, Los Angeles.

mandatory sampling using TRUS standard biopsy. The presence of significant cancer was reported by none of the studies; insignificant cancer was present in 45.9% (IQR: NA). The probability of 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% of patients (IQR: NA). Pad-free continence rates were not available. Potency preservation was achieved in 88.4% (IQR: NA), respectively.

3.4. 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 photosensitivisers. The laser fibers are positioned transperineally or transrectally; the number of fibers is dependent by the volume of the target tissue.

Four prospective Stage 1 to 2a studies evaluating focal LITT in 50 patients have been reported in 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. The median age was 63.5 yr (IQR: 57.6–66 yr); median PSA was 5.4 ng/ml (IQR: 4.5–5.7 ng/ml).

Median follow-up was 4.5 mo (IQR: 0.8–6 mo) 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, the presence of significant and insignificant cancer were 4.8% (IQR: NA) and 22.2% (IQR: NA), respectively. The probability of transition to secondary local treatment was 0% (IQR: NA); overall and disease-specific survival were 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.

3.5. 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 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 a median age of 62.3 yr (IQR: NA) and a median of PSA of 6 ng/ml (IQR: NA).

One series did not report the length of follow-up, while the other had a median follow-up of 61 mo (IQR: 33–88 mo). Both series incorporated TRUS standard biopsy, although in one sampling was mandatory, whereas in the other it was *for cause*. Overall, the presence of significant and insignificant cancer were 1.8% (IQR: NA) and 5.1% (IQR: NA), respectively. No patient had secondary local treatment (IQR: NA). Overall survival was not reported by any study, whilst disease-specific survival was 99.9% (IQR: NA). SAE were reported by no series using a standardized classification. Pad-free continence was reported only by one series and was at 95.2%. Potency preservation was not reported by any series.

3.6. 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 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 a median age of 65 yr (IQR: NA) and a median PSA of 6.1 ng/ml (IQR: NA).

Median follow-up was 6 mo (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, the presence of significant cancer and insignificant cancer were 13.4% (IQR: NA) and 32.4%. The probability of transition to secondary local treatment was 11.9%. Overall and disease-specific survival were 100% (IQR: 100–100%) and 100% (IQR: 100–100%), respectively. SAE occurred in 0% of patients (IQR: NA). Pad-free continence and potency preservation were achieved in 100% (IQR: 100–100%) and 95% (IQR: NA), respectively.

3.7. RFA

RFA is another thermal procedure delivering medium frequency alternating current in order to generate killing heat within the target area. Similarly to all other sources of energy except HIFU of 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 outcomes could be extrapolated. Residual tumor was found in all men, although there was no intention to treat in this study.

4. 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

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assessed in up to Stage 2b studies including 346, 1950, 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 a 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 further discuss the results. The assessment of novel sources of energy should be distinguished from 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 multiparametric MRI has a 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 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. Firstly, 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 a wide variation in the definition of clinically significant disease. Secondly, 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 [49]. 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 a formal meta-analysis to be performed or to draw a reliable comparison between the different sources of energy. In this setting, with the intent to summarize these limited and heterogeneous data, we chose to use simple descriptive statistics. For instance, although focal therapy has been lately defined as ablation of the index lesion only by a group of experts, there was intrastudy and interstudy variability in the ablation strategy with many early series using pragmatic template such as hemiablation [50]. Also, in the case of lesion-only ablation, the location of the tumor has a great impact on functional outcomes; in particular the distance from the sphincter and neurovascular bundles is likely to influence continence and potency, respectively. There is room for improvement also in the use of validated PROMs. While most studies included did not use PROMs to elicit functional outcomes, recent prospective studies and ongoing trials do employ these outcome measures.

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 as of the untreated area after 3 yr of follow-up. These studies will verify not only the ablation results of these two modalities in the midterm, 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 RCT 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 the 2-yr 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 mo points to further assessment needed. This is under the way in three Stage 1 to 2a trials with longer monitoring up to 3 yr. Focal brachytherapy is currently recruiting in four Stage 2a to 2b prospective studies. While the

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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 centers. 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 [51]. 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 [51]. These challenges are very likely to be encountered in a RCT comparing focal therapy with 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 [52]. Alternative trial designs are more easily embedded in clinical practice, and allow measuring the effectiveness of a given intervention in the real world rather than its efficacy in a trial setting. Examples of alternative trial designs which might be adopted in this field are: cohort-embedded multiple RCT, cluster RCT, patient preference trials, and parallel prospective cohort studies.

5. Conclusions

Seven sources of energy have been delivered in a focal manner in men with localized 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.

Author contributions: Massimo Valerio had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Valerio, Cerantola, Eggener, Lepor, Polascik, Villers, Emberton.
Acquisition of data: Valerio, Cerantola.
Analysis and interpretation of data: Valerio, Cerantola.
Drafting of the manuscript: Valerio, Cerantola.
Critical revision of the manuscript for important intellectual content: Eggener, Lepor, Polascik, Villers, Emberton.
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