Editorial
Prostate cancer

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health Published online Oct 16, 2023
https://doi.org/10.5534/wjmh.230160

The World Journal of MEN's HEALTH

Revisiting Delphi to Create a Basis for the Future of Focal Therapy for Prostate Cancer

Lara Rodríguez-Sánchez[1], Mark Emberton[2], Theo de Reijke[3], Phillip Stricker[4], Bernardino Miñana[5], Fernando Bianco[6], Jose Luis Dominguez Escrig[7], Anna Lantz[8], Rafael Sanchez-Salas[9]

[1]*Urology Department, Institut Mutualiste Montsouris, Paris, France,* [2]*Division of Surgery and Interventional Science, University College London, London, UK,* [3]*Department of Urology, UMC Amsterdam University Hospital, Amsterdam, the Netherlands,* [4]*Department of Urology, St. Vincent's Private Hospital and Clinic, Melbourne, Australia,* [5]*Department of Urology, Clinica Universidad de Navarra, Madrid, Spain,* [6]*Urological Research Network, Nova Southeastern University, Hollywood, FL, USA,* [7]*Department of Urology, Instituto Valenciano de Oncologia, Valencia, Spain,* [8]*Department of Molecular Medicine and Surgery, Section of Urology, Karolinska Institutet, Stockholm, Sweden,* [9]*Department of Surgery, Division of Urology, McGill University, Montreal, QC, Canada*

Prostate cancer (PCa) is a disease that exhibits heterogeneity in terms of its clinical behavior [1]. Therefore, it is not surprising that heterogeneity also affects the way we treat PCa.

Radical treatments such as radical prostatectomy (RP) and radiation therapy (RT) have for years been considered the standard of care for most men with non-metastatic PCa [2,3]. During the last 120 years, many changes regarding surgical and radiation techniques have arose to reduce morbidity and improve oncological and functional outcomes [4]. However, despite all of the effort behind these advances, the negative effects on sexual, urinary and bowel function remain unsolved [5].

Active surveillance (AS) emerged in the early 2000s, to address this issue, offering a significant number of patients the option to avoid or delay treatment. Unfortunately, only those with low and favorable intermediate-risk PCa can benefit from this approach [6].

Aside from AS and whole-gland treatment, focal therapy (FT) has been developed over the past 20 years with the aim of improving functional outcomes without compromising metastasis and cancer specific survival for men with localized PCa who are not suitable for AS.

In 2023, oncological outcomes following FT remain a challenge mainly due to a lack of both well-designed trials and long-term follow-up which is essential given the good prognosis of low and favorable intermediate localized PCa, with 10-year distant metastasis rates <10% [7]. However, many studies have already demonstrated significant functional benefits, with a low impact on continence and erectile function [8]. These findings suggest that further research and development of FT as an alternative treatment for PCa is warranted.

Over time, improvements in diagnostic accuracy—using magnetic resonance imaging (MRI) and targeted biopsies (TBx) [9] which are essential for selecting appropriate candidates for FT—have contributed to the rapid evolution of FT. In addition, the number of energy sources—high-intensity focused ultrasound (HIFU), irreversible electroporation (IRE), cryoablation, focal laser

Received: Jun 9, 2023 **Revised:** Jul 15, 2023 **Accepted:** Jul 19, 2023 **Published online** Oct 16, 2023
Correspondence to: Lara Rodríguez-Sánchez https://orcid.org/0000-0001-6939-2645
Urology Department, Institut Mutualiste Montsouris, 42 Bd Jourdan, Paris 75014, France.
Tel: +33-652131231, **E-mail:** lara.rodriguez-sanchez@imm.fr

ablation (FLA), focal brachytherapy, photodynamic therapy (PDT), and radiofrequency ablation (RFA), among others—has increased significantly in recent years, and the selection of the most appropriate option has been refined with clinical experience [10]. Nevertheless, the process of obtaining robust oncological results with FT has lagged behind these advancements.

As FT continues to evolve, it has been used on a diverse patient population with varying treatment strategies and a growing number of energy sources [11]. Furthermore, relapse criteria, follow-up protocols, and the reporting of outcomes are not standardized.

In this context, where there is a high degree of heterogeneity in terms of selection, treatment, and follow-up, the utilization of Delphi consensus may be highly useful in guiding our practice and advancing our understanding in the near future, especially in situations where more robust evidence is still pending.

CONTROVERSIAL ASPECTS OF FOCAL THERAPY

There are multiple controversial points in FT that explain the existing diversity in patient selection, treatment, and follow-up.

1. Accuracy of diagnosis

The multifocality of PCa is a significant challenge in the application of FT for PCa. Despite the detection of multiple lesions on MRI and bilateral positive biopsies, FT for PCa is focused on treating the lesion that is deemed the most clinically significant and likely to influence the progression of the cancer [12].

Accurate diagnosis is crucial for the success of FT. MRI and biopsies have played a significant role in the development of this treatment. Since 2017, several studies have demonstrated that MRI-TBx can improve the detection of clinically significant PCa (csPCa) while reducing the detection of insignificant PCa [13]. The Trio Study found that the percentage of upgrading after RP was lower with combined biopsies (7%) compared to target biopsies alone (18%) or systematic biopsies alone (30%) [14]. These findings highlight the importance of using MRI together with target and systematic biopsies in the diagnosis of PCa for optimal planning of FT treatment.

Nevertheless, diagnosis of PCa using MRI-TBx together with systematic biopsies may not be sufficient for planning FT, and the optimal number of biopsy cores to take outside the index lesion is not yet clear. Lee et al [15] showed that the detection rate of csPCa increased with the number of biopsy cores taken. In their study, using a systematic biopsy that only included cores not within the lesions identified on MRI (non-targeted systematic saturation biopsy), the csPCa detection rate was 21% with a median of 22 cores. However, when the number of cores was reduced to 14, the csPCa detection rate decreased to 16%. The proportion of men who needed to change their treatment plans also increased as the number of biopsy cores taken increased, with most of the cases showing an increase in the FT ablation zone. Ganzer et al [16] analyzed 155 patients who underwent RP following MRI-TBx followed by 12 systematic biopsies and observed that the concordance with prostatectomy histopathology was >75% for the unilateral csPCa, stage pT2, or no International Society for Urological Pathology (ISUP) grade group (GG) upgrading. However, when all these parameters were considered together, accuracy decreased to 54%–64%. Interestingly, the authors found that the concordance was slightly higher when cases of ISUP GG3 PCa were evaluated, compared to cases of ISUP≤GG2 PCa.

High PI-RADS scores and index lesion volumes have been linked to worse oncological outcomes [17]. Meng et al [18] found that 18% of patients with PI-RADS ≥4 abnormalities on MRI had no cancer on MRI-guided biopsies. Nevertheless, in most cases, a repeat MRI revealed less aggressive lesions, but when it did not, repeat MRI-guided biopsy was positive in over 60% of patients. Hence, when a patient has multiple lesions on MRI and only one is positive on MRI-guided biopsy, a re-evaluation of the MRI and even repeat biopsies may be recommended before proceeding with FT [19].

When considering FT, it is essential to make sure that the diagnosis is as accurate as possible, and it appears that using MRI alone may not provide enough precision. Moreover, the quality of MRI and the interpretation of those images in clinical practice has largely been questioned. To address this issue, the Prostate Imaging Quality (PI-QUAL) score was proposed in 2020 as a standardized scoring system to evaluate multiparametric MRI quality using a 5-point Likert scoring system. This is crucial as PI-QUAL scores <3 have been linked to higher rates of upstaging from organ-confined to locally advanced PCa, lower detection rates for PI-RADS 5 lesions and extra prostatic extension,

and fewer suspicious lesion detections [20].

It has been shown that Gallium-68 prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has a greater sensitivity and specificity than conventional imaging for patients with high-risk PCa before curative-intent surgery or radiotherapy [21]. The benefit of PSMA-PET in this context is a matter of debate, as the potential effect of adapted treatment is uncertain in terms of oncological outcomes. Even more questionable is the impact that PSMA-PET may have on oncological outcomes for patients with intermediate-risk PCa who undergo FT. Eiber et al [22] explored the role of simultaneous 68Ga-PSMA PET/MRI on the localization of primary PCa and observed that each technique detected tumor-involved areas that were negative in the other modality, concluding that a combined image improves diagnostic accuracy for PCa localization compared with both MRI and PET imaging alone. Furthermore, some authors have identified a significant correlation between the tumor-maximum standardized uptake value and Gleason score [23]. In conclusion, PSMA PET/MRI might help to increase the chances of finding the most clinically significant lesion when planning FT.

Finally, when MRI is not possible for clinical or other reasons, FT may not be completely contraindicated. In such cases, an alternative approach may be a transperineal template-mapping biopsy using a 5 to 10 mm sampling frame, as proposed in the CHRONOS trial [24].

2. Patient selection

The inclusion criteria for FT treatment are not consistent among centers. The threshold for prostate-specific antigen (PSA) level, clinical stage based on digital rectal examination or MRI, ISUP grade, number of visible lesions on MRI, and volume limit of the index lesion, among other variables, are debated and vary among study protocols. Table 1 summarizes several trials on FT for PCa, demonstrating the significant variability in inclusion criteria deemed acceptable for the success of this treatment [24-30].

Among all the variables mentioned above, the ISUP grade may be considered one of the most controversial. As with every experimental technique, FT initially focused on low-risk PCa due to uncertainty about the effects on cancer control. In this sense, the first and only randomized control trial (RCT) on FT that began enrolling patients in 2011 only included those with low-risk PCa. This study compared Vascular-targeted PDT to AS and found that FT was linked to fewer conversions to radical treatments, but also had a higher rate of complications [31].

It has been established that AS is effective for patients at low risk of developing metastases, making FT for ISUP GG1 PCa an unnecessary treatment whit possible adverse effects [3]. Consequently, nowadays Gleason 7 (3+4) seems to be accepted as the best candidate for FT, but the question of whether the treatment indication should be extended to ISUP GG3 PCa is still being debated [32].

Additionally, the intraductal and cribriform patterns have been deemed as an aggressive Gleason 4 subtype with unfavorable oncological outcomes after RP and thus are exclusion criteria for AS. It remains unclear if they should also be considered as an exclusion criteria for FT [33].

Reddy et al [34] analyzed data from 1,379 patients recorded in the HIFU Evaluation and Assessment of Treatment (HEAT) registry from 13 UK centers. The study found that more than 50% of men treated with FT had ISUP GG2 PCa, while 16% had ISUP GG3 PCa. Additionally, 17 patients with high-risk PCa underwent FT. As expected, the failure-free survival rate (FFS), which includes whole-gland salvage treatment, a third FT treatment, systemic treatment, and/or the development of PCa metastases and/or PCa-specific death, was lower for patients with D'Amico intermediate and high-risk PCa. The study also found significant differences in FFS between ISUP GG2 and GG3 patients. A longer follow-up is needed to determine whether salvage treatment following FT is able to control disease progression to metastatic PCa, but the study found 7-year metastasis-free and PCa-specific survival rates greater than 99% [34]. In a recent study, Scheltema et al [35] published a median 5-year outcome of primary IRE for localized PCa. Once again, most of the patients included in the study harbored ISUP GG2 PCa, but 16% of patients harbored ISUP GG3 PCa. Despite the short follow-up time, the study found no significant differences in terms of FFS—defined as no need for radical treatment and/or nodal/distant PCa after initial IRE treatment with one re-treatment of IRE allowed—per ISUP grade.

It is also important to note that for patients with ISUP>GG2 PCa, lymph node control may be necessary during RT or RP [3]. Thus, the requirement for

https://doi.org/10.5534/wjmh.230160

Table 1. Trials on focal therapy for localized prostate cancer and inclusion criteria regarding PSA, ISUP score, presence of MRI lesions outside of the treatment field, presence of positive biopsies outside the index lesion, clinical stage, and index tumor volume

Study	ClinicalTrials.gov Identifier	Type of study	Objective of the study	Inclusion criteria					
				PSA	ISUP	PIRADS ≥3 present in an area outside of the treatment field with a negative biopsy for cancer	Positive biopsies outside the index lesion	Clinical stage	Index tumor volume
Comparative healthcare research outcomes of novel surgery in prostate cancer (IP4-CHRONOS): a prospective, multi-centre therapeutic phase II parallel randomised control trial [24]	NCT04049747	RCT	HIFU or cryotherapy *vs*. whole gland treatment	≤20 ng/mL	ISUP GG1 provided ≥6 mm cancer core length in any one core ISUP GG2 or GG3 of any length ISUP GG4 in some cores but where the overall Gleason score is 7	Pathology must be reviewed and confirm the presence of inflammation or atrophy	Not contraindication if ISUP GG1 ≤5 mm outside of the treatment field	≤cT3a (T2b/T3a will require central review regarding suitability for FT)	<50% of one lobe (require central review prior to enrolment if ≥50%)
Prostate cancer IRE study (PRIS): a randomized controlled trial comparing focal therapy to radical treatment in localized prostate cancer [25]	NCT05513443	RCT	IRE *vs*. whole gland treatment	≤20 ng/mL	ISUP GG2 or GG3 without any Gleason grade 4 in systematic biopsies outside of the target	Only single MRI-visible lesion allowed	ISUP GG1 outside of target lesion allowed	≤cT2b	<1.5 cm^3 lesion volume
Evaluation of HIFU hemiablation and short term androgen deprivation therapy combination to enhance prostate cancer control (ENHANCE) [26]	NCT03845751	Phase II trial. Single Arm	Evaluation of short-term hormone therapy together with HIFU	≤15 ng/mL	ISUP GG2	Not contraindication for FT	Not contraindication if ISUP GG1 ≤1 mm	≤cT2b	Not defined
Focal MR-guided focused ultrasound treatment of localized intermediate risk prostate lesions [27]	NCT01657942	Phase II trial. Single Arm	Evaluation of safety and effectiveness of HIFU	≤20 ng/mL	ISUP GG2 or GG3 with no more than 15 mm cancer in maximal linear dimension in any single core	Only single MRI-visible lesion allowed	Not contraindication if ISUP GG1	≤cT2b	Not defined

Table 1. Continued

Study	ClinicalTrials.gov Identifier	Type of study	Objective of the study	Inclusion criteria					
				PSA	ISUP	PIRADS ≥3 present in an area outside of the treatment field with a negative biopsy for cancer	Positive biopsies outside the index lesion	Clinical stage	Index tumor volume
Pivotal study of the NanoKnife system for the ablation of prostate tissue (PRESERVE) [28]	NCT04972097	Phase II trial. Single Arm	Evaluation of safety and effectiveness of IRE	PSA ≤15 ng/mL or PSA density <0.2 if PSA is >15 ng/mL	ISUP GG2 or GG3	Not defined	Not contraindication if ISUP GG1 ≤6 mm linear extent of prostate-bearing tissue in a single core on standard biopsy	≤cT2b	Not defined
Focal brachytherapy in patients with selected "low-risk" prostate cancer - a phase-II-trial (FOKAL-BT) [29]	NCT02391051	Phase II trial. Single Arm	Evaluation of safety and effectiveness of focal brachytherapy	≤10 ng/mL	ISUP GG1	Not defined	Not defined	≤cT2a	Not defined
A multicenter, randomized, single-blind, 2-arm intervention study evaluating the adverse events and quality of life after irreversible electroporation for the ablation of localized low-intermediate risk prostate cancerr [30]	NCT01835977	RCT	Focal *vs.* extended ablation in localized PCa with IRE	PSA <15 ng/mL or PSA >15 ng/mL counseled with caution	ISUP GG1 or GG2	Not defined	Not defined	Not defined	Not defined

This table presents some of the ongoing studies on focal therapy for prostate cancer, highlighting the variability in inclusion criteria, which reflects the lack of consensus regarding patient selection. RCT: randomized control trial, PCa: prostate cancer, PSA: prostate-specific antigen, ISUP: International Society for Urological Pathology, GG: grade group, MRI: magnetic resonance imaging, RP: radical prostatectomy, HIFU: high-intensity focused ultrasound, IRE: irreversible electroporation.

lymph node treatment should be carefully evaluated when considering FT as an alternative treatment for this group of patients [36]. The questions of timing and methodology remains unresolved, which may result in even greater heterogeneity in FT treatment [2,3].

The issue of multiplicity may be the second most debated aspect in patient selection, after ISUP grade. The decision to consider patients with multiple lesions on MRI for FT is not clear, as it, might depend on factors such as lesion location, size, correspondence with positive biopsies, and biopsy grade. For instance, the PRIS trial only included patients with single lesions on MRI, while the CHRONOS trial may allow patients with multiple lesions after reviewing the pathology [24].

3. Energy selection

Since the 1990s, several energy sources for PCa tissue ablation have been developed but no comparative studies have been conducted [8].

Treatment choice recommendations, such as an *à la carte* approach [10], have attempted to propose specific types of energy to be used based on the location of the lesion, but this approach is not universally accepted and only HIFU, cryotherapy and brachytherapy were considered. In a recent study by Stabile et al [37], it was observed that both HIFU and cryotherapy for PCa likely achieve similar medium-term oncologic results regardless of PCa location. They also found that lesions on the prostatic base were associated with a higher rate of salvage treatment. On the other hand, even though brachytherapy is proposed as the energy to be used, apical lesions remain a problem when using it [38].

Blazevski et al [39] evaluated the efficacy of IRE for treating apical PCa. With a median follow-up of 44 months, 50 patients with PCa lesions within 3 mm of the apical capsule were treated with IRE. Only one patient experienced incontinence 12 months after treatment and one had in-field residual disease on repeat biopsy. The results suggested that using IRE for distal apex PCa is safe and feasible.

Lastly, the lack of a standardized set of tools and equipment for FT in each center, has resulted in a continued problem, as it is unclear whether all energies provide similar results.

4. Treatment considerations

The uncertainty surrounding the selection of patients and the type of energy to be used is further complicated by the ongoing debate on how to perform the treatment.

For instance, there is an open discussion about the benefit of MRI-guided *versus* ultrasound-guided HIFU treatment. MRI-guided HIFU allows to monitor the therapy in real time with magnetic resonance thermometry thermal feedback and evaluate the ablated tissue immediately following treatment. Nevertheless, the hypothetical benefit that this new technology may have in terms of functional or oncological results is still unknown [27].

Concerning the extent of the ablated area, it may be debated whether it should be limited to the lesion, the region, or the lobe. de la Rosette et al [30] found in a 2-arm intervention study that intermediate PCa patients receiving local IRE treatment had the same oncological outcomes as those receiving extensive IRE treatment. However, more patients in the extended treatment arm experienced sexual function impairment, despite no differences in urinary symptoms.

If a focal approach is selected, the importance of margins becomes critical. In 2015, Le Nobin et al [40] compared the boundaries of prostate tumors on MRI and those observed during RP histological examination, proving that MRI underestimated tumor size with a maximal discrepancy between imaging and histological boundaries of an average of 1.99±3.1 mm. They also observed that maximum distance between radiological and anatomopathological boundaries was significantly greater for high suspicion lesions and for high grade lesions. A simulated treatment volume based on a 9 mm treatment margin achieved complete histological tumor destruction in 100% of patients. More recently, Aslim et al [41] also studied the correlation between the size of lesions on MRI and the whole mount histopathology. They found that for tumors up to 12 mm, a 6-mm margin would achieve complete ablation of high-grade tumors. They also noted that larger tumors and those with Gleason 4–5 components were more likely to be underestimated in size. Based on this, they concluded that the optimal tumor size for FT was less than 12 mm, and the optimal treatment margin was 5 to 6 mm. In the same lines, Brisbane et al [42] observed that biopsies taken from a 10-mm radius area surrounding MRI lesions contain most cores of csPCa that are not present within the lesion. These results leave the debate open as to whether a margin of 5 or 10 mm should be considered when planning a FT treatment. Probably the

answer must be adapted to the characteristics of the lesion and the energy used.

5. Follow-up

Contrast enhanced MRI, PSA, and biopsies are crucial for identifying patients suitable for FT and also for monitoring their progress post-treatment.

The percentage of PSA reduction has been identified as an independent predictor of any additional treatment following FT. In the context of a median time of 5 months to reach the PSA nadir, a decrease of at least 50% in PSA levels may be used as an indicator of the effective quality and efficacy of treatment. This also corresponds to a 20% chance of requiring additional radical treatment within 5 years of FT [43].

The appropriate level of PSA that should trigger further testing is uncertain. While MRI has been proposed as a more effective method than PSA testing in identifying remaining tumor tissues after FT [44], its ability to evaluate the results after FT is also limited due to its low sensitivity (less than 50%) in detecting csPCa (55). These limitations have not been overcome by newer techniques such as PSMA-PET [45].

In this scenario, it is crucial that post-treatment biopsies are not skipped to ensure proper monitoring of the disease. The timing and method remain a subject of debate.

CONSENSUS AS A STRONG MOVEMENT TO UNIFY CRITERIA

To address the aforementioned gaps in our knowledge of the effectiveness of FT as an alternative treatment for localized PCa, several RCTs are underway as shown in Table 2 [24,25,46-49]. However, it will likely take several more years to obtain the first results from these studies.

While we await the results of these RCTs, it is important to standardize the way in which FT is performed to ensure consistent, high-quality care. This

Table 2. Randomized controlled trials on focal therapy for localized prostate cancer

Title	ClinicalTrials.gov Identifier	Country	Experimental comparator	Active comparator	Primary outcome
Comparative healthcare research outcomes of novel surgery in prostate cancer (IP4-CHRONOS): a prospective, multi-centre therapeutic phase II parallel randomised control trial [24]	NCT04049747	United Kingdom	HIFU or cryotherapy	Whole gland treatment	Progression-free survival
Evaluation of HIFU in treatment of localized prostate cancer and of recurrence after radiotherapy (HIFI) [46]	NCT04307056	France	HIFU	RP	Recurrence-free survival
Phase 3, multicenter, randomized study, evaluating the efficacy and tolerability of focused HIFU (high intensity focused ultrasound) therapy compared to active surveillance in patients with significant low risk prostate cancer (HIFUSA) [47]	NCT03531099	France	HIFU	AS	Patient proportion who needed radical treatment
Focal prostate ablation *versus* radical prostatectomy (FARP) [48]	NCT03668652	Norway	HIFU	RP	Treatment failure
Partial prostate ablation *versus* radical prostatectomy [49]	ISRCTN99760303	United Kingdom	HIFU or IRE	RP	Treatment failure
Prostate cancer IRE study (PRIS): a randomized controlled trial comparing focal therapy to radical treatment in localized prostate cancer [25]	NCT05513443	Sweden	IRE	RP (PRIS1) RT (PRIS2)	Urinary continence (PRIS1) Irritative urinary symptoms (PRIS2)

This table presents a compilation of ongoing RCTs comparing FT with radical treatments such as RP or RT, as well as AS. It is important to note that unlike in the past, the comparators for FT are now primarily whole-gland treatments instead of AS. HIFU followed by cryotherapy and IRE are the main energy modalities used in current RCTs.
RCT: randomized control trial, FT: focal therapy, RP: radical prostatectomy, RT: radiotherapy, AS: active surveillance, HIFU: high-intensity focused ultrasound, IRE: irreversible electroporation.

may involve establishing guidelines for patient selection, treatment planning, and follow-up care.

According to the recommendations of the Agency for Health Care Policy and Research, Delphi techniques are considered to provide the lowest level of evidence [50]. However, at present, they are the only scientific tools available for generating consensus on the use of the utilization of new diagnostic methods, treatments, or monitoring tools.

Over the last decade, at least 10 consensuses on FT have been published, covering a range of topics such as definitions, patient selection, biomarker use, and follow-up protocols [51]. However, many of these consensuses had relatively small respondent pools, with less than 100 people participating, and a majority of these respondents being urologists and experts on the field.

At this stage, the primary approach to improving the quality of consensus and promoting adherence to its results is to involve a considerable and diverse range of participants. The ongoing Falcon project, a broad Delphi consensus on FT, aims to enhance the current body of literature by engaging a significant number of potential participants from different fields of specialization, encompassing diverse backgrounds and healthcare practices across multiple countries. Furthermore, this project aims to address all the aforementioned controversies pertaining to FT, ranging from patient selection to patient follow-up.

In a situation characterized by uncertainty and ongoing skepticism surrounding FT, it is hopeful that this project will successfully accomplish its objective of providing updated, robust, and consensus-driven guidance in the treatment of patients with PCa suitable for FT.

Conflict of Interest

All the authors of this manuscript have direct involvement with the Falcon Project. A Delphi consensus on focal therapy financially supported by Angiodynamics.

Funding

None.

Acknowledgements

We would like to express our sincere gratitude to all the authors of this paper for their dedication and commitment to improving the lives of prostate cancer patients. In particular, we want to acknowledge their ongoing efforts to explore alternative treatments that may improve the quality of life of patients.

Author Contribution

Conceptualization: LRS, ME, TR, PS, BM, FB, JLDE, AL, RSS. Data/Information curation: LRS. Supervision: RSS. Validation: ME, TR, PS, BM, FB, JLDE, AL, RSS. Visualization: ME, TR, PS, BM, FB, JLDE, AL, RSS. Writing – original draft: LRS. Writing – review & editing: LRS. All authors prepared the manuscript and/or figures; all authors approved the submitted manuscript.

REFERENCES

1. Haffner MC, Zwart W, Roudier MP, True LD, Nelson WG, Epstein JI, et al. Genomic and phenotypic heterogeneity in prostate cancer. Nat Rev Urol 2021;18:79-92.
2. Schaeffer EM, Srinivas S, Adra N, An Y, Barocas D, Bitting R, et al. NCCN guidelines® insights: prostate cancer, version 1.2023. J Natl Compr Canc Netw 2022;20:1288-98.
3. Mottet N, Cornford P, van den Bergh RCN, Briers E, Expert Patient Advocate, Eberli D, et al. EAU - EANM - ESTRO - ESUR - ISUP - SIOG guidelines on prostate cancer. European Association of Urology; 2023.
4. Howard JM. Robotic, laparoscopic, and open radical prostatectomy-is the jury still out? JAMA Netw Open 2021;4:e2120693.
5. Hoffman KE, Penson DF, Zhao Z, Huang LC, Conwill R, Laviana AA, et al. Patient-reported outcomes through 5 years for active surveillance, surgery, brachytherapy, or external beam radiation with or without androgen deprivation therapy for localized prostate cancer. JAMA 2020;323:149-63.
6. Klotz L. Active surveillance with selective delayed intervention using PSA doubling time for good risk prostate cancer. Eur Urol 2005;47:16-21.
7. Spratt DE. Performance and utility of prognostic genomic biomarkers after prostatectomy: decipher-ing the data. J Clin Oncol 2017;35:2977-8.
8. Hopstaken JS, Bomers JGR, Sedelaar MJP, Valerio M, Fütterer JJ, Rovers MM. An updated systematic review on focal therapy in localized prostate cancer: what has changed over the past 5 years? Eur Urol 2022;81:5-33.
9. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al.; PROMIS Study Group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study.

Lancet 2017;389:815-22.
10. Sivaraman A, Barret E. Focal therapy for prostate cancer: an "à la carte" approach. Eur Urol 2016;69:973-5.
11. Abreu AL, Kaneko M, Cacciamani GE, Lebastchi AH. Focal therapy for prostate cancer: getting ready for prime time. Eur Urol 2022;81:34-6.
12. Buhigas C, Warren AY, Leung WK, Whitaker HC, Luxton HJ, Hawkins S, et al. The architecture of clonal expansions in morphologically normal tissue from cancerous and non-cancerous prostates. Mol Cancer 2022;21:183.
13. Rodríguez Sánchez L, Macek P, Barbé Y, Cathelineau X, Sanchez-Salas R. Re: MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. Eur Urol 2020;78:469-70.
14. Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med 2020;382:917-28.
15. Lee AYM, Chen K, Tan YG, Lee HJ, Shutchaidat V, Fook-Chong S, et al. Reducing the number of systematic biopsy cores in the era of MRI targeted biopsy-implications on clinically-significant prostate cancer detection and relevance to focal therapy planning. Prostate Cancer Prostatic Dis 2022;25:720-6. Erratum in: Prostate Cancer Prostatic Dis 2022;25:802.
16. Ganzer R, Mangold A, Siokou FS, Brinkschmidt C, Brummeisl W. Value of magnetic resonance imaging/ultrasound fusion prostate biopsy to select patients for focal therapy. World J Urol 2022;40:2689-94.
17. Miszczyk M, Rembak-Szynkiewicz J, Magrowski Ł, Stawiski K, Namysł-Kaletka A, Napieralska A, et al. The prognostic value of PI-RADS score in CyberKnife ultra-hypofractionated radiotherapy for localized prostate cancer. Cancers (Basel) 2022;14:1613.
18. Meng X, Chao B, Chen F, Huang R, Taneja SS, Deng FM. Followup of men with PI-RADS™ 4 or 5 abnormality on prostate magnetic resonance imaging and nonmalignant pathological findings on initial targeted prostate biopsy. J Urol 2021;205:748-54.
19. Imperial College London. Comparative health research outcomes of novel surgery in prostate cancer (IP4-CHRONOS) [Internet]. Bethesda (MD): U.S. National Library of Medicine; c2021 [cited 2023 Jul 12]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04049747
20. Windisch O, Benamran D, Dariane C, Favre MM, Djouhri M, Chevalier M, et al. Role of the prostate imaging quality PI-QUAL score for prostate magnetic resonance image quality in pathological upstaging after radical prostatectomy: a multicentre European study. Eur Urol Open Sci 2022;47:94-101.
21. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al.; proPSMA Study Group Collaborators. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020;395:1208-16.
22. Eiber M, Weirich G, Holzapfel K, Souvatzoglou M, Haller B, Rauscher I, et al. Simultaneous 68Ga-PSMA HBED-CC PET/MRI improves the localization of primary prostate cancer. Eur Urol 2016;70:829-36.
23. Ferraro DA, Hötker AM, Becker AS, Mebert I, Laudicella R, Baltensperger A, et al. 68Ga-PSMA-11 PET/MRI versus multiparametric MRI in men referred for prostate biopsy: primary tumour localization and interreader agreement. Eur J Hybrid Imaging 2022;6:14.
24. Reddy D, Shah TT, Dudderidge T, McCracken S, Arya M, Dobbs C, et al. Comparative healthcare research outcomes of novel surgery in prostate cancer (IP4-CHRONOS): a prospective, multi-centre therapeutic phase II parallel randomised control trial. Contemp Clin Trials 2020;93:105999.
25. Lantz A, Nordlund P, Falagario U, Jäderling F, Özbek O, Clements M, et al. Prostate cancer IRE study (PRIS): a randomized controlled trial comparing focal therapy to radical treatment in localized prostate cancer. Eur Urol Open Sci 2023;51:89-94.
26. Institut Mutualiste Montsouris. Evaluation of HIFU hemiablation and short term androgen deprivation therapy combination to enhance prostate cancer control. (ENHANCE) [Internet]. Bethesda (MD): U.S. National Library of Medicine; c2023 [cited 2023 Jul 12]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03845751
27. InSightec. Focal MR-guided focused ultrasound treatment of localized intermediate risk prostate lesions [Internet]. Bethesda (MD): U.S. National Library of Medicine; c2020 [cited 2023 Jul 12]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT01657942
28. Angiodynamics. Pivotal study of the NanoKnife system for the ablation of prostate tissue (PRESERVE) [Internet]. Bethesda (MD): U.S. National Library of Medicine; c2023 [cited 2023 Jul 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT04972097
29. University of Erlangen-Nürnberg Medical School. Focal brachytherapy in patients with selected "low-risk" prostate cancer - a phase-II-trial (FOKAL-BT) [Internet]. Bethesda (MD): U.S. National Library of Medicine; c2017 [cited 2023 Jul 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT02391051

30. de la Rosette J, Dominguez-Escrig J, Zhang K, Teoh J, Barret E, Ramon-Borja JC, et al. A multicenter, randomized, single-blind, 2-arm intervention study evaluating the adverse events and quality of life after irreversible electroporation for the ablation of localized low-intermediate risk prostate cancer. J Urol 2023;209:347-53.
31. Azzouzi AR, Vincendeau S, Barret E, Cicco A, Kleinclauss F, van der Poel HG, et al.; PCM301 Study Group. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. Lancet Oncol 2017;18:181-91.
32. Tay KJ, Scheltema MJ, Ahmed HU, Barret E, Coleman JA, Dominguez-Escrig J, et al. Patient selection for prostate focal therapy in the era of active surveillance: an international Delphi consensus project. Prostate Cancer Prostatic Dis 2017;20:294-9.
33. Czaja RC, Tarima S, Wu R, Palagnmonthip W, Iczkowski KA. Comparative influence of cribriform growth and percent Gleason 4 in prostatic biopsies with Gleason 3+4 cancer. Ann Diagn Pathol 2021;52:151725.
34. Reddy D, Peters M, Shah TT, van Son M, Tanaka MB, Huber PM, et al. Cancer control outcomes following focal therapy using high-intensity focused ultrasound in 1379 men with nonmetastatic prostate cancer: a multi-institute 15-year experience. Eur Urol 2022;81:407-13.
35. Scheltema MJ, Geboers B, Blazevski A, Doan P, Katelaris A, Agrawal S, et al. Median 5-year outcomes of primary focal irreversible electroporation for localised prostate cancer. BJU Int 2023;131 Suppl 4:6-13.
36. Ashrafi A, de Castro Abreu AL, Tafuri A, Cacciamani G, Shakir A, Winter M, et al. Concomitant focal therapy and robotic lymphadenectomy in prostate cancer: initial series. J Urol 2019;201(Suppl 4):e1148-9.
37. Stabile A, Sanchez-Salas R, Tourinho-Barbosa R, Macek P, Pellegrino F, Gandaglia G, et al. Association between lesion location and oncologic outcomes after focal therapy for localized prostate cancer using either high intensity focused ultrasound or cryotherapy. J Urol 2021;206:638-45.
38. Srougi V, Barret E, Nunes-Silva I, Baghdadi M, Garcia-Barreras S, Pierrat N, et al. Focal brachytherapy for localized prostate cancer: urinary toxicity depends on tumor location. Brachytherapy 2017;16:988-92.
39. Blazevski A, Amin A, Scheltema MJ, Balakrishnan A, Haynes AM, Barreto D, et al. Focal ablation of apical prostate cancer lesions with irreversible electroporation (IRE). World J Urol 2021;39:1107-14.
40. Le Nobin J, Rosenkrantz AB, Villers A, Orczyk C, Deng FM, Melamed J, et al. Image guided focal therapy for magnetic resonance imaging visible prostate cancer: defining a 3-dimensional treatment margin based on magnetic resonance imaging histology co-registration analysis. J Urol 2015;194:364-70.
41. Aslim EJ, Law YXT, Fook-Chong SMC, Ho HSS, Yuen JSP, Lau WKO, et al. Defining prostate cancer size and treatment margin for focal therapy: does intralesional heterogeneity impact the performance of multiparametric MRI? BJU Int 2021;128:178-86.
42. Brisbane WG, Priester AM, Ballon J, Kwan L, Delfin MK, Felker ER, et al. Targeted prostate biopsy: umbra, penumbra, and value of perilesional sampling. Eur Urol 2022;82:303-10.
43. Stabile A, Orczyk C, Giganti F, Moschini M, Allen C, Punwani S, et al. The role of percentage of prostate-specific antigen reduction after focal therapy using high-intensity focused ultrasound for primary localised prostate cancer. Results from a large multi-institutional series. Eur Urol 2020;78:155-60.
44. Dickinson L, Ahmed HU, Hindley RG, McCartan N, Freeman A, Allen C, et al. Prostate-specific antigen vs. magnetic resonance imaging parameters for assessing oncological outcomes after high intensity-focused ultrasound focal therapy for localized prostate cancer. Urol Oncol 2017;35:30.e9-15.
45. Nazemi A, Huang WC, Wysock J, Taneja SS, Friedman K, Gogaj R, et al. A prospective pilot study investigating performance of 18F-fluciclovine PET imaging for detection of prostate cancer 2 years following primary partial gland cryoablation. Nucl Med Mol Imaging 2022;56:196-201.
46. Association Francaise d'Urologie. Evaluation of HIFU in treatment of localized prostate cancer and of recurrence after radiotherapy (HIFI) [Internet]. Bethesda (MD): U.S. National Library of Medicine; c2023 [cited 2023 Jul 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT04307056
47. Hospices Civils de Lyon. Phase 3, multicenter, randomized study, evaluating the efficacy and tolerability of focused HIFU (high intensity focused ultrasound) therapy compared to active surveillance in patients with significant low risk prostate cancer (HIFUSA) [Internet]. Bethesda (MD): U.S. National Library of Medicine; c2021 [cited 2023 Jul 12]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03531099
48. Baco E; Oslo University Hospital. Focal prostate ablation versus radical prostatectomy (FARP) [Internet]. Bethesda (MD): U.S. National Library of Medicine; c2021 [cited 2023 Jul 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT03668652
49. University of Oxford. ISRCTN99760303: partial prostate ablation versus radical prostatectomy [Internet]. London: BioMed Central; c2023 [cited 2023 Jul 12]. Available from: https://www.isrctn.com/ISRCTN99760303

50. Niederberger M, Spranger J. Delphi technique in health sciences: a map. Front Public Health 2020;8:457.
51. Ong S, Chen K, Grummet J, Yaxley J, Scheltema MJ, Stricker P, et al. Guidelines of guidelines: focal therapy for prostate cancer, is it time for consensus? BJU Int 2023;131:20-31.