Review Article

Focal therapy for prostate cancer: what is really needed to move from investigational to valid therapeutic alternative?—a narrative review

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Background and Objective: The most widely accepted therapeutic alternatives for men with intermediate risk prostate cancer (PCa) are mainly represented by whole gland therapies such as surgery or radiotherapy. However, these treatments can carry in some cases profound functional side effects. With the improvement of risk assessment tools and imaging modalities, in particular with the introduction of multiparametric magnetic resonance imaging of the prostate, a fine topographic characterisation of PCa lesions within the prostatic gland is now possible. This has allowed the development of gland-sparing therapies such as focal therapy (FT) as a means to provide an even more tailored approach in order to safely reduce, where feasible, the harms carried by whole gland therapies. Unfortunately, adoption of FT has been considered so far investigational due to some unsolved issues that currently hamper the use of FT as a valid alternative. Here, we aim to identify the main aspects needed to move FT forward from investigational to a valid therapeutic alternative for clinically localized PCa.

Methods: The literature discussing the evolution of focal therapy in the years and its current landscape was broadly searched to identify the factors hindering FT adoption and possible solutions.

Key Content and Findings: There are three broad areas hindering FT as a valid therapeutic alternative: (I) Correct patient selection; (II) harmonising the different FT technologies; (III) the lack of oncological outcomes.

Conclusions: By targeting the three aforementioned weaknesses of FT, greater adoption is expected, finally making FT a valid therapeutic alternative, potentially reshaping prostate cancer treatment and functional outcomes.

Keywords: Prostate cancer (PCa); focal therapy; treatment; minimally invasive; tissue-sparing surgery

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Introduction

The introduction of prostate-specific antigen (PSA) screening marked a trend towards the early diagnosis of more localised and less aggressive prostate cancer (PCa) (1). Treatment of localised PCa has historically been with whole-gland techniques such as radical prostatectomy (RP) and radiotherapy (RT) which even though offer treatment with a curative intent, can leave patients with important functional sequelae as a consequence of neurovascular bundle and external sphincter damage, such as erectile dysfunction and urinary incontinence in RP and rectal toxicity in RT (2,3).

The choice to undergo radical treatment and risk the emergence of functional complications is more difficult to accept when considering available evidence suggesting that there is a marginal difference in 10-year overall and cancer-specific survival in selected patients with low to intermediate-risk PCa treated with either active monitoring, or RP or RT (4), making complications associated with active treatment difficult to accept. To this end, strategies such as active surveillance (AS) have increased for low-risk PCa to prevent overtreatment in the past 20 years. However, approximately 50% will ultimately require whole-gland treatment due to disease progression at 10 years and only 40% of patients eligible for AS will actually opt for this treatment strategy with the rest choosing directly radical therapy to avoid the added burden of repeat hospital visits, PSA tests and biopsies without any evidence of clinical progression (4).

For these reasons, there appears to be a need for a gland-sparing focal therapy (FT) to bridge the gap between AS and radical therapy and to provide patients with more tailored approaches that aim to reduce the harms carried by radical therapies. There are various forms of FT in use, including cryotherapy, high-intensity focused ultrasound and photodynamic therapy (PDT). However, as of today, adoption of FT in clinical practice has been scarce. Indeed, the vast majority of evidence supporting the role of FT as a valid therapeutic alternative comes from retrospective series with medium term follow-up and lack of standardized treatment protocols and follow-up strategies (5). As a consequence, agreement among urologists concerning FT as a treatment strategy is scarce.

Surveys recently performed on European urologists exploring the community's view on FT revealed that, while most agreed FT will become a standard option for localised PCa in the near future, the same cohort converged on the suggestion that some areas of debate must first be resolved before it be considered as a valid alternative to radical treatment for some patients (6). Among the most critical issues undermining the introduction of FT as a therapeutic alternative to RP there seem to be a few crucial aspects that need to be assessed. Firstly, optimizing patient selection seems pivotal in order to achieve the right balance between oncological and functional outcomes. Secondly, given the presence of several FT techniques, a standardization of treatment and follow-up protocols is mandatory. Finally, to provide strong and reliable evidence supporting the efficacy of FT, valid clinical endpoints, surrogate of treatment response, and valid salvage therapies in case of failure need to be identified, as there is currently no reliable comparable data comparing FT to RP. In this study we aimed at exploring and identifying the key factors that might push FT forward among the set of PCa therapeutic alternatives. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-50/rc).

Methods

In this study we aimed to explore and evaluate what is really needed to push forward FT from the "investigational" status to that of a valid alternative that needs to be considered and to be proposed to selected patients. To do this, we reviewed relevant literature on FT, and described and compared available studies, in order to generate a comprehensive overview of the recommendations regarding FT.

No specific time-period was used to determine relevant studies, as FT is a nascent technique, and as such, characterised by numerous biases and differing methodologies. That said, most evidence provided in this review comes from studies published after 2016, as larger studies were emerging. The search strategy is shown in *Table 1*.

Patient selection

Although partial-gland therapies have been adopted in most other organ systems in oncologic surgery, the prostate has been particularly challenging for three aspects: cancer multifocality (7), accurate imaging mapping tumor foci (8), and a significant heterogeneity among PCa patients in terms of PCa aggressiveness (9).

When first introduced, FT was proposed to patients with low-risk disease, therefore as an alternative to AS, raising criticisms that FT was itself a form of overtreatment. On

Table 1 Search strategy summary

Items	Specification
Date of search (specified to date, month and year)	15th September 2021
Databases and other sources searched	PubMed/MEDLINE, Cochrane library's Central, EMBASE, Scopus databases
Search terms used (including MeSH and free text search terms and filters)	"Prostate cancer Focal Therapy", "Salvage radical prostatectomy post-focal therapy", "Salvage Radiotherapy post-focal therapy"
Timeframe	Studies published between 2000 and October 2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Inclusion criteria: all studies, over the last 22 years, that reported or mentioned functional and oncological outcomes of focal therapy and subsequent salvage therapies were included. The search strategy was limited to articles written in English language
	Exclusion criteria: papers regarding animal studies were excluded
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	Two independent authors analysed the literature and assessed the eligibility of studies in abstract form and in full text by assessing if the inclusion criteria and outcome measures were met. Discrepancies were resolved by consensus
Any additional considerations, if applicable	No

the other hand, the few studies that have performed FT on patients with high-risk PCa however have shown an increased risk for biochemical failure, recurrent cancer and treatment failure (10). The best potential candidates for FT are those patients with a well-defined, low-volume intermediate-risk PCa, with Gleason Group 2 to 3 (11). A correct selection of the disease to treat represents the first important step to provide acceptable outcomes and to avoid misleading results that undermine the reliability of FT as a therapeutic alternative.

As FT is based on selective ablation of a region of the prostate containing cancerous tissue, regardless of the type of FT used, treatment success is largely dependent on patient selection and precise index lesion characterization. An index lesion is defined as the largest and highest grade lesion within the prostate, which some studies have shown to be the main driver of PCa progression (12).

That said, in the past, eligibility for enrolment in AS was through systematic sextant random biopsies, meaning that approximately 25% of patients enrolled in AS were likely harbouring a more aggressive disease with a higher Gleason score and/or tumor volume than reported (13,14). Introduction of prostate mpMRI and standardized reporting systems (e.g., PI-RADS) with both targeted and systematic biopsies to patient selection has allowed a superior patient definition and correct identification of the candidate index lesion in more than 80% of cases (8). This enabled a growing confidence of correctly identifying ideal FT candidates and consequently the treatment was safely extended to include intermediate-risk patients (15).

A study by Nassiri *et al.* assessed this topic. The aim of the study was to refine the impact of patient selection criteria on FT eligibility (16). Applying FT eligibility criteria based on the NCCN (National Comprehensive Cancer Network) intermediate risk definition (17), the authors retrospectively studied 454 men who underwent MRI/US fusion biopsy. They examined whole organ concordance of eligibility assessment in a subset of patients who underwent radical prostatectomy to confirm biopsy findings and derive the accuracy of fusion biopsy for FT eligibility. Eligibility determined by fusion biopsy was concordant with whole mount histology in 75% of cases. In addition, the study showed that using intermediate risk eligibility criteria, more than a third of men with a targeted biopsy proven lesion identified on mpMRI imaging would have been eligible for focal therapy (16).

As of today, mpMRI allows a reliable visualization of the prostate and PCa index lesions, enabling safe adoption of FT. However, there is room for improvement. When compared to whole-mount pathology, mpMRI has been shown to underestimate tumor boundaries by as much as 10 mm (8,18). In fact, to overcome this, it is common practice for urologists to add a 10 mm treatment margin surrounding the index lesion when planning needle positioning to ensure complete ablation (19). A list of the main studies improving patient selection is shown in *Table 2*.

Table 2 List of studies assessing patient selection for FT

Author (ref)	Year	Aspect investigated	Key findings	Key recommendations
Priester *et al.* (8)	2017	Efficacy of mpMRI in describing index lesion	mpMRI correctly identifies index lesion in approximately 80% csPCa; mpMRI consistently underestimates index lesion size by 10 mm	When designing FT probe placement, extend margins by 10 mm to ensure complete lesion targeting
Ahmed *et al.* (15)	2012	To assess targeting of cancer areas with a margin of normal tissue across all PCa-risk categories	FT of individual prostate cancer lesions, whether multifocal or unifocal, leads to a low rate of genitourinary side-effects and an encouraging rate of early absence of clinically significant prostate cancer	Prioritization and support of a pragmatic, randomized, clinical trial comparing focal therapy with whole-gland treatments is urgently needed
Nassiri *et al.* (16)	2018	Refining the impact of patient selection criteria on FT eligibility	Eligibility determined by fusion biopsy was concordant with whole mount histology in 75% of cases. Using intermediate risk eligibility criteria, more than a third of men with a TBx proven lesion identified on mpMRI imaging would have been eligible for focal therapy	Correctly identifying ideal FT candidates allows to extend the treatment to include intermediate-risk patients
Oishi *et al.* (10)	2019	Oncological outcomes after FT at 5 years based on D'Amico risk group	Higher baseline PSA independently predicted treatment failure, biochemical failure, recurrence and radical treatment. Grade Group 3 or greater independently predicted treatment failure (P=0.04)	Due to the elevated risk treatment failure, FT should not be proposed to patient with High risk PCa
Sorce *et al.* (18)	2021	Assessing the relationship between the volume of the IL measured at mpMRI and at RP, stratifying it according to PI-RADS score	mpMRI significantly underestimated the exact volume of the IL, especially for small visible lesions, regardless of PI-RADS score	Consider these findings when planning tailored focal therapy approaches, especially if delivered to men harbouring smaller prostatic lesions
Le Nobin *et al.* (19)	2015	Comparing prostate tumor boundaries on mpMRI and RP histological assessment to define an optimal treatment margin for achieving complete tumor destruction	mpMRI underestimates histologically determined tumor boundaries, especially for lesions with a high imaging suspicion score and a high Gleason score	A 9 mm treatment margin around a lesion visible on magnetic resonance imaging would consistently ensure treatment of the entire histological tumor volume during focal ablative therapy

csPCa, clinically significant prostate cancer; FT, Focal Therapy; IL, Index Lesion; mpMRI, multiparametric magnetic resonance imaging; PCa, prostate cancer; PI-RADS, Prostate Imaging-Reporting and Data System; RP, radical prostatectomy; TBx, targeted biopsy; PSA, prostate-specific antigen.

In the future, further technical advances in prostate mpMRI such as the introduction of ultra-high field mpMRI, with a higher signal-to-noise ratio should lead to greater spatial and temporal resolutions, resulting in improved lesion details and higher diagnostic confidence (20). Moreover, advances in machine learning could provide better consistency in identifying prostate lesions and more accurately distinguish between clinically significant and indolent cancers (21).

A recent addition to PCa imaging assessment on top of mpMRI is the use of prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) to identify intra- and extra-prostatic disease localization. While currently used mostly in the setting of PCa recurrence, recent evidence suggests a potential role in the primary setting, in particular for evaluating lymph node invasion (22,23) and improving the detection of clinically significant prostate cancer (csPCa)

when paired with mpMRI (22). In fact, recent studies are assessing the role of adding PSMA-PET to previously developed nomograms. Therefore, addition of PSMA PET/CT in the pre-operative assessment alongside mpMRI for FT may help to precociously identify those patients with extra-prostatic disease extension where a local, gland-sparing surgery may not be sufficient for disease eradication. The use of accurate imaging modalities represents a cornerstone of the patient selection that could help in selecting men with less probability to harbour multifocal significant disease, overcoming one of the most important obstacles to FT use.

On top of adding superior imaging methods to improve patient selection for FT, genetic testing for aberrations associated with more aggressive forms of cancer may aid in improving patient selection in the near future. Genetic testing, according to the European Association of Urology guidelines, is currently offered to patients with metastatic disease or young newly diagnosed patients with a strong family history (24). As of today, germline and somatic testing still have prohibitive costs and are not deemed cost-effective in the assessment of localised PCa, since they currently have little impact on management (25). That said, genetic testing may have its role in enrolling patients to FT and determining whether it is considered an overtreatment and best suited for AS or conversely the disease may be more aggressive than perceived, therefore it best be treated using whole-gland radical therapy.

Taken together, patients which would benefit the most from FT are intermediate-risk PCa patients and assessed using mpMRI with both systematic and index lesions' targeted biopsies. That said, patient selection process needs to be better calibrated through improved imaging modalities and patient risk assessment, further strengthening the choice to perform FT compared to whole-gland therapy, ultimately decreasing patient morbidity in the correct sub-population of patients. Lastly, a better comprehension of biological behaviour of multifocal disease as compared to unifocal disease and insights on index lesion and satellite foci subcellular differences are needed to implement the selection of best potential candidate to FT for PCa.

Standardization and definition of FT

As with most newly introduced treatment modalities, there is a high level of heterogeneity regarding FT (26). FT can be defined by the type of technology modality used and by the treatment strategy used.

High-intensity focused ultrasound (HIFU) uses thermal energy generated from high-intensity ultrasound to cause tissue ablation via coagulative necrosis and tissue cavitation. Cryotherapy is another form of thermal energy, which however relies on very low temperatures to cause tissue ablation via osmotic injury, apoptosis and vascular injury. Laser interstitial thermal therapy (LITT) uses thermal energy as well, however unlike HIFU, LITT delivers heat generated from a laser device directly to the target area. PDT ablation relies on the activation of a vascular photosensitizer resulting in the generation of reactive oxygen species within the target area causing apoptosis, vessel damage and necrosis. Irreversible electroporation (IRE) ablation relies on trans-perineal electrodes which deliver high voltage, low energy electric current within the target tissue. Each technique described has a different indication depending on both prostate and lesion characteristics (26).

Besides the several energy modalities, among the aspects considered mandatory to affirm FT as a valid therapeutic alternative, standardization and widely used definitions represent pivotal points that need to be addressed (27). In particular, starting from definition and moving through treatment modalities, different energies and follow-up protocols are the main fields that need discussion. A list of the main studies improving standardization in FT is shown in *Table 3*.

Treatment definition

Prior consensus statements have made a distinction between PGA (Partial Gland Ablation) therapies (based on regional tumor localization as defined by biopsy or by imaging), and the image targeted FT (27,28). There are various minimally invasive tissue ablation strategies generically labeled as FT of the prostate (33). A recent consensus by Lebastchi *et al.* considers that the specific term "Focal Therapy" must be meant to describe guided ablation of an image-defined, biopsy confirmed, cancerous lesion(s) with a safety margin surrounding the target lesion (28). The Consensus panel also reached agreement that the current standard of care regarding the imaging modality is mpMRI (28).

Uniforming the administration of PGA and FT is possible. Treatment templates for PGA do not depend on imaging identification of the tumor but instead on their biopsy location only. PGA makes use of the anatomic boundaries of the prostate in order to preserve its functionality while achieving tumor treatment and it

Table 3 List of studies assessing FT standardization

Author (ref)	Year	Aspect investigated	Key findings	Key recommendations
Postema *et al.* (27)	2016	To reach standardized terminology in FT for PCa	FT is a rapidly evolving field of prostate cancer treatments that intends to prevent or delay whole gland treatment associated morbidity without compromising oncologic safety	For the development and implementation of FT, it is important to have standardized reporting criteria.
Lebastchi *et al.* (28)	2020	To reach standardized terminology and follow-up in FT for PCa	The specific term "Focal Therapy" must be meant to describe guided ablation of an image-defined, biopsy confirmed, cancerous lesion(s) with a safety margin surrounding the target lesion	The panel recommends the use of standardized nomenclature and follow-up protocols to generate reliable data
Espinós *et al.* (29)	2016	Evaluating what type of energy would be the optimal for FT	Lesion localization, technical characteristics of each type of energy, patient`s profile and secondary effects must be considered in every choice of focal therapy	The authors propose the "á la carte" model, based on localization of the lesion
Stabile *et al.* (30)	2021	To assess whether PCa location might affect oncologic outcomes after FT	The PCa location does not significantly affect the rate of failure after FT. Both HIFU and cryotherapy likely achieve similar medium-term oncologic results regardless of PCa location even though cryotherapy might be preferable for patients with apical disease	Cryotherapy might be preferable for patients with apical disease. The presence of an apical lesion should not be considered an exclusion criteria for FT
Muller *et al.* (31)	2015	International multidisciplinary consensus for follow-up after FT	Large heterogeneity within current studies with regards to follow-up after FT. It is important to standardize to allow for comparability and safe adoption	The follow-up after focal therapy should be a minimum of 5 years. A mpMRI systematic 12-core biopsy combined with 4–6 targeted biopsy cores of the treated area and any suspicious lesion(s) should be performed after 1 year, and thereafter only when there is suspicion on imaging. PSA should be performed, in the first year, every 3 months, and after the first year, every 6 months. Imaging should be performed at 6 months and at 1 year following treatment. After the first year post-treatment, it should be performed every year until 5 years following treatment
Dickinson *et al.* (32)	2017	To assess the diagnostic performance of PSA parameters and MRI compared to histological outcomes following FT	Early and late MRI performed better than PSA measurements in the detection of residual tumor after focal therapy. MRI, in the form of early and later mpMRI, strongly predicts a negative biopsy after focal therapy for localized PCa	In the context of FT Follow-up, PSA parameters are less reliable than mpMRI

FT, focal therapy; HIFU, High intensity focused ultrasound; mpMRI, multiparametric magnetic resonance imaging; PCa, prostate cancer; PSA, prostate-specific antigen.

is for this reason standardizable. The Multidisciplinary Consensus lists four types of PGA. (I) Quadrant Ablation: destruction of all prostate tissue within a quadrant of the prostate; (II) Hemiablation (lateral or anterior): destruction of all the prostatic tissue within a lateralized hemisphere or the anterior half of the prostate; (III) Hockey stick Ablation: destruction of all the prostatic tissue within a lateralized hemisphere plus anterior contralateral region;

(IV) Subtotal Ablation: destruction of all the prostatic tissue with the preservation of a posterior lateral region (28). On the other hand, FT, as stated by its own definition, is an image-targeted, biopsy-confirmed treatment modality. In this context attention should not be so much placed on a treatment template to be respected, rather on the correct localization of the neoplastic burden and the ablation of the previously described safety margin (34). As aforementioned, the implementation of preoperative diagnostic modalities is needed in order to deliver a disease tailored approach. Indeed, with the goal of achieving the lowest rate of side effect while obtaining cancer control, a true FT approach (with proper safety margins) should be considered as standard of care.

Energy type

Regarding the type of energy, to date, there is no evidence in support of the use of a specific FT modality over another and there are very few studies in literature that try to provide evidence.

Linares Espinós *et al.* considered the PCa location within the prostate as pivotal to define the best modality to be used (29). The proposed "à la carte" approach considers not only the lesion's location, but also the technical characteristics of each type of energy, the patient profile and the possible side effects. This model essentially guides the choice of the type of treatment by focusing on the site of the lesion: Cryotherapy is recommended for anterior lesions, while HIFU is particularly beneficial for posterior lesions (29).

In a more recent study, Stabile *et al.* tried to validate the "à la carte" approach using a propensity-score match analysis according to disease location in a population of men receiving FT with HIFU or cryotherapy (30). Results showed that both HIFU and cryotherapy likely achieve similar medium-term oncologic results regardless of PCa location even though cryotherapy seemed to be preferable for patients with apical disease (30).

What is certain about this aspect of the FT is that not all energies are the same and that each of them might have its own best case scenario of application. However, since no prospective comparative trial has been carried out yet, HIFU represents the most widely and supported energy modality used to date (35). Therefore the use of HIFU may be considered the "gold standard" of FT strategy, until other modalities wait for further and more reliable data to be provided.

Follow-up protocols

To include focal therapy as a valid therapeutic alternative, standardized follow-up is necessary, but literature is still scarce on patient follow-up after focal therapy and there is currently no validated method for monitoring treatment success.

A consensus conducted according to the Delphi method by Muller *et al.* recommends a minimum follow-up duration of 5 years and suggests the tools that should be included in assessing post-treatment outcomes: multiparametric MRI (mpMRI), biopsies, assessment of erectile function, quality of life (QoL), urinary symptoms and incontinence (31). Although it is clear what the tools are, unfortunately there is no agreement on how to use them.

In a study from 2016, Dickinson *et al.* assessed the diagnostic performance of prostate-specific antigen (PSA) parameters (post-HIFU PSA nadir, 6-month PSA, PSA density) *vs.* mpMRI (performed early: <3 weeks from the treatment, and late: 6 months from the treatment) compared to histological outcomes following focal therapy. The mpMRI strongly predicted a negative biopsy after focal therapy and their results showed that early and late mpMRI performed better than PSA measurements in the detection of residual tumor after focal therapy (32).

There is a lack of consensus regarding the optimal frequency and thresholds for prostate-specific antigen (PSA) monitoring after FT. PSA nadir had been proposed as a post-FT tool (36,37), but its value is highly influenced by several factors. There is a need for new PSA based follow-up tools after FT.

In a recent study, Stabile *et al.* tried to determine the relationship of the percentage of PSA reduction (%PSA reduction) after FT using HIFU in predicting the risk of any additional and radical treatment. Their findings endorse the use of %PSA reduction as a practical follow-up clinical tool (38). They showed how a %PSA reduction of >80% should be considered a proxy for excellent treatment quality and efficacy, while patients with a %PSA reduction of <40% have a high risk of receiving additional treatment within 5 years from treatment, suggesting that this subgroup of patients might be served by a stricter follow-up with mandatory biopsy at 12 months after FT (38).

Even though a few data exist on clinical tools to predict PCa recurrence after FT, almost all data come from retrospective series. So far, the use of serial PSA, mpMRI seem to be mandatory after FT for PCa. Furthermore,

given the lack of evidence supporting the accuracy of neither PSA nor mpMRI in predicting PCa recurrence after FT, protocol follow-up biopsies seem to be so far mandatory. The prompt identification of PCa recurrence is mandatory at this stage of FT evaluation, in order to deliver salvage therapies [i.e., salvage radical prostatectomy, salvage (RT)] at an early stage to avoid unfavorable outcomes after salvage therapies for recurrence after FT. Providing reliable data on the validity of salvage therapies is of utmost importance for both patients' counseling and to support the presence of a feasible safety net in case of PCa recurrence.

Further studies are needed to improve evidence in order to identify subset of patients potentially cured after FT without the need of performing further biopsies.

Proving oncological effectiveness

The initial studies assessing the primary outcomes of FT were mostly proof-of-concept, single-arm, retrospective studies geared towards the feasibility of delivering FT safely and with few functional repercussions (5). Such trials therefore recruited mostly men with low-risk disease, which today would be offered AS (5).

One of the most debated topic in the field of FT effectiveness is represented by the possibility and the need to perform follow-up biopsies. As in other types of focal treatments for other organs, there is a risk (in some series not negligible) of treatment failure after FT for PCa (39). The preferred biopsy in the post-FT setting is mpMRI-Targeted, always combined with systematic sampling to also evaluate the area of the untreated prostate parenchyma. Indeed, follow-up biopsy assessment needs to be investigated with a discrimination of in-field and out-of-field site of disease recurrence (28).

The in-field failure is defined as residual tumor identified within the treated area of the prostate, while the out-of-field failure is represented by the presence of disease within untreated areas. The out-of-field recurrence might be represented by wither disease that already existed prior to the initial treatment but missed by the initial assessment or de-novo PCa foci become clinically apparent (28). Most of the studies available in the literature refer to an overall biopsy failure when talking about of FT failure (35). This method of reporting disease recurrence is both inaccurate and potentially underestimating FT effectiveness. In order to being able to assess more accurately and correctly the FT oncological outcomes, both for retrospective and prospective studies it should be considered mandatory to separately report in-field and out-of-field PCa recurrence.

In studies performed in the past decade, FT has always shown acceptable functional outcomes. For instance, studies assessing HIFU reported a pad-free rate of 95% and emergence of erectile dysfunction in up to 20% patients after treatment (26).

Nonetheless, it is the lack of comparable oncological outcomes that hinders the most FT acceptance in the urological community when considered an alternative therapeutic strategy against radical therapies. Unlike functional outcomes, oncological outcomes should be assessed with randomised controlled trials (RCTs) with a comparator arm offering standard of care (SOC). As FT is a possible treatment modality in patients with clinically significant PCa, (RT)or RP should be used to compare outcomes and efficacy of treatment. However, the clinical endpoints commonly used to show whole-gland treatments efficacy (i.e., post-operative PSA, biochemical recurrence, etc.) cannot be applied to FT, as it is a treatment that spares part of the prostatic tissue. To this end, a recent systematic review (26) identified six studies (35,40-44) which were considered IDEAL stage 3 or greater (45). Of these, five studies (40-44) compared FT to SOC, where RP was used as the comparator only in 3 studies, of which two were propensity score matched studies (40,43) and one was a feasibility randomised controlled trial (44). None of the studies were prospective comparative studies of RP versus FT. A weakness common to all studies previously mentioned was that the longest follow-up present was 36 months, too short a time to determine any oncological benefit of receiving FT compared to RP for PCa. Furthermore, a few attempts in comparing FT with radical therapies were performed by carrying out matched analysis comparing the need for local salvage or systemic therapy or emergence of metastases after FT and RP (46). The study showed that FT had a similar cancer control to RP, albeit with a follow-up of less than 10 years. Unfortunately, no evidence was provided regarding the proportion of men in the FT arm receiving a follow-up biopsy and reporting the proportion of men that had a persistence/recurrence of PCa. Moreover, no standardized protocol was used to decide on whether to deliver additional treatments.

In addition to the lack of comparable oncological outcomes, as aforementioned, reliable follow-up clinical tools are needed to identify men at risk of PCa recurrence. To this end, the percentage PSA reduction 6 months post-treatment was recently proposed as an ideal candidate for follow-up, as it correlated with favourable oncological

Table 4 List of studies assessing tools for proving oncological effectiveness

Author (ref)	Year	Aspect investigated	Key findings	Key recommendations
Hopstaken *et al.* (26)	2022	Assessing the effectiveness of FT in patients with localized PCa in terms of functional and oncological outcomes	HIFU and photodynamic therapy have shown most progression toward advanced research stages and show favorable results	More high-quality evidence is required before FT can become available as a standard treatment
Shah *et al.* (46)	2021	Comparing oncological outcomes of FT to RP	In patients with non-metastatic low-intermediate PCa, oncological outcomes over 8 years were similar between FT and RP	Waiting for the results of ongoing RCTs directly comparing focal therapy to radical therapy, data such as these should be used to better counsel patients about their treatment options
Stabile *et al.* (38)	2020	Assessing the value of %PSA reduction after FT in predicting the likelihood of any additional treatment or any radical treatment	%PSA reduction after FT using HIFU for PCa is inversely associated with the need for additional treatment. A %PSA reduction of >80% should be considered a proxy for excellent treatment quality and efficacy. Patients with a %PSA reduction of <40% have a high risk of receiving additional treatment within 5 years from treatment	The percentage of prostate-specific antigen reduction is a useful tool to assess men following FT and its use is recommended to provide useful information to both urologists and patients. Men who have a %PSA reduction of <25% could be considered for more intensive post-treatment surveillance
Huber *et al.* (47)	2020	Investigating the role of the PSA nadir following therapy of nonmetastatic PCa using HIFU	After focal HIFU, PSA nadir + 1.0 ng/mL at 12 months and PSA nadir + 1.5 ng/mL at 24 to 36 months might be used to triage men requiring further tests	mpMRI and biopsy should be the optimal approach after PSA changes meet the criteria for possible failure
Day *et al.* (48)	2021	To deliver FT oncological outcomes by using an innovative RCT framework	The study provides an innovative trial design in what is recognised as a difficult-to-recruit disease space	The authors demonstrated the feasibility of two parallel RCTs within an overarching strategy that fits with existing patient and physician equipoise and maximises the chances of success and potential benefit to patients and healthcare services

FT, focal therapy; PCa, prostate cancer; RP, radical prostatectomy; PSA, prostate-specific antigen; HIFU, high intensity focused ultrasound; RCT, randomized clinical trial.

outcomes and a reduced risk of requiring any additional treatment (38). Indeed, a PSA reduction of greater than 80% correlated with less than 20% requiring a radical treatment at 5 years. Conversely, a reduction of less than 25% increased the risk of additional treatment. Granted the limitation of a short follow-up, this regimen allows physicians to tailor follow-up in patients undergoing FT, increasing patient and physician confidence, improving technique adoption.

In addition, an interesting finding comes from a very recent study by Huber *et al.* investigating the role of the PSA nadir following therapy of non-metastatic Prostate Cancer using HIFU (47). The aim of the study was to test whether prostate specific antigen criteria could diagnose treatment failure. After a retrospective analysis conducted on 598 patients (from a prospectively maintained national database) the authors concluded that after focal HIFU, PSA nadir + 1.0 ng/mL at 12 months and PSA nadir + 1.5 ng/mL at 24 to 36 months might be used to triage men requiring further tests (mpMRI and biopsy). As also recalled by the authors, in light of the retrospective nature of the study, these results need further prospective validation (47).

A list of the main studies improving providing tools for oncological effectiveness is shown in *Table 4*.

Robust oncological outcomes coming from investigations are still lacking. This could be due to the inherent long

Table 5 List of ongoing RCTs comparing FT to whole gland treatment

Trial name	Chief investigator; Country	Estimated completion year	Target enrolment; status	Interventions	Primary outcome
NCT03668652 (FARP)	Baci; Sweden	2024	250; recruiting	HIFU *vs.* RP	Treatment failure: (I) for HIFU: need for secondary whole-gland treatment (RP or EBRT); (II) for RP: PSA >0.2 ng/mL and need for EBRT
ISRCTN17249875 (PART)	Leslie; UK	2026	800; recruiting	HIFU *vs.* radical treatment (RP or RT: EBRT or brachytherapy)	(I) Oncological outcomes (II) Side effects and patient-reported outcomes
NCT04278261	Wang; China	2027	438; not yet recruiting	IRE *vs.* RP	5-year progression-free survival
NCT04049747 (CHRONOS-A)	Ahmed; UK	2027	2450; recruiting	FT (HIFU or cryotherapy) *vs.* radical treatment (RP or RT: EBRT or brachytherapy)	Progression-free survival

RCT, randomized clinical trial; FT, focal therapy; HIFU, high intensity focused ultrasound; RP, radical prostatectomy; EBRT, external beam radiotherapy; IRE, irreversible electroporation; FT, focal therapy; RT, radiotherapy; PSA, prostate-specific antigen.

natural history and high event-free rate of localised PCa mean resulting in outcomes such as time-to-metastasis and cancer-specific mortality requiring a very large sample size and a 10–15-year follow-up period in order to demonstrate any significance. Secondly, there have been numerous failures of setting up RCTs in localised PCa, due to low accrual rates and low compliance (49).

Hence, due to the numerous failures of 'traditional' RCTs in localised PCa, the Imperial Prostate (IP4) Comparative Health Research Outcomes of Novel Surgery in prostate cancer (IP4-CHRONOS) was established to deliver FT oncological outcomes by using an innovative RCT framework (48). It does so by running two separate parallel RCTs where on one side a 'traditional' head-to-head RCT comparing FT to radical treatment is assessed, and on the other, for those who express a strong preference for focal therapy, a surgical multi-arm, multi-stage (MAMS) RCT. A MAMS trial offers multiple different treatment options, all under the same regulatory framework. In this case, the MAMS RCT compares focal therapy alone to focal therapy combined with different neoadjuvant agents, which allows to determine whether failure can be improved with these additional treatments. The choice of enrolment in the parallel RCT is determined by participant and physician preference and discussion. This framework allows better recruitment, acceptance of randomisation and compliance to the allocated arm, overcoming the difficulties encountered in the past.

There are currently four RCTs comparing FT to whole gland treatment [NCT04278261, NCT03668652, ISRCTN17249875 (44), NCT04049747 (50)]. In detail, these are: two large RCTs from the United Kingdom (ISRCTN17249875, n=800; and NCT04049747, n=2,450) comparing FT with radical treatment (RP or EBRT or brachytherapy), a RCT in China (NCT04278261, n=438) comparing focal IRE to RP and a RCT in Sweden (NCT03668652, n=250) is comparing HIFU to RP. Therefore, it seems high quality data will be generated from these studies. Unfortunately, the study with the earliest estimated completion date is the British PART study, which should be concluded in 2024 (44). All studies aforementioned should be completed by 2027. This means that before these dates, we must accept that there will be a lack of comparable data between whole-gland treatment and FT. A list of the ongoing RCTs comparing FT to whole gland treatment and their most relevant characteristics is offered in *Table 5*.

A way to overcome the long natural history of localised PCa, and facilitate the early introduction of FT in clinical practice is to identify intermediate clinical endpoints (ICEs) predicting long-term overall survival (OS) may also be useful (51). These surrogate markers might include the need for local re-intervention or systemic therapy [as previously mentioned (46)], changes in PSA dynamics or changes in PSMA/PET imaging.

To conclude, available evidence demonstrates encouraging results. In recent years, there has been an increase in investigations regarding FT. Such studies are nowadays rightly focused on intermediate-risk PCa, as an alternative to

RP. However, standardization of definitions and interventions in the field of FT is important to lower the sample size required to demonstrate oncological efficacy. Moreover, notwithstanding the consensus meetings performed in the past, trials are still relatively heterogeneous, hindering evidence acquisition. There are ongoing trials investigating FT in its correct therapeutical window, i.e., as an alternative to RP and not AS, albeit it will take until the second half of the decade before results will be available. Finally, with improvements in imaging, identifying patients most suitable for gland-sparing interventions should improve.

Salvage therapies for FT failure

Notwithstanding important advances in patient selection, up to a third of patients may require further local salvage treatment after ablative therapy failure (52). Options for patients experiencing recurrence after FT include salvage robotic-assisted radical prostatectomy (sRARP), salvage radiotherapy (sRT) and repeat FT. Literature regarding salvage therapies for FT failure is limited, mostly descriptive in nature and with small cohorts.

In the past, sRARP was avoided as it was considered complex and unsafe, as prior FT generated peri-prostatic fibrosis, adhesions and loss of anatomical planes (53). However, a study by Pierrard *et al.* (54), showed that sRARP post vascular-targeted PDT was feasible and safe without difficulty for most of the surgeons involved. In most cases the reported difficulty was due to lateral fibrosis during dissection of the nerve bundles on the PDT treated lobe. A second difficulty encountered was linked to posterior fibrosis with consequent adherence to the rectum (54). Accordingly, in another study comparing sRARP and RARP, it was found that while operating times are longer in sRARP compared to primary RARP, and general surgical perception agrees that sRARP are more complex procedures, a matched analysis demonstrated no significant differences in post-operative Clavien-Dindo scores (55). The same study also showed that while sRARP had a 25% increased risk of positive surgical margins and a three-fold greater incidence of PSA persistence, there was no substantial difference in BCR incidence, albeit with a short 36 month follow-up (55). On the other hand, functional outcomes diverged significantly between sRARP and primary radical treatment. Indeed, only 55% of patients treated with sRARP recovered continence at three years, as opposed to 83% in the second group (55). Similarly, recovery of potency was achieved only in 13% patients undergoing sRARP, half compared to primary RARP. Part of the divergence in functional outcomes may be attributed to the feasibility in performing a full or partial nerve-sparing procedure. Indeed, nerve sparing was performed less in patients undergoing sRARP, due to peri-prostatic fibrosis (55). However, in a separate propensity score-matched analysis between sRARP after FT and primary RARP, a sub-analysis on patients who underwent a full nerve-sparing procedure showed that potency rates remained inferior in the cohort with prior FT, possibly owing to a lower quality of nerve-sparing and prior direct nerve damage from FT (56).

Salvage radiotherapy (sRT) is another possibility. Indeed, a recent single-institution study compared sRARP and sRT with concomitant hormone therapy in patients previously treated with FT (57). The study confirmed that like sRARP, oncological and functional outcomes of sRT are inferior compared with primary radical outcomes. When compared in the salvage setting, it appears that sRT may provide better medium-term oncological control compared to sRARP, as overall BCR-free survival at 3 years was 89% and 69%, respectively (57). A potential explanation for this outcome in this particular study was the higher prevalence of high-risk disease in the sRARP cohort (indeed, no significant oncological difference was present in patients with intermediate-risk disease) and concomitant hormone therapy in sRT, resulting in a biochemical suppression. Cumulative sRT-related bowel and urinary toxicity was 25% and 61%, respectively. When comparing functional outcomes, sRT provides a similar urinary continence rate, but a superior erectile function (EF) profile, as potency at 2 years was 21% and 73% for sRARP and sRT, respectively (57).

If FT failure is due to a low volume intermediate-risk disease, repeat FT is a viable option. Indeed, in a previously cited study looking at oncological outcomes in men treated with HIFU, patients were followed for 3 years. Twenty-six per cent required salvage treatment, of which 193 (71%) opted for a repeat focal HIFU, with 74% of these patients not requiring further treatment (35).

In conclusion, sRARP performed by experienced surgeons is a feasible treatment option in patients experiencing FT failure. Both sRARP and sRT appear to provide acceptable oncological control, albeit at the cost of worse functional outcomes when compared to a primary radical treatment. Definitive evidence of oncological control using 'hard'endpoints such as overall survival are still needed in this setting. Potency was significantly more preserved in patients which had undergone sRT, therefore careful counselling and patient preference should be performed

when deciding on the ideal salvage treatment option.

However, it is worth mentioning that current data in the salvage setting are afflicted by the poor disease features of current patients candidate for salvage therapies. For instance, in the previously cited study by Bhat *et al.* (55), 50% of patients had at least ISUP Grade Group 3 or more disease. Furthermore, at the final pathology assessment, 66% and 9% of men had locally advanced disease and nodal metastasis, respectively. Again, this is most probably due to poor patient selection and lack of a standardized post-FT follow-up. This leads to poor outcomes in the salvage setting and consequent hesitation towards welcoming FT as a valid therapeutic alternative (58). A list of the main studies improving patient selection is shown in *Table 6*.

Conclusions and future directions

In conclusion, it appears that FT for PCa is in a transition phase, exiting from being an experimental treatment, albeit too premature to be considered an established treatment.

The shift from treating low-risk to intermediate-risk PCa patients is the correct direction, considering the effectiveness of current management in the former cohort. Moreover, the continuous improvement in imaging modalities should allow a better characterization of the index lesion, improving patient selection and further justifying treating solely the index lesion, ensuring optimal functional outcomes. Equally important, standardising and harmonising the different FT approaches will be important to allow comparability and promote widespread adoption of FT. Finally, the ultimate step in consolidating the transition and establishing FT as valid alternative is the generation of robust long-term oncological outcomes.

However, the need to wait several years for RCT data to be published might be overcome by providing solid data based on well-selected comparative series with standardized follow-up, in order to understand as soon as possible whether or not FT could be considered among the set of therapeutic alternatives and providing patients with a further option that is awaited in the field of treatment of clinically localized PCa.

Table 6 List of main studies assessing salvage therapies after FT failure

Author (ref)	Year	Study design	Salvage therapy investigated	Population characteristics pre-salvage therapy	Key findings	
					Peri-operative	Outcomes
Pierrard *et al.* (54)	2019	Retrospective study on 42 patients which underwent vascular targeted photodynamic therapy (TOOKAD®). Intervention type: 16 were RARP, 6 were laparoscopic and 20 were open surgery	Non-comparative, descriptive study of sRARP	Median age at RP: 65 years, mean PSA 5.9 ng/mL, post-FT positive biopsies before salvage: cancer in treated lobe: 63%, cancer in non-treated lobe: 67, bilateral cancer: 33%	Surgical feasibility: median operative time: 180 min (IQR 150–223), median blood loss: 200 mL (IQR 155–363), perceived difficulty: easy in 69%, difficult in 31%	Oncological and functional outcomes: PSM in 31%, undetectable PSA at 1 yr in 88%, 4/42 had final PSA >0.2 ng/mL at 23 months (IQR 12–36), at 1 year 64% were completely continent (no pads) and 24% had low incontinence (1 pad), 11% recovered potency without treatment and 64% recovered potency with appropriate treatment

Table 6 *(continued)*

Table 6 *(continued)*

Author (ref)	Year	Study design	Salvage therapy investigated	Population characteristics pre-salvage therapy		Key findings	
						Peri-operative	Outcomes
Bhat *et al.* (55)	2021	Retrospective study on 53 patients who underwent sRARP following failure of FT compared to a matched control sample of men who had undergone primary RARP	sRARP *vs.* pRARP	sRARP: Mean PSA 3.2 ng/mL Pre-operative ISUP GG: ≤ GG2 49%, ≥ GG3 50% Pre-op SHIM score: 18 Pre-op AUA symptom score: 8	pRARP: Mean PSA 3.6 ng/mL Pre-operative ISUP GG: ≤ GG2 62%, ≥ GG3 38% Pre-op SHIM score: 16 Pre-op AUA symptom score: 8	Surgical comparison: operative time: 121 min *vs.* 108 min (sRARP *vs.* pRARP), median blood loss: 100 mL in both groups, degree of full nerve sparing: 0% *vs.* 32% (sRARP *vs.* pRARP), degree of partial nerve sparing: 85% *vs.* 66% (sRARP *vs.* pRARP), post-operative Clavien-Dindo score 1–2: 21% *vs.* 11% (sRARP *vs.* pRARP; NS)	Oncological outcomes: PSM incidence: 40% *vs.* 15% (sRARP *vs.* pRARP), pN+: 9.4% *vs.* 5.7% (sRARP *vs.* pRARP), BCR-free at 3 yrs: 64% *vs.* 81% (sRARP *vs.* pRARP; NS), BCR at 3 yrs: 17.0% *vs.* 13.2% (sRARP *vs.* pRARP; NS), PSA persistence: 15.1% *vs.* 5.6% (sRARP *vs.* pRARP; NS) Functional outcomes: continence at 3 yrs (no pads): 54.7% *vs.* 83% (sRARP *vs.* pRARP), potency (non-pharmacological): 13.2% *vs.* 34% (sRARP *vs.* pRARP), patients with 2 FT treatments prior sRARP 57.1% were incontinent; 100% impotent
Nunes-Silva *et al.* (56)	2017	Retrospective matched analysis of 22 men who underwent sRARP and 44 patients treated with pRARP.	sRARP *vs.* pRARP	sRARP: Mean PSA 9.24 ng/mL D'Amico risk group: low risk 27.3%, intermediate risk 59.1%, high risk 13.6% TNM: T1c 90.9%, T2a 9.1%, no differences in IPSS/IIEF5 score	pRARP: Mean PSA 8.73 ng/mL D'Amico risk group: low risk 29.5%, intermediate risk 56.8%, high risk 13.6% TNM: T1c 79.5%, T2a 20.4%, No differences in IPSS/IIEF5 score	Surgical comparison: mean operative time, hospital stay, catheterization time, blood loss and complications were comparable in sRARP and pRARP, degree of full nerve sparing: No 9% *vs.* 2%; unilateral 36% *vs.* 13%; bilateral 54% *vs.* 84% (sRARP *vs.* pRARP)	Oncological outcomes: comparable PSM between two groups, BCR-free survival at 2 years: 56% *vs.* 92% (sRARP *vs.* pRARP) Functional Outcomes: Continence at 2 yrs (no pads): 73% *vs.* 76% (sRARP *vs.* pRARP; NS), IIEF-5 score in patients which underwent unilat. Or bilat. Nerve Sparing at 1 yr: 3 *vs.* 9 (sRARP *vs.* pRARP)
Nathan *et al.* (57)	2022	Prospective study comparing 100 patients undergoing sRARP *vs.* 100 patients undergoing sRT	sRARP *vs.* sRT	sRARP: Mean PSA 5.8 ng/mL D'Amico risk group: low risk 0%, intermediate risk 34%, high risk 66% TNM: T1 2%, T2 61%, ≥T3 37%	sRT: Mean PSA 4.6 ng/mL D'Amico risk group: low risk 1%, intermediate risk 51%, high risk 48% TNM: T1 0%, T2 64.9%, ≥T3 35%	Therapy derived complications: sRT: bowel RTOG grade 1-3: 39%, urinary RTOG grade 1-3: 61%; sRARP: Clavien-Dindo 1-3: 9%	Oncological Outcomes: comparable BCR overall, BCR in High-risk: 21% *vs.* 10% (sRARP *vs.* sRT), cancer-specific Mortality: 0% *vs.* 4% (sRARP *vs.* sRT) Functional Outcomes: continence at 2 yrs (no pads): 84% *vs.* 74% (sRARP *vs.* sRT), potency at 2 years: 21% *vs.* 73% (sRARP *vs.* sRT)

FT, focal therapy; PSA, prostate-specific antigen; IQR, interquartile range; RARP, robotic-assisted radical prostatectomy; pRARP, primary robotic-assisted radical prostatectomy; sRARP, salvage robotic-assisted radical prostatectomy; PSM, positive surgical margins; pN+, positive lymph nodes at pathology; NS, non significant; sRT, salvage radiation therapy; IPSS, International Prostatic Symptoms Score; IIEF5, The International Index of Erectile Function; SHIM, Sexual Health Inventory for Men; RP, radical prostatectomy.

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Footnote

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References

1. Tarone RE, Chu KC, Brawley OW. Implications of stage-specific survival rates in assessing recent declines in prostate cancer mortality rates. Epidemiology 2000;11:167-70.
2. Wallis CJ, Herschorn S, Saskin R, et al. Complications after radical prostatectomy or radiotherapy for prostate cancer: results of a population-based, propensity score-matched analysis. Urology 2015;85:621-7.
3. Briganti A, Chun FK, Salonia A, et al. Complications and other surgical outcomes associated with extended pelvic lymphadenectomy in men with localized prostate cancer. Eur Urol 2006;50:1006-13.
4. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med 2016;375:1415-24.
5. Valerio M, Ahmed HU, Emberton M, et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. Eur Urol 2014;66:732-51.
6. Marra G, Ploussard G, Ost P, et al. Focal therapy in localised prostate cancer: Real-world urological perspective explored in a cross-sectional European survey. Urol Oncol 2018;36:529.e11-22.
7. Andreoiu M, Cheng L. Multifocal prostate cancer: biologic, prognostic, and therapeutic implications. Hum Pathol 2010;41:781-93.
8. Priester A, Natarajan S, Khoshnoodi P, et al. Magnetic Resonance Imaging Underestimation of Prostate Cancer Geometry: Use of Patient Specific Molds to Correlate Images with Whole Mount Pathology. J Urol 2017;197:320-6.
9. Tosoian JJ, Antonarakis ES. Molecular heterogeneity of localized prostate cancer: more different than alike. Transl Cancer Res 2017;6:S47-S50.
10. Oishi M, Gill IS, Tafuri A, et al. Hemigland Cryoablation of Localized Low, Intermediate and High Risk Prostate Cancer: Oncologic and Functional Outcomes at 5 Years. J Urol 2019;202:1188-98.
11. Tay KJ, Scheltema MJ, Ahmed HU, 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.
12. Liu W, Laitinen S, Khan S, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nat Med 2009;15:559-65.
13. Berglund RK, Masterson TA, Vora KC, et al. Pathological upgrading and up staging with immediate repeat biopsy in patients eligible for active surveillance. J Urol 2008;180:1964-8.
14. Louie-Johnsun M, Neill M, Treurnicht K, et al. Final outcomes of patients with low-risk prostate cancer suitable for active surveillance but treated surgically. BJU Int 2009;104:1501-4.
15. Ahmed HU, Hindley RG, Dickinson L, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol 2012;13:622-32.
16. Nassiri N, Chang E, Lieu P, et al. Focal Therapy Eligibility Determined by Magnetic Resonance Imaging/Ultrasound Fusion Biopsy. J Urol 2018;199:453-8.
17. Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate

Cancer, Version 1.2016. J Natl Compr Canc Netw 2016;14:19-30.
18. Sorce G, Stabile A, Lucianò R, et al. Multiparametric magnetic resonance imaging of the prostate underestimates tumour volume of small visible lesions. BJU Int 2022;129:201-7.
19. Le Nobin J, Rosenkrantz AB, Villers A, 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.
20. Vos EK, Lagemaat MW, Barentsz JO, et al. Image quality and cancer visibility of T2-weighted magnetic resonance imaging of the prostate at 7 Tesla. Eur Radiol 2014;24:1950-8.
21. Yuan Y, Qin W, Buyyounouski M, et al. Prostate cancer classification with multiparametric MRI transfer learning model. Med Phys 2019;46:756-65.
22. Emmett L, Buteau J, Papa N, et al. The Additive Diagnostic Value of Prostate-specific Membrane Antigen Positron Emission Tomography Computed Tomography to Multiparametric Magnetic Resonance Imaging Triage in the Diagnosis of Prostate Cancer (PRIMARY): A Prospective Multicentre Study. Eur Urol 2021;80:682-9.
23. Stabile A, Pellegrino A, Mazzone E, et al. Can Negative Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Avoid the Need for Pelvic Lymph Node Dissection in Newly Diagnosed Prostate Cancer Patients? A Systematic Review and Meta-analysis with Backup Histology as Reference Standard. Eur Urol Oncol 2022;5:1-17.
24. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol 2021;79:243-62.
25. Sokolova AO, Cheng HH. Genetic Testing in Prostate Cancer. Curr Oncol Rep 2020;22:5.
26. Hopstaken JS, Bomers JGR, Sedelaar MJP, et al. 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.
27. Postema AW, De Reijke TM, Ukimura O, et al. Standardization of definitions in focal therapy of prostate cancer: report from a Delphi consensus project. World J Urol 2016;34:1373-82.
28. Lebastchi AH, George AK, Polascik TJ, et al. Standardized Nomenclature and Surveillance Methodologies After Focal Therapy and Partial Gland Ablation for Localized Prostate Cancer: An International Multidisciplinary Consensus. Eur Urol 2020;78:371-8.
29. Linares Espinós E, Barret E, Sivaraman A, et al. Localized prostate cancer Focal Therapy: "A la carte" Model. Arch Esp Urol 2016;69:345-52.
30. Stabile A, Sanchez-Salas R, Tourinho-Barbosa R, 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.
31. Muller BG, van den Bos W, Brausi M, et al. Follow-up modalities in focal therapy for prostate cancer: results from a Delphi consensus project. World J Urol 2015;33:1503-9.
32. Dickinson L, Ahmed HU, Hindley RG, 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.e9-30.e15.
33. Ward JF, Jones JS. Classification system: organ preserving treatment for prostate cancer. Urology 2010;75:1258-60.
34. Stabile A, Moschini M, Montorsi F, et al. Focal therapy for prostate cancer - index lesion treatment vs. hemiablation. A matter of definition. Int Braz J Urol 2019;45:873-6.
35. Stabile A, Orczyk C, Hosking-Jervis F, et al. Medium-term oncological outcomes in a large cohort of men treated with either focal or hemi-ablation using high-intensity focused ultrasonography for primary localized prostate cancer. BJU Int 2019;124:431-40.
36. Kongnyuy M, Lipsky MJ, Islam S, et al. Predictors of biochemical recurrence after primary focal cryosurgery (hemiablation) for localized prostate cancer: A multi-institutional analytic comparison of Phoenix and Stuttgart criteria. Urol Oncol 2017;35:530.e15-9.
37. Kongnyuy M, Islam S, Mbah AK, et al. PSA kinetics following primary focal cryotherapy (hemiablation) in organ-confined prostate cancer patients. World J Urol 2018;36:209-13.
38. Stabile A, Orczyk C, Giganti F, 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.
39. Tay KJ, Amin MB, Ghai S, et al. Surveillance after prostate focal therapy. World J Urol 2019;37:397-407.
40. Scheltema MJ, Chang JI, Böhm M, et al. Pair-matched patient-reported quality of life and early oncological

control following focal irreversible electroporation versus robot-assisted radical prostatectomy. World J Urol 2018;36:1383-9.
41. Gill IS, Azzouzi AR, Emberton M, et al. Randomized Trial of Partial Gland Ablation with Vascular Targeted Phototherapy versus Active Surveillance for Low Risk Prostate Cancer: Extended Followup and Analyses of Effectiveness. J Urol 2018;200:786-93.
42. Azzouzi AR, Vincendeau S, Barret E, et al. 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.
43. Garcia-Barreras S, Sanchez-Salas R, Sivaraman A, et al. Comparative Analysis of Partial Gland Ablation and Radical Prostatectomy to Treat Low and Intermediate Risk Prostate Cancer: Oncologic and Functional Outcomes. J Urol 2018;199:140-6.
44. Hamdy FC, Elliott D, le Conte S, et al. Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. Health Technol Assess 2018;22:1-96.
45. McCulloch P, Altman DG, Campbell WB, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet 2009;374:1105-12.
46. Shah TT, Reddy D, Peters M, et al. Focal therapy compared to radical prostatectomy for non-metastatic prostate cancer: a propensity score-matched study. Prostate Cancer Prostatic Dis 2021;24:567-74.
47. Huber PM, Afzal N, Arya M, et al. Prostate Specific Antigen Criteria to Diagnose Failure of Cancer Control following Focal Therapy of Nonmetastatic Prostate Cancer Using High Intensity Focused Ultrasound. J Urol 2020;203:734-42.
48. Day E, Prevost AT, Sydes MR, et al. Feasibility of Comparative Health Research Outcome of Novel Surgery in prostate cancer (IP4-CHRONOS): statistical analysis plan for the randomised feasibility phase of the CHRONOS study. Trials 2021;22:547.
49. Ahmed HU, Berge V, Bottomley D, et al. Can we deliver randomized trials of focal therapy in prostate cancer? Nat Rev Clin Oncol 2014;11:482-91.
50. Reddy D, Shah TT, Dudderidge T, 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.
51. Martini A, Gandaglia G, Karnes RJ, et al. Defining the Most Informative Intermediate Clinical Endpoints for Predicting Overall Survival in Patients Treated with Radical Prostatectomy for High-risk Prostate Cancer. Eur Urol Oncol 2019;2:456-63.
52. Guillaumier S, Peters M, Arya M, et al. A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. Eur Urol 2018;74:422-9.
53. Barret E, Harvey-Bryan KA, Sanchez-Salas R, et al. How to diagnose and treat focal therapy failure and recurrence? Curr Opin Urol 2014;24:241-6.
54. Pierrard V, Lebdai S, Kleinclauss F, et al. Radical Prostatectomy after Vascular Targeted Photodynamic Therapy with Padeliporfin: Feasibility, and Early and Intermediate Results. J Urol 2019;201:315-321.
55. Bhat KRS, Covas Moschovas M, Sandri M, et al. Outcomes of Salvage Robot-assisted Radical Prostatectomy After Focal Ablation for Prostate Cancer in Comparison to Primary Robot-assisted Radical Prostatectomy: A Matched Analysis. Eur Urol Focus 2021. [Epub ahead of print].
56. Nunes-Silva I, Barret E, Srougi V, et al. Effect of Prior Focal Therapy on Perioperative, Oncologic and Functional Outcomes of Salvage Robotic Assisted Radical Prostatectomy. J Urol 2017;198:1069-76.
57. Nathan A, Ng A, Mitra A, et al. Comparative Effectiveness Analyses of Salvage Prostatectomy and Salvage Radiotherapy Outcomes Following Focal or Whole-Gland Ablative Therapy (High-Intensity Focused Ultrasound, Cryotherapy or Electroporation) for Localised Prostate Cancer. Clin Oncol (R Coll Radiol) 2022;34:e69-e78.
58. Montorsi F, Stabile A, Gandaglia G, et al. Re: K.R. Seetharam Bhat, Marcio Covas Moschovas, Marco Sandri, et al. Outcomes of Salvage Robot-assisted Radical Prostatectomy After Focal Ablation for Prostate Cancer in Comparison to Primary Robot-assisted Radical Prostatectomy: A Matched Analysis. Eur Urol Focus. In press. https://doi.org/10.1016/j.euf.2021.10.005 [published online ahead of print, 2022 Feb 18]. Eur Urol Focus. 2022;S2405-4569(22)00046-3. doi:10.1016/j.euf.2022.01.022.

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