Guidelines of guidelines: focal therapy for prostate cancer, is it time for consensus?

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Objective
To provide a summary and discussion of international guidelines, position statements and consensus statements in relation to focal therapy (FT) for prostate cancer (PCa).

Methods
The European Association of Urology-European Association of Nuclear Medicine-European Society for Radiotherapy and Oncology-European Society of Urogential Radiology-International Society of Urological Pathology-International Society of Geriatric Oncology and American Urological Association-American Society for Radiation Oncology-Society of Urologic Oncology guidelines were interrogated for recommendations for FT. PubMed and Ovid Medline were searched for consensus statements. Only studies in English since 2015 were included. Reference lists of the included articles were also interrogated and a manual search for studies was also performed.

Results
Our results showed a lack of long-term randomised data for FT. International Urological guidelines emphasised the need for more high-quality clinical trials with robust oncological and toxicity outcomes. Consensus and positions statements were heterogenous.

Conclusion
A globally accepted guideline for FT planning, technique and follow-up are still yet to be determined. Well-designed studies with long-term follow-up and robust clinical and toxicity endpoints are needed to improve our understanding of FT and create uniform guidelines to streamline management and follow-up.

Keywords
focal therapy, prostate cancer, guidelines, consensus, prostate carcinoma

Introduction
Focal therapy (FT) for prostate cancer (PCa) encompasses a group of minimally invasive techniques used to focally ablate an area of PCa whilst preserving the surrounding benign tissue. Several energy sources are available including high-intensity focussed ultrasound (HIFU), cryotherapy, irreversible electroporation (IRE), laser, photodynamic therapy, and brachytherapy (BT) can be used to ablate PCa. The aims of FT are to achieve the same oncological outcomes as radical treatment whilst sparing men from the potential side-effects of whole-gland therapy. By utilising this treatment, men should have treatment strategy de-escalated to active surveillance.

Currently, the evidence in support of FT is still limited. Whilst there are several publications in the literature, there is a lack of long-term and randomised data in this field. Clinical endpoints, definitions and patient selection varies between trials. Diagnostic methods for PCa include multiparametric MRI (mpMRI), prostate-specific membrane antigen positron emission tomography CT (PSMA PET/CT), biomarkers and transrectal or transperineal (saturation) biopsies; however, these are not streamlined in the selection of patients for FT.
Due to the investigative status, current treatment guidelines do not offer much guidance on the use of FT; however, several groups have published consensus statements on the different aspects of FT.

This review article contains a summary of the recommendations on FT, from international PCa guidelines, position statements as well as a summary of recent consensus statements regarding FT and a list of ongoing clinical trials for FT.

**Major International Guidelines**

The European Association of Urology (EAU)-European Association of Nuclear Medicine (EANM)-European Society for Radiotherapy and Oncology (ESTRO)-European Society of Urological Radiology (ESUR)-International Society of Urological Pathology (ISUP)-International Society of Geriatric Urological Radiology (ISUR)-International Society of Urogential Radiology (ESUR)-International Society of Urology (SIU)-American Society for Radiation Oncology (ASTRO)-Society of Urologic Oncology (SUO) (referred to as ‘EAU+’ in this article), AUA-American Society for Radiation Oncology (ASTRO)-Society of Urologic Oncology (SUO) (referred to as ‘AUA+’ in this article) and National Comprehensive Cancer Network (NCCN) PCa guidelines were interrogated for recommendations about FT. Of note, the National Institute for Health and Care Excellence (NICE) were not included in this article given that specific FT guidelines had not been updated since 2012. The EAU+ and AUA+ guideline recommendations are summarised in Table 1.

The EAU+ performed a systematic review of literature to update their guideline on FT [1]. Comparative studies of FT vs either radical treatment, active surveillance or alternative FT published between 2000 to 2020 were included in the analysis. Of 1119 articles found in the search, only four met inclusion criteria of which only one was prospective. The authors found that clinical endpoints in the studies were heterogenous and risk of bias was overall moderate to high. Due to this low quality of evidence, the EAU+ recommendation for FT for newly diagnosed PCa is to only offer FT within a clinical trial setting or well-designed prospective cohort study.

A position statement on primary treatment of PCa with FT from the EAU+ echoed the above recommendations [2]. Using a similar search to the EAU+ guidelines, the authors formed five concluding statements:

1. FT can ablate cancer cells, but currently, imaging methods cannot reliably identify all high-risk cancer clones within the prostate.
2. The literature suggests that the oncological effectiveness of FT remains unproven due to the lack of reliable comparative data against standard of care including active surveillance. We recommend awaiting prospective comparative trial data before implementing FT in routine clinical practice.
3. FT studies targeting smaller regions of the prostate have reported reduced toxicity compared with whole-gland treatment options, but robust comparative studies with toxicity endpoints are still lacking.
4. Given the considerable uncertainties regarding the optimal follow-up of men treated with FT, patients should only be treated within the context of a clinical trial using predefined criteria.
5. Better understanding of the toxicity of secondary treatments and re-treatments after FT is needed, and its assessment should be part of prospective investigations.

In addition, they emphasised the need for more high-quality (randomised) clinical trials with robust oncological and toxicity endpoints.

The EAU+ guidelines also mention the use of HIFU and cryotherapy for recurrent PCa. They state that in systematic reviews and meta-analyses on HIFU and cryotherapy, the majority of men received whole-gland ablation, whereas only <15% received FT. Given the lack of data available, their recommendation is that focal HIFU and focal cryotherapy should only be performed in selected patients in experienced centres as part of a clinical trial or well-designed prospective cohort study [3].

The AUA+ guidelines [4] on FT were formed by expert opinion and classified as low-grade evidence. They recommend FT to be performed only in the context of a trial. Furthermore, patients should be informed that there is a lack of robust evidence and that they may require further treatment. For HIFU specifically, it states that apical lesions have a higher level of cancer persistence. The AUA+ guidelines do not mention FT in the radiotherapy (RT)-recurrent setting.

The NCCN guidelines [5] state that cryotherapy or other local therapies are not recommended as routine primary therapy for localised PCa due to lack of long-term data comparing these treatments to RT or radical prostatectomy (RP). The panel also recommended only cryosurgery and HIFU as local therapy options for RT recurrence in the absence of metastatic disease.

**Consensus Statements**

As can be seen, the guidelines above currently offer limited advice that is mostly expert opinion given the lack of good-quality long-term data for FT. As such, multiple consensus statements have been published, formulated by experts in the field, to guide practice and identify areas that require refinement through further research. Below, we summarise published consensus statements on FT and demonstrate the evolution of these statements over time.

PubMed and Ovid Medline were searched for consensus statements using the search strategy ((focal therapy) AND...
Definitions/Nomenclature

Defining nomenclature is an integral step in consistent FT research across the globe and advancing this field of PCa management.

Table 1 Summary of EAU-EANM-ESTRO-ESUR-ISUP-SIOG [3] and AUA/ASTRO/SUO guidelines [4].

| Definition               | EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines | AUA/ASTRO/SUO guidelines | NCCN guidelines |
|--------------------------|------------------------------------------|--------------------------|-----------------|
| Newly diagnosed PCa     | • Only offer FT within a clinical trial setting or well-designed prospective cohort study (for low- and intermediate-risk disease (Strong)) • Do not offer either whole-gland therapy or FT to patients with high-risk localised disease (Strong) | FT                       | • Cryotherapy or other local therapies are not recommended as routine primary therapy for localised PCa due to lack of long-term data comparing these treatments to RT or RP. |
| Recurrent PCa           | • Only cryotherapy and HIFU mentioned • Salvage cryotherapy and HIFU systematic reviews had very small percentage of FT cases involved (<15%). Overwhelming majority whole-gland ablation. • Therefore FT ablative data are very limited • Recommendation – Only offer salvage RP, BT, HIFU or cryosurgical ablation to highly selected patients with biopsy-confirmed local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres. (Strong) | At this time, the panel recommends only cryosurgery and HIFU (Category 2B) as local therapy options for RT recurrence in the absence of metastatic disease. |

FDA, United States Food and Drug Administration.

Postema et al. [6] published outcomes of a Delphi consensus on FT definitions in 2016. The final (third) round incorporated 73 responses from Urologists (75%), Radiologists (11%), Radiotherapists (4%), Researchers (4%), Pathologists (3%) and Medical Oncologists (3%). The level of agreement necessary to achieve consensus was defined as >80%. A more recent Delphi consensus, led by The Focal Therapy Society, was published by Lebastchi et al. [7] in 2020. The final (third) round incorporated 48 responses from Urologists (72%) and Radiologists (28%). The level of

(prostate cancer)) AND (consensus). Only studies in English since 2015 were included. Reference lists of the included articles were also interrogated and a manual search for studies was also performed. The last search was performed on 1 May 2022.
agreement necessary to achieve consensus was defined as >80%.

A summary of their findings can be seen in Table 2 [6,7].

### Selection of Energy Source

There are multiple energy sources used to focally ablate PCa tissue including HIFU, cryotherapy, focal laser ablation, focal BT (FBT), stereotactic ablative RT, IRE, and vascular-targeted photodynamic therapy (VTP). To date, there is no global consensus on which energy source to choose for a given clinical situation. A position statement by the European Section of Uro-Technology (ESUT) aimed to highlight advantages of each technique depending on patient and tumour characteristics (Ganzer, 2018 #4).

Ganzer et al. [8] carried out a literature search between April 2016 and November 2017 of published articles and abstracts relating to each FT technique. All relevant articles as determined by the list of authors were screened for morbidity, repeatability, tumour risk category, tumour size and location, MRI/TRUS fusion and anatomical issues (Ganzer, 2018 #4). Given this search was performed in 2017, perhaps an updated review is warranted. The main findings of the article are outlined below:

- **Morbidity** – only one randomised prospective article has compared outcomes of FT to standard treatment. This showed an increase in Grade 1–2 morbidity (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03) in VTP compared to active surveillance. No other studies or case reports reported severe morbidity.
- **Repeatability** – repeat HIFU, cryotherapy and FBT has been described in a small number of patients. More investigation is needed to provide more valuable information in this area.
- **Tumour risk category** – most FT studies have been focussed on treating low-risk disease; however, the authors acknowledge that guideline recommendations for low-risk disease are for active surveillance. Feasibility of HIFU and cryotherapy in the primary setting has been studied in the intermediate-risk group with acceptable results. Poor outcomes have been shown for men receiving FT for high-risk disease.
- **Tumour location** – anterior lesions are more easily accessible with transperineal techniques and have been

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**Table 2 Summary of selected results from Postema et al. [6] and Lebastchi et al. [7].**

| Definition                      | Postema et al. [6]                                                                 | Lebastchi et al. [7]                                                                 |
|--------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| **Study methodology**          | Three-round Delphi method.                                                       | Three-round Delphi method.                                                        |
|                                | The final round incorporated 73 responses (Urologists [75%), Radiologists [11%, | The final round incorporated 48 responses (Urologists [72%] and Radiologists [28%], |
|                                | Radiotherapists [4%], Researchers [4%], Pathologists [3%] and Medical Oncologists  | The level of agreement necessary to achieve consensus was defined as >80% [6].      |
|                                | [3%]). The level of agreement necessary to achieve consensus was defined as >80% [5].|                                                                                   |
| **Main findings**              | Definitions:                                                                      | Definitions:                                                                      |
|                                | 
| **FT**                        | - an anatomy-based (zonal) treatment strategy (e.g., targeting a quadrant, a lobe or both lobes sub-totally). | 
| **Index lesion**               | - the single dominant lesion in terms of grade and size, where grade is more important. There can be only one index lesion. The term index lesion itself may be of limited use in the context of FT. It is more important to have an overview of all significant lesions that warrant treatment rather than a single defined index lesion. | 
| **Ablation failure**           | - ablation failure is a failure of the technique to destroy the tissue in the treated zone, evidenced by tumour found within the treated zone. Ablation failure is just one of the causes that can lead to failure of FT as a whole. Other types of failure include targeting failure and selection failure. Must be confirmed by targeted biopsy. | 
| **Selection failure**          | - FT was inappropriately indicated, evidenced by short-term post-treatment identification of metastatic or locally advanced disease. There is no agreement on whether significant PCa in short-term biopsies taken inside or outside the treatment zone and the need for whole-gland treatment during follow-up constitute selection failure. | 
| **Serious side-effects**       | - Clavien-Dindo-scale ≥II as ‘serious’ side-effects | 

GG1, Grade Group 1. The level of agreement necessary to achieve consensus was defined as >80%.
shown to have low rates of urethral damage. Caution must be exercised when treating posterior lesions with cryotherapy given the possibility of ablating normal surrounding tissues such as the neurovascular bundles.

- **Tumour size and prostate volume** – HIFU devices are limited by the focal distance length of the probe used. Caution must be exercised when treating smaller glands with cryotherapy given the possibility of ablating normal surrounding tissues such as the neurovascular bundles and urethra. Other modalities do not seem to be restricted by prostate volume.
- **MRI fusion** – MRI fusion and in-bore interventions are still being explored.
- **Anatomical abnormalities** – Rectal anomalies render transrectal approaches unusable.

Borkowetz et al. [9] formed the German S3 guidelines for FT in localised PCa. Their recommendations were based on either their literature search or consensus from 18 FT experts (urologists, radio-oncologists, radiologists, and pathologists). In regard to each individual energy source, they recommend:

- No comparative data between the different technologies for FT are available that would allow an assessment of effectiveness, adverse events, and safety parameters (Consensus-based recommendation - Agreement 100%)
- Focal VTP using padeliporin is the only focal technology for which outcomes of a prospective, randomised, controlled trial comparing FT with active surveillance in low-risk PCa are available (Evidence-based recommendation - Agreement 96%)
- The available data are insufficient to assess the oncological effectiveness and safety of focal HIFU (Evidence-based recommendation - Agreement 95%)
- The available data are insufficient to assess the oncological effectiveness and safety of focal cryotherapy (Evidence-based recommendation - Agreement 98%)
- The available data are insufficient to assess the oncological effectiveness and safety of focal IRE, in particular concerning long-term outcomes (Evidence-based recommendation - Agreement 97%)
- The available data are insufficient to assess the oncological effectiveness and safety of focal laser ablation, FBT, focal radiofrequency ablation, focal microwave therapy, or focal transurethral ultrasound ablation (Evidence-based recommendation - Agreement 97%)

**Patient Selection**

Patient selection is key for the outcomes of FT. Selection is usually based on patient and disease characteristics obtained after thorough screening and is used for informed decision making and FT planning. Below we summarise consensus statements published from 2015–2022, the evolution over time, which is also depicted in Table 3 [9-14].

A total of six consensus statements were found from our search. Four studies [10-13] were conceived using Delphi method, the other two studies [9,14] were formulated by expert panels. Five studies [9-12,14] published consensus statements for all FT modalities, whereas one focussed on patient selection for focal laser ablation [13].

**Patient Factors**

Interestingly, the evolution of consensus regarding patient factors has become less apparent over time. In 2015, Donaldson et al. [14] agreed upon age, life expectancy, performance status and previous treatment parameters. In 2017, Tay et al. [10] did not reach consensus in regard to age and life expectancy but did reach consensus on reasons for choosing FT. In 2019, Van Luijtelaar et al. [13] reached consensus on life expectancy and reasons for choosing focal laser ablation. In 2021, Tan et al. [11] only reached consensus for age parameters.

**Diagnosis**

All six studies mentioned the diagnostic evaluation of PCa in their publication. All studies agreed that mpMRI was the imaging modality of choice when diagnosing PCa before FT. All studies agreed that mpMRI targeted biopsy AND systematic biopsies are required in the diagnostic evaluation of the patient before FT. If no mpMRI is available, Donaldson et al. [14] and Tan et al. [11] agreed that transperineal three-dimensional (3D) mapping biopsies are sufficient, whereas Tay et al. [10] agreed that systematic TRUS biopsies are sufficient. Borkowetz et al. [9] recommended a template-based biopsy if mpMRI was not available.

**Disease Factors**

The consensus statements regarding disease factor parameters for FT were highly variable between studies. Criteria for calculating PCa risk groups were different (D’Amico vs NCCN) and only two studies reached consensus for tumour volume and serum PSA parameters. All studies agreed that FT should only be reserved for men with Gleason score 6 or 7; however, there was inconsistency regarding the amount of Gleason score 6 that should be treated.

**Molecular Biomarkers**

Serum, urinary and tissue-based molecular biomarkers have been introduced as a risk-stratification tool for PCa. This may be particularly important in FT given the current uncertainty in patient selection and the imperfections of imaging modalities. The majority of molecular biomarker literature is focussed on selecting men for active surveillance or radical
Table 3 Summary of consensus statements for patient selection in FT.

| Authors, year            | Donaldson et al. [14]                                                                 | Tay et al. [10]                                                                                                                                                                                                 | Scheltema et al. [12]                                                                                                                                 |
|--------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Topic                    | Patient selection and treatment                                                       | Patient selection Three-round Delphi Method. Level of agreement necessary to achieve consensus was defined as >80%. 47 respondents by final (third) round.                                                                 | Utilisation of mpMRI Three-round Delphi Method. Level of agreement necessary to achieve consensus was defined as >80%. 79 respondents by final (third) round (Urologists 72%, Radiologists 16%, Pathologists 3%, Radiation Oncologists 3%, Scientists 6%). |
| Study methodology        | 15 person expert panel of Urologists (13) and Oncologists (two). 237 items were formulated and scored by each panelist. Level of consensus was calculated by inter-percentile range adjusted for symmetry (IPRAS) method (>0 indicated consensus). |                                                                                                                                                                                                                 | Diagnosis:                                                                                                                                         |
| Consensus                | Patient factors:                                                                      | Patient factors:                                                                                                                | • mpMRI should be performed for FT planning after TRUS-guided biopsy confirmed PCa                                                                                                                          |
|                          | • Age should not be determinant of FT                                                 | • Potential for preserving sexual function is an important reason for choosing FT                                               | • MRI-TRUS fusion is the recommended biopsy technique following mpMRI                                                                                                                                       |
|                          | • WHO performance status of 0 or 1                                                   | • Mild to moderate LUTS is not a contraindication for FT                                                                     | • Systematic biopsy is required along with targeted biopsy for biopsy naive patients                                                                                                                       |
|                          | • Life expectancy >10 years                                                           | • Men with prostate volume <50 mL are suitable for FT                                                                       | • Stand-alone MRI targeted biopsy is sufficient for patients with previous negative biopsy                                                                                                                   |
|                          | • Should not be offered for life expectancy <5 years                                   | • Prostate volume <50 mL depends on location and size of tumour, type of energy source                                        | • Lesion size and extension cannot be accurately assessed by mpMRI                                                                                                                                         |
|                          | • Can be offered in men who have previous FT or whole-gland treatment                  | Diagnosis:                                                                                                                     | • Final decision to undergo FT should be based on targeted histological results and should not be based on mpMRI results                                                                                     |
|                          | • Prostate volume should not be determinant of FT                                      |                                                                                                                                                                                                                 |                                                                                                                                                    |
|                          | Diagnosis:                                                                            |                                                                                                                                                                                                                 |                                                                                                                                                    |
|                          | • Confirmatory tissue diagnosis should be available                                   |                                                                                                                                                                                                                 |                                                                                                                                                    |
|                          | • mpMRI targeted or standard TRUS biopsy should be concordant with high quality mpMRI |                                                                                                                                                                                                                 |                                                                                                                                                    |
|                          | • Where mpMRI unavailable/ contraindicated, only a full transperineal template-mapping biopsy is sufficient to perform FT |                                                                                                                                                                                                                 |                                                                                                                                                    |
|                          | Disease factors:                                                                     |                                                                                                                                                                                                                 |                                                                                                                                                    |
|                          | • Treat both low- AND intermediate-risk men (based on NCCN risk)                      | • Lesion size and extension cannot be accurately assessed by mpMRI                                                                 |                                                                                                                                                    |
|                          | • At least index lesion should be targeted                                             | • Final decision to undergo FT should be based on targeted histological results and should not be based on mpMRI results                                                                                     |                                                                                                                                                    |
|                          | • Acceptable to not treat Gleason 6 maximum core length up to 5 mm                    | • Systematic biopsies required to assess mpMRI negative areas prior to FT                                                    |                                                                                                                                                    |
|                          | • Not acceptable to leave Gleason 3 + 4 (maximum core length 5 mm) or any Gleason 4 + 3 | Where mpMRI unavailable/ contraindicated, 12-core TRUS biopsy is sufficient to perform FT                                     |                                                                                                                                                    |
|                          | Treatment:                                                                            |                                                                                                                                                                                                                 |                                                                                                                                                    |
|                          | • Optimal circumferential margin for treatment is 5 mm                                 | Disease factors:                                                                                                               |                                                                                                                                                    |
|                          | • Re-treatment rate of <20% is acceptable                                             | • Treat both low- AND intermediate-risk men (based on D’Amico criteria)                                                      | • mpMRI should be performed for FT planning after TRUS-guided biopsy confirmed PCa                                                                                                                          |
|                          | Selected statements that did not reach consensus:                                      | • Gleason 3 + 4 and 4 + 3 are acceptable for FT                                                                            | • MRI-TRUS fusion is the recommended biopsy technique following mpMRI                                                                                                                                       |
|                          | • Tumour volume                                                                      | • Cancer foci <1.5 mL or occupying up to 20% of prostate are suitable for FT                                                   | • Systematic biopsy is required along with targeted biopsy for biopsy naive patients                                                                                                                       |
| Authors, year            | Van Luijtelaar et al. [13]                                                            | • Men with PSA <10 ng/mL are suitable for FT                                                                               | • Stand-alone MRI targeted biopsy is sufficient for patients with previous negative biopsy                                                                                                                   |
| Topic                    | Patient selection and treatment for focal laser ablation                               | • Gleason 3 + 3 1 mm in one core is acceptable in untreated area                                                             | • Lesion size and extension cannot be accurately assessed by mpMRI                                                                                                                                         |
| Study methodology        | Four-round Delphi Method. Level of agreement necessary to achieve consensus was defined as >70%. 24 respondents by final (fourth) round (Urologists 51%, Radiologists 38%, Engineer 3%, Radiation Oncologists 3%, Researcher 3%, technical physician 3%). | Selected statements that did not reach consensus:                                                                          | • Final decision to undergo FT should be based on targeted histological results and should not be based on mpMRI results                                                                                     |
|                          | FT for men coming off active surveillance                                            | • Age and life expectancy of patients                                                                                        |                                                                                                                                                    |
|                          | Three-round Delphi Method. Level of agreement necessary to achieve consensus was defined as >80%. 49 respondents by final (third) round (all Urologists). | • Cancer foci >3 mL or occupying >25% of prostate                                                                           |                                                                                                                                                    |
|                          | German guidelines for FT in localised PCa                                             | • Gleason 4 + 4 cancer                                                                                                        |                                                                                                                                                    |
|                          | Recommendations are either evidence-based or based on 18 person expert panel (urologists, radio-oncologists, radiologist, and pathologist) consensus. |                                                                                                                                                                                                                 |                                                                                                                                                    |
Given the lack of data regarding molecular biomarkers for patient selection and follow-up for FT, Marra et al. [15] published results of a Delphi consensus with the aim of framing the potential role of molecular biomarkers in FT. In this project a 38-item questionnaire was created covering the current evidence, future role and important tests to be included in future studies for assessing the role of molecular biomarkers. The final (third) round incorporated 42 responses from Urologists (95%) and Radiologists (5%). The level of agreement necessary to achieve consensus was defined as ≥70% (Marra, 2021 #3) The results are summarised in Table 4 [15].

### Follow-Up Protocol

Men following FT should be subject to follow-up protocol for their PCs. To our knowledge there has been no globally adopted guideline for the follow-up of FT; however, four studies [7,12,16,17] since 2015 have published consensus statements regarding this. A summary of their recommendations is given in Table 5 [7,12,16,17].

Three studies agreed on similar follow-up protocols. Men should be followed for at least 5 years. Serum PSA should be checked every 3 months for the first year and every 6 months thereafter. The first follow-up mpMRI should be performed at 6 months. The first follow-up prostate biopsy (targeted and systematic) should be performed at around 6–12 months. Functional outcomes should be assessed every 3–6 months until stability or back to baseline.

Scheltema et al. [12] commented specifically on the use of mpMRI in the follow-up of FT patients. They concluded that mpMRI should be part of the follow-up (standardised care) following FT (91% consensus), excluding magnetic resonance spectroscopic imaging (MRSI) (79%, with panel agreement). MRI-TRUS fusion biopsies should be performed following...
mpMRI if a lesion is seen (78%, with panel agreement). mpMRI with MRI-TRUS fusion targeted biopsy cannot serve as stand-alone follow-up modality following FT and standard repeat (random) biopsies should be taken (78%, with panel agreement).

Of note, repeat biopsy was mentioned as a standard part of follow-up in both studies. This is particularly pertinent as we are still unsure of the accuracy of PSA and mpMRI in detecting significant lesions after FT. In fact, a recent study the diagnostic accuracy of mpMRI to detect residual PCa lesions was low [18]. Interestingly, PSMA PET/CT scans were not mentioned in any follow-up protocol.

**Ongoing Clinical Trials for FT**

Several trials are currently active investigating the outcomes of FT. We searched clinicaltrials.gov and the Australian New Zealand Clinical Trials Registry (ANZCTR) for HIFU, cryotherapy, IRE, laser, photodynamic therapy and BT trials. Only ‘recruiting’, ‘enrolling by invitation’ and ‘active’ trials were included. Ongoing trials known to the authors not on clinicaltrials.gov were also included. Comparative clinical trials are tabulated in Table 6. All other trials can be found in Tables S1 and S2.

Our results show that there are numerous trials currently interrogating different aspects of FT management. However, the majority of studies are observational single-arm studies with heterogenous and undefined clinical endpoints. This confirms the need for a more consistent approach to FT management and follow-up, as well as a unified strategy for obtaining meaningful and practice changing results.

**Discussion**

The aim of FT is to obtain oncological clearance of tumour, whilst at the same time avoiding significant treatment complications and maintaining quality of life. Thus, de-escalating the treatment strategy to active surveillance. As increasing data becomes available on long-term outcomes of FT, guidelines will need to continue to be updated. Below we discuss some aspects that need to be considered in future clinical trials relating to FT.

**Clinical Trial Design**

It is clear from the evidence presented here that well-designed prospective and comparative trials are needed to fully assess the effectiveness of FT against standard of care treatment. However, this is easier said than done.

Due to the low aggressiveness of low- and intermediate-risk PCa, a randomised non-inferiority design that is powered on metastasis-free survival is simply not feasible. A trial like this would require >1000 patients and potentially 12–15 years of follow-up to reach maturity, which infers significant cost and commitment from physicians and patients. These issues have been highlighted by the premature closure of several trials testing new therapies for localised PCa for reasons including cost, poor accrual, lack of physician equipoise, patient choice, and change of clinical practice [19]. Furthermore, recruitment issues were highlighted by the feasibility trial by Hamdy et al. [20], although strategies were developed to optimise recruitment and results also showed an >90% return rate of clinical report forms from men in the trial.
The solution to this dilemma may lie in the discovery of more practical outcome measures to power a trial. Given the goal of FT (to preserve functional outcomes while approaching the oncological outcomes of radical treatment), one option could be a conjoint outcome measure weighing risk of subsequent radical treatment vs the risk of developing urinary incontinence or sexual dysfunction. A study from Smith et al. [21] has reported the relative risk men are willing to accept. This is particularly pertinent given that only certain ablative modalities may be available to offer at a time and allows for regular long-term data collection. This perhaps suits more a ‘à la carte’ type approach described by Sivaraman et al. [22], where each energy modality has an ideal PCa profile that it can treat.

Until the FT community has consensus about FT aims and trial design, register data will struggle to change clinical practice. For the moment, outcomes such as cost and patient-reported outcomes can be analysed in this space.

### Patient Selection

The increasing use of active surveillance in Gleason score 3 + 3 PCa will impact upon the potential use of FT in this cohort. Some may argue that younger patients with low-risk
PCa but concerning features (such as anxiety, high PSA density, high volume Gleason 3 + 3 malignancy or a Prostate Imaging-Reporting and Data System [PI-RADS] 4–5 MRI lesion) may remain a potential cohort for FT despite the low risk of metastatic potential on surveillance. Perhaps a definition of ‘high-volume’ Gleason 6 PCa or the addition of novel imaging such as PSMA PET/CT may help distinguish those who may be eligible or those who may not. On the contrary, there may also be no harm in active surveillance for these men until detection of significant disease before embarking on FT or radical treatment. In essence, whether men in this category benefit from FT needs further clarification.

Many clinicians remain disinclined to consider active surveillance in intermediate-risk PCa, particularly with unfavourable features. Long-term oncological results of FT in this cohort are lacking, but in-field clearance following FT based on mpMRI and in-field target biopsies remains high. It has been shown in a matched-paired cohort that the outcomes of FT are comparable to a RP over an 8-year period [23]. This group seems to be the ‘sweet spot’ for FT where clinicians can offer the option of FT to de-escalate management from radical treatment to active surveillance without the high risk of biochemical progression seen in high-risk PCa.

Concerns remain about considering FT in high-grade PCa, due to the increasing risk of recurrence based on biochemical progression. However, biochemical progression risk also increases in management of high-grade PCa following whole-gland therapy, due to the higher risk of underlying micro-metastatic disease. There is not enough data to fully inform on the risk of local recurrence after FT in the high-grade cohort. A high-risk cohort from a focal HIFU series by Reddy et al. [24] found that of 386 patients, 65% had failure-free survival at 7 years and 73% had no salvage (local or systemic) treatment at 7 years. Conversely, results from a smaller series reported by Yaxley et al. [25] found that risk of in-field recurrence on biopsy for men with high-grade PCa after focal IRE was low (none of seven patients).

In regard to salvage RP (sRP) after FT, there is evidence that salvage treatment for local recurrence after FT has oncological and functional results similar to that in the primary setting [26,27]. However, of note, in a smaller study of 39 men following sRP, a positive margin rate of 25% was found related to local expertise in certain centres suggesting that sRP after FT should be performed at high-volume and experienced centres for best outcomes [28].

The role of FT in radio-recurrent PCa also needs further investigation. Certainly, this is an attractive option for men who are at risk of morbidity after sRP. A systematic review by Khoo et al. [29] showed that salvage FT may provide acceptable oncological outcomes with low rates of complications. However, more data are needed as this was based on low level evidence with short-term follow-up that only included salvage BT, cryotherapy, and HIFU.

New Imaging Considerations

Finally, as technology improves, so too will the criteria for FT selection and follow-up. New technologies including PSMA PET/CT can potentially improve selection for FT. PSMA PET/CT can identify tumours not found on MRI [30]. With concordance between MRI, PSMA PET/CT and biopsy histology, there will be more confidence for clinicians that there is no undiagnosed significant out-of-field malignancy at diagnosis. The maximum standardised uptake value of the PSMA PET/CT scan can also be used

| NCT number   | Title                                                                 | Enrolment | Intervention                  | Control   | Primary outcome measurement                      |
|--------------|------------------------------------------------------------------------|-----------|-------------------------------|-----------|--------------------------------------------------|
| NCT04307056 | Evaluation of HIFU in TREATMENT OF LOCALIZED PROSTATE CANCER and OF RECURRENCE AFTER RADIOTHERAPY 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 | 4022      | HIFU                          | RP        | Recurrence-free survival                          |
| NCT03531099 | Comparative Health Research Outcomes of NOvel Surgery in Prostate Cancer | 146       | HIFU                          | Active surveillance | Need for radical treatment                        |
| NCT04049747 | Focal Prostate Ablation Versus Radical Prostatectomy                   | 2450      | HIFU or cryotherapy           | Radical treatment | Progression-free survival                        |
| NCT03668652 | Partial ablation vs radical prostatectomy in intermediate-risk prostate cancer: the PART | 800       | HIFU                          | RP        | Treatment failure                                 |

NCT, National Clinical Trial number.

Table 6 Ongoing comparative clinical trials for FT.
as a prognostic marker to indicate men not suitable for active surveillance and also at an increased risk of recurrence after primary treatment [31].

Not all physicians or countries have access to formal clinical FT trials. Therefore, FT will continue to be performed out of a trial setting in the majority of circumstances. It is important for clinicians to collaborate and publish their FT results, preferably in a prospective manner, but consider referral to clinical trials where available.

**Conclusion**

Here we present a summary of the current recommendations for FT in major international guidelines and published consensus and position statements since 2015. A globally accepted guideline for FT planning, technique and follow-up are still yet to be determined. Consensus statements are heterogenous, therefore making it difficult to create meaningful study designs. When created, studies need long-term follow-up and robust clinical and toxicity endpoints to improve our understanding of FT and create uniform guidelines to streamline management and follow-up of this treatment modality.

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Abbreviations: (F)BT, (focal) brachytherapy; (s)RP, (salvage) radical prostatectomy; 3D, three-dimensional; ASTRO, American Society for Radiation Oncology; EANM, European Association of Nuclear Medicine; EAU, European Association of Urology; ESTRO, European Society for Radiotherapy and Oncology; ESUR, European Society for Urogential Radiology; FT, focal therapy; HIFU, high-intensity focussed ultrasound; IRE, irreversible electroporation; ISUP, International Society of Urological Pathology; mpMRI, multiparametric; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer; PET, positron emission tomography; PI-RADS, Prostate Imaging-Reporting and Data System; PSMA, prostate-specific membrane antigen; RCT, randomised controlled trial; RT, radiotherapy; SIOG, International Society of Geriatric Oncology; SUO, Society of Urologic Oncology; VTP, vascular-targeted photodynamic therapy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Ongoing observational clinical trials for FT from clinicaltrials.gov.

Table S2 Ongoing observational clinical trials for FT from Australian New Zealand Clinical Trials Registry.