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Review

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 Urogential Radiology (ESUR)-International Society of Urological Pathology (ISUP)-International Society of Geriatric Oncology (SIOG) (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

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 • Clinicians should inform patients WITH low-risk PCa who are considering FT or HIFU that these interventions are not standard of care options because comparative outcome evidence is lacking. (Expert Opinion) • Clinicians should inform patients WITH intermediate-risk PCa who are considering FT or HIFU that these interventions standard of care options because comparative outcome evidence is lacking. (Expert Opinion) • Cryosurgery, FT and HIFU treatments are not recommended for men with high-risk localised PCa outside of a clinical trial. (Expert Opinion) • As PCa is often multifocal, clinicians should inform patients with localised PCa considering FT that FT may not be curative and that further treatment for PCa may be necessary. (Expert Opinion) HIFU specifically • Clinicians should inform patients who are considering HIFU that even though it is approved by the FDA for the destruction of prostate tissue, it is not approved explicitly for the treatment of PCa. (Expert Opinion) • Clinicians should advise patients with localised PCa considering HIFU that tumour location may influence oncological outcome. Limiting apical treatment to minimise morbidity increases the risk of cancer persistence. (Moderate Recommendation; Evidence Level: Grade C)	• 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)	Not mentioned	• 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.

(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.

Definitions/Nomenclature

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

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

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. The final round incorporated 73 responses (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% [5].	Three-round Delphi method. The final round incorporated 48 responses (Urologists [72%] and Radiologists [28%]). The level of agreement necessary to achieve consensus was defined as >80% [6].
Main findings	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 ≥III as 'serious' side-effects	Definitions: *FT* - guided ablation of an image-defined, biopsy-confirmed, cancerous lesion with a safety margin surrounding the targeted lesion. *Partial gland ablation* - includes quadrant ablation, hemi-ablation, hockey-stick ablation, and subtotal ablation. *Index lesion* - could not achieve consensus that an index lesion can be defined solely by being the largest lesion. Also, no consensus that GG1 cancers could be defined as index lesion.

GG1, Grade Group 1. The level of agreement necessary to achieve consensus was defined as >80%.

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 low 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 have 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

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 padeliporfin 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	Utilisation of mpMRI
Study methodology	15 person expert panel of Urologists (13) and Oncologists (two). 237 items were formulated and scored by each panellist. Level of consensus was calculated by inter-percentile range adjusted for symmetry (IPRAS) method (>0 indicated consensus).	Three-round Delphi Method. Level of agreement necessary to achieve consensus was defined as >80%. 47 respondents by final (third) round.	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%).
Consensus	Patient factors • Age should not be determinant of FT • WHO performance status of 0 or 1 • Life expectancy >10 years • Should not be offered for life expectancy <5 years • Can be offered in men who have previous FT or whole-gland treatment • 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) • At least index lesion should be targeted • Acceptable to not treat Gleason 6 maximum core length up to 5 mm • Not acceptable to leave Gleason 3 + 4 (maximum core length 5 mm) or any Gleason 4 + 3 Treatment: • Optimal circumferential margin for treatment is 5 mm • Re-treatment rate of <20% is acceptable Selected statements that did not reach consensus: • Tumour volume	Patient factors: • Potential for preserving sexual function is an important reason for choosing FT • Mild to moderate LUTS is not a contraindication for FT • Men with prostate volume <50 mL are suitable for FT • Prostate volume >50 mL – depends on location and size of tumour, type of energy source Diagnosis: • mpMRI is standard imaging tool • Histological confirmation is required for PI-RADS 4/5 lesions prior to FT • MRI-TRUS fusion biopsy is adequate • Systematic biopsies required to assess mpMRI negative areas prior to FT • Where mpMRI unavailable/ contraindicated, 12-core TRUS biopsy is sufficient to perform FT Disease factors: • Treat both low- AND intermediate-risk men (based on D'Amico criteria) • Gleason 3 + 4 and 4 + 3 are acceptable for FT • Cancer foci <1.5 mL or occupying up to 20% of prostate are suitable for FT • Men with PSA <10 ng/mL are suitable for FT • Gleason 3 + 3 1 mm in one core is acceptable in untreated area Selected statements that did not reach consensus: • Age and life expectancy of patients • Cancer foci >3 mL or occupying >25% of prostate • Gleason 4 + 4 cancer	Diagnosis: • mpMRI should be performed for FT planning after TRUS-guided biopsy confirmed PCa • MRI-TRUS fusion is the recommended biopsy technique following mpMRI • Systematic biopsy is required along with targeted biopsy for biopsy naïve patients • Stand-along MRI targeted biopsy is sufficient for patients with previous negative biopsy • Lesion size and extension cannot be accurately assessed by mpMRI • Final decision to undergo FT should be based on targeted histological results and should not be based on mpMRI results

Authors, year	Van Luijtelaar et al. [13]	Tan et al. [11]	Borkowetz et al. [9]
Topic	Patient selection and treatment for focal laser ablation	FT for men coming off active surveillance	German guidelines for FT in localised PCa
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%).	Three-round Delphi Method. Level of agreement necessary to achieve consensus was defined as >80%. 49 respondents by final (third) round (all Urologists).	Recommendations are either evidence-based or based on 18 person expert panel (urologists, radio-oncologists, radiologist, and pathologist) consensus.

Table 3 (continued)

Authors, year	Van Luijtelaar et al. [13]	Tan et al. [11]	Borkowetz et al. [9]
Consensus	Patient factors: • Patient seeking alternative to radical treatment • Should not be offered to men with life expectancy <10 years unless treatment may delay local disease progression • Patient with desire to preserve erectile or sphincter function • LUTS are not a contraindication for FT Diagnosis: • Offer to patients with mpMRI visible recurrence • Require histological confirmation of mpMRI visible lesion • Require systematic biopsies along with targeted biopsy • Volume of lesion should be based on mpMRI Disease factors: • Offer to patients with de novo clinically significant PCa less than or equal to Gleason 4 + 3 • Do not offer if tumour volume >10–15 mL	Patient factors: • Age 60–80 years should consider FT when coming off active surveillance Diagnosis: • An increasing PSA or a biomarker test indicating higher risk of adverse pathology should not prompt FT, but instead prompt re-interrogation of the prostate. • mpMRI/ultrasound-guided fusion biopsy and a 12-core systematic biopsy is recommended for men on active surveillance prior to considering FT • If unable to undergo mpMRI, patients will require a 3D-mapping biopsy of the prostate to determine if they are a candidate for FT • No metastatic evaluation is usually required prior to considering FT (if men are low or favourable intermediate risk) Disease factors: • Gleason 3 + 4 and PSA <10 ng/mL are suitable for FT • Men with multifocal Gleason ≥3 + 4 disease are not ideal candidates for FT Selected statements that did not reach consensus: Ideal template for FT	Patient factors: • Education about FT should state that the equivalence of the FT to standard therapies is not proven (97% consensus) • Education about FT should state, in addition to what is described in recommendation a., that salvage therapy may potentially yield poorer functional and oncological outcomes in case of salvage therapy should become necessary (95%) Diagnosis: • Patients considering FT should undergo mpMRI, mpMRI fusion biopsy, and systematic biopsy (95%) • If MRI fusion biopsy is not possible, a template-based biopsy may be considered to be performed as an alternative (95%) Disease factors: • Patients with unilateral, localised low-risk PCa can be offered FT if they decline both standard therapies and active surveillance while meeting the following requirements (81%) ○ Gleason score 6 ○ PSA <10 ng/mL ○ Unsuspected DRE ○ Maximum 50% positive biopsy cores of only one lobe only in systematic biopsy diagnosis by mpMRI, fusion biopsy, and systematic biopsy

treatment. However, some of this has been extrapolated for patient selection and follow-up for FT.

Given the lack of data regarding molecular biomarkers 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 PCa. 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

Table 4 Summary of results from Marra et al. [15].

Current evidence/role of molecular biomarkers in FT	Future/potential role of molecular biomarkers in the context of FT	Tests to be included in future studies assessing role of molecular biomarkers in FT
Agree: • Evidence for molecular biomarkers in FT is absent/low (80% agreement) • Molecular biomarkers should not be used in routine clinical decision-making (71%) • Prostate mpMRI is more useful than molecular biomarkers for FT at present (87%) • Prostate mpMRI is more accessible than molecular biomarkers for FT at present (87%) *Disagree*: • Evidence on the role of molecular biomarkers in FT is high (84%)	*Agree*: • PSA has potential role in context of FT (77%) • PSA-density has potential role in context of FT (73%)> *Disagree*: • PCA3 has potential role in context of FT (72%)> *Uncertain*: • SelectMDx (76%), 4 k score (76%), ConfirmMDx (78%), Promark (74%), ExoDx (72%) has potential role in FT> *No consensus* • PHI, prolaris, OncotypeDx, Decipher, Mi-Prostate score	*Agree*: • PSA (81%), PSA density (85%), targeted and systematic biopsy (94%), mpMRI (100%), PCa risk calculators (88%) should be included in studies assessing the role of molecular biomarkers> *Disagree*: • Choline-PET (74%), CT scan (87%), bone scan (82%) should be included in studies assessing the role of molecular biomarkers> *No consensus* • PSMA PET (27% disagree, 31% uncertain, 43% agree)

PCA3, prostate cancer antigen 3. The level of agreement necessary to achieve consensus was defined as >70%. Level of agreement in () after point.

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.

Table 5 Summary of consensus statements for follow up protocols for FT.

Authors, year	Muller et al. [16]	Tay et al. [17]	Scheltema et al. [12]	Lebastchi et al. [7]
Study methodology	Three-round Delphi Method. Level of agreement necessary to achieve consensus was defined as >75%. 46 respondents by final (third) round.	Systematic review of the literature yielding 17 studies that were synthesised by expert panel to form consensus recommendations	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%).	Three-round Delphi Method. Level of agreement necessary to achieve consensus was defined as >80%. 48 respondents by final round (Urologists 72%, Radiologists 28%)
Follow-up recommendation	PSA • 3 monthly for the first year • Then 6 monthly up to 5 years MRI • 6 monthly for the first year • Then yearly up to 5 years Biopsy • Systematic + image-guided biopsy at 12 months after • Then biopsy only if clinical suspicion Functional outcomes assessment • Every 3–6 months for 2 years	PSA - no recommendations MRI • First one at 6–12 months Biopsy • Treated area biopsy at 3–6 months • Systematic ± targeted biopsy at 12–24 months • Then biopsy only if clinical suspicion	• mpMRI should be part of the follow-up (standardised care) following FT (91%), excluding 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)	PSA • 3 monthly for the first year • Then 6 monthly up to 5 years Imaging • At 6 months then at 18 months after • Then as per institutional active surveillance protocol Biopsy • Systematic + image-guided biopsy at 6–12 months after • If negative, then as per institutional active surveillance protocol Functional outcomes assessment • Every 3–6 months until stability/baseline attained

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 take in order to preserve these functional outcomes, this could be used to obtain this conjoint outcome measure. A publication by Ahmed et al. [19] suggested the use of composite medium-term outcome measures such as need for salvage (local or systemic) therapy or genitourinary and rectal functional status, which may lead to subsequent long-term mortality data embedded into a national cohort or registry. However, this is not a randomised controlled trial (RCT).

This begs the question, is a RCT the only acceptable trial design option? Or can data from long-term registries and cohort studies be used to shape clinical practice. Furthermore, can a trial from a single ablative modality be extrapolated to other modalities? This is particularly pertinent given that only certain ablative modalities may be available to offer at a single institution. Ahmed et al. [19] proposed a cohort-embedded RCT design that has the benefit of running 'multiple RCTs' 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

Table 6 Ongoing comparative clinical trials for FT.

NCT number	Title	Enrolment	Intervention	Control	Primary outcome measurement
NCT04307056	Evaluation of HIFU in TREATMENT OF LOCALIZED PROSTATE CANCER and OF RECURRENCE AFTER RADIOTHERAPY	4022	HIFU	RP	Recurrence-free survival
NCT03531099	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	146	HIFU	Active surveillance	Need for radical treatment
NCT04049747	Comparative Health Research Outcomes of NOvel Surgery in Prostate Cancer	2450	HIFU or cryotherapy	Radical treatment	Progression-free survival
NCT03668652	Focal Prostate Ablation Versus Radical Prostatectomy	200	HIFU	RP	Biochemical recurrence or need for further treatment
-	Partial ablation vs radical prostatectomy in intermediate-risk prostate cancer: the PART	800	HIFU	RP	Treatment failure

NCT, National Clinical Trial number.

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 can 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

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 of 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.