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Bates, AS, Ayers, J, Kostakopoulos, N et al. (30 more authors) (2021) A Systematic Review of Focal Ablative Therapy for Clinically Localised Prostate Cancer in Comparison with Standard Management Options: Limitations of the Available Evidence and Recommendations for Clinical Practice and Further Research. European Urology Oncology, 4 (3). pp. 405-423. ISSN 2588-9311

https://doi.org/10.1016/j.euo.2020.12.008

A systematic review of focal ablative therapy for clinically localised prostate cancer in comparison with standard management options: Limitations of the available evidence and recommendations for clinical practice and further research

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Abstract

Context: The clinical effectiveness of focal therapy (FT) for localised prostate cancer (PCa) remains controversial. ***Objective:*** To analyse the evidence base for primary FT for localised PCa via a systematic review (SR) to formulate clinical practice recommendations. ***Evidence acquisition:*** A protocol-driven, PRISMA-adhering SR comparing primary FT (sub-total, focal, hemi-gland or partial ablation) versus standard options (active surveillance [AS], radical prostatectomy [RP] or radiotherapy [EBRT]) was undertaken. Only comparative studies with ≥50 patients per arm were included. Primary outcomes included oncological, functional and quality of life outcomes. Risk of bias (RoB) and confounding assessments were undertaken. Eligible SRs were reviewed and appraised (AMSTAR) and

ongoing prospective comparative studies were summarised. ***Evidence synthesis:*** Out of 1,119 articles identified, 4 primary studies (one RCT and 3 retrospective studies) recruiting 3961 patients and 10 eligible SRs were identified. Only qualitative synthesis was possible due to clinical heterogeneity. Overall, RoB and confounding were moderate to high. An RCT comparing vascular-targeted focal photodynamic therapy (PDT) with AS found a significantly lower rate of treatment failure at 2 years with PDT. There were no differences in functional outcomes although PDT was associated with worse transient adverse events. However, the study's external validity was contentious. A retrospective study comparing focal HIFU with robotic RP found no significant differences in treatment failure at 3 years, with focal HIFU having better continence and erectile function recovery. Two retrospective SEER-based cohort studies compared focal laser ablation (FLA) against RP and EBRT, reporting statistically worse oncological outcomes for FLA. The overall data quality and applicability of the primary studies were limited due to clinical heterogeneity, RoB and confounding, lack of long-term data, inappropriate outcome measures and poor external validity. Virtually all identified SRs concluded there was insufficient high certainty evidence to make definitive conclusions regarding the clinical effectiveness of FT, with the majority of SRs judged to have low or critically low confidence rating. Eight ongoing prospective comparative studies were identified. Ways of improving the evidence base are discussed. ***Conclusions:*** The certainty of the evidence regarding the comparative effectiveness of FT as a primary treatment for localised PCa was low, with significant uncertainties. Until higher certainty evidence emerges from robust prospective comparative studies measuring clinically meaningful outcomes at long-term time points, FT should ideally be performed within clinical trials or well-designed prospective cohort studies. **Patient summary**: We examined the literature to determine the effectiveness of prostate targeted treatment (FT) compared with standard treatments for untreated localised prostate cancer. There was no strong evidence showing that FT compares favourably with standard treatments; consequently, FT is not recommended for routine standard practice.

Key words: Systematic review, evidence synthesis, focal ablative therapy, radical treatment, localised prostate cancer, oncological and functional outcomes, limitations of evidence base, clinical practice guidelines and recommendations.

Word count:
Abstract: 428 words
Main text: 4,691 words

1. Introduction

The majority of men with prostate cancer (PCa) present with localised disease. Patients with life expectancy >10 years are managed either via a deferred active treatment policy (i.e. active surveillance, AS) or curatively with radical prostatectomy, radical radiotherapy, and brachytherapy.(1) In men with low-risk disease, surveillance has been shown to have equivalent oncological outcomes to curative treatments at 10 years, although metastatic progression, albeit generally infrequent, is more common.(2) Conversely, radical treatments may be associated with deterioration in urinary, sexual and bowel function.(2) Focal ablative therapy (FT) has emerged as an intermediate option between AS and radical treatments, by selectively targeting and destroying specific parts of the prostate gland harbouring the most aggressive cancer foci (i.e. index lesion with or without secondary significant lesions). Although PCa is often a multifocal disease, prognosis may be driven by these index lesions.(3) FT offers immediate treatment with the aim of limiting impact on urinary, sexual and bowel function. Modern FT modalities include image-guided delivery of different types of energy, such as cryotherapy, high-intensity focused ultrasound (HIFU), vascular targeted photodynamic therapy, laser ablation, thermal ablation, focal brachytherapy (including low-dose rate [LDR] and high-dose rate [HDR]), radiofrequency waves, microwave ablation, focal external beam radiotherapy (e.g. CyberKnife), and irreversible electroporation (IRE) (e.g. NanoKnife).

As part of its guideline update for 2020, the EAU PCa Guideline Panel undertook a systematic review (SR) aimed at appraising the evidence base for FT as a treatment strategy for clinically localised PCa in comparison with standard management options, in order to issue recommendations for clinical practice and further research.

2. Evidence acquisition

2.1 Search strategy and PICO elements

The study protocol was published *a priori* (4) and the search strategies are included as Supplementary File 1. Briefly, the SR was undertaken in accordance with PRISMA (5) and Cochrane guidelines (6). Databases including MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (7) and ClinicalTrials.gov (8) were systematically searched for articles published in English between 1st January 2000 to 12th June 2020. Men with histologically-proven clinically localised PCa (cT1-T2N0M0) who were treatment naïve prior to recruitment were included. The index intervention was primary FT, including all examples listed above. Lesions must have been targeted in real-time by any imaging modality during treatment. Sub-total ablative therapy (including hemi-gland, partial or non-whole-gland ablation) were regarded as FT if identified lesions were targeted for treatment. The comparator intervention was any standard management option for localised PCa, including radical prostatectomy, external beam radiotherapy (EBRT), whole-gland brachytherapy or active surveillance/monitoring. Studies including whole-gland ablative therapy as a comparator, or studies comparing FT vs FT were excluded. Primary outcomes included oncological (treatment failure defined as need for radical treatment, histologically-proven disease absence/persistence and recurrence, metastatic progression, cancer-specific and overall survival), adverse events, complications and functional and quality of life (QoL) outcomes. Only comparative studies recruiting at least 50 patients in every arm were included. Relevant SRs and ongoing prospective comparative studies which aligned fully with our inclusion criteria were included, in order to compare our review findings with those of other relevant studies and to explore differences where they exist to improve transparency of the link between evidence and recommendations for clinical practice and future research.

2.2 Data extraction, risk of bias and confounding assessments

Abstract and full text screening, data extraction and risk of bias (RoB) and confounding assessments were performed independently in duplicate (AB, JA, TL, IS). The Cochrane RoB tool for randomised controlled trials (RCTs) (6) and a modified Cochrane tool for non-randomised comparative studies (NRCS) incorporating additional domains based on confounding (8, 9) were used. The main confounders were indication bias, D'Amico risk group, clinical stage, Gleason score/ISUP grade and follow-up duration. Grading of Recommendations, Assessment, Development and Evaluations (10) assessment was planned for.(10)

2.3 Appraisal of relevant systematic reviews (AMSTAR)

Relevant SRs were identified, screened and data extracted, applying the same search strategy and PICO elements. SRs incorporating non-comparative studies and studies recruiting <50 patients per arm were included. SRs were appraised using the critical domains of the AMSTAR-2 checklist, which provides an objective measure of the methodological and reporting quality and reliability of SRs relating to a specific topic.(11)

2.4 Data analysis

A narrative synthesis was perfomed due to the anticipated clinical and methodological heterogeneity in included studies. If data homogeneity allowed pooling of data, a formal meta-analysis was also planned for.(4)

3. Evidence synthesis

3.1 Quantity of evidence identified

The study selection process is outlined in the PRISMA flow diagrams (Fig. 1A and 1B). Five articles reporting on four comparative studies (one RCT and three retrospective NRCS) recruiting a total of 3,961 patients were included (12-16). Ten SRs were eligible for inclusion.(17-26) Thirteen comparative studies were excluded, with the majority of these studies including less than 50 patients in at least one study arm, or incorporating whole-gland ablative therapy mixed with FT as the index intervention, or using whole-gland ablative therapy as a comparator (Supplementary Table 1).(27-39) 45 full-text SRs were excluded; the commonest reason for exclusion was the inclusion of whole-gland treatment with FT in the analysis (i.e. contamination).

3.2 Risk of bias and confounding assessment

Figure 2 summarises the results of the RoB and confounding assessment for the four primary studies. The overall RoB and confounding was moderate to high for most domains. GRADE assessment was not possible due to extreme clinical heterogeneity affecting index interventions, comparators and outcome measures.

3.3 Characteristics of included studies and summary of results

3.3.1 Primary comparative studies assessing FT

Table 1 outlines the baseline characteristics and summary of findings of all four included comparative studies.(12-16)

Azzouzi et al. (12) performed an RCT comparing vascular-targeted focal photodynamic therapy (PDT; Padeliporfin) (n=206) against AS (n=207) in patients with low-risk PCa. Co-primary outcomes were treatment failure (defined as histological progression to moderate or high-risk disease, or death), and absence of histologically-proven cancer. At 24 months, less PDT patients progressed (28% vs 58%, p<0.0001; adjusted HR: 0.34, 95% CI: 0.24-0.46), and needed less radical therapy (6% vs 29%; p<0.0001). More PDT patients had a negative biopsy (49% vs 14%, p<0.001; adjusted RR: 3.67, 95% CI: 2.53–5.33). Updated results (13) showed differences were maintained after 4 years. For secondary outcomes, there was a transient deterioration in erectile and urinary function with PDT, but there was no difference between the groups by 24 months. Health-related QoL deteriorated transiently for FT. The frequency and severity of adverse events were higher with PDT; most men reported an adverse event, most of which were mild or moderate in severity, with 15% complaining of perineal pain. Internal validity was moderate (Fig. 2) but external validity was low (discussed below).

Albisinni et al.(14) conducted a retrospective matched-pair analysis study, comparing focal HIFU (n=55) versus robotic-assisted laparoscopic radical prostatectomy (RALP) (n=55) in a population consisting of patients with a mixture of low-risk (approximately two-thirds) and intermediate-risk disease. The authors concluded at 36 months' follow-up that focal HIFU was comparable to RALP in controlling localised unilateral PCa, with no significant differences observed in need for salvage therapies (i.e. either EBRT or systemic androgen deprivation therapy [ADT] [12.7% vs 10.9%, p=0.76, respectively]), although 12.5% of focal HIFU patients required additional treatment by way of contralateral hemi-ablation due to development of contralateral cancer. Focal HIFU patients had better continence (82% fully continent at 1-month versus 40%, p<0.001) and erectile function (erectile dysfunction rate 20% vs 44% at 24 months, p=0.03). However, internal validity was low (Fig. 2).

Zheng et al.(15) performed a retrospective, propensity score-matched (PSM) cohort study based on the Surveillance, Epidemiology, and End Results (SEER) database, comparing focal laser ablation (FLA) (n=442) with radical prostatectomy (RP) (n=12433). Inclusion criteria included Gleason <8 disease, cT1c-cT2a and PSA≤10 ng/L; most patients had Gleason 3+3=6 disease (57% and 63% respectively). Mean follow-up was 60 months. Before PSM, FLA patients had higher any-cause mortality (ACM) (HR, 2.35; 95% CI, 1.38-3.98; p=0.0016) although cancer-specific mortality (CSM) was not statistically significantly different (HR, 0.61; 95% confidence interval [CI], 0.15-2.45; p=0.4879). The PSM cohort (ACM: HR, 2.35; 95% CI, 1.38-3.98; p= 0.0016) and standardised mortality ratio weighting model (ACM:

HR, 2.01; 95% CI, 1.18-3.42; p=0.0103) showed FLA to be significantly inferior to RP. For CSM, the FLA group had numerically lower but statistically insignificant CSM (HR, 0.82; 95% CI, 0.18-3.67; p=0.7936). The study had extremely low internal validity (Fig. 2).

The same group performed a similar propensity-matched study (Zhou et al.)(16) based on the SEER database comparing FLA (n=428) with definitive radiotherapy (EBRT) (n=2,568). FLA patients had lower overall survival (OS) in adjusted analysis (HR=1.49; 95%CI: 1.18– 1.87; p<0.001). After PSM, FLA patients still had worse OS (HR=1.50; 95%CI: 1.17–1.93; p=0.001). Internal validity was extremely low (Fig. 2).

3.3.2 Systematic reviews assessing FT

Table 2 summarises the baseline characteristics, results and conclusions as stated by the authors of all 10 included SRs (17-26); Table 3 summarises the results of the AMSTAR quality assessment. The overview of all eligible SRs showed that there were some low quality data, mostly derived from single-arm case series, showing FT was as effective oncologically as radical therapy, but with superior functional and quality of life outcomes in the short to medium term. The vast majority of SRs included very heterogeneous studies with low patient numbers, most of which were uncontrolled single-arm case series, with no data on longer-term outcomes. Most SRs also had significant limitations. The AMSTAR quality assessment revealed all but two SRs had either critically low (n=7) or low (n=1) confidence rating. The two SRs with moderate to high confidence rating (18, 19) concluded that although the data on FT appeared promising, there was insufficient high certainty evidence to make definitive conclusions regarding their clinical effectiveness, and that prospective, well-controlled studies were required. In summary, the findings of our SR agree with those of pre-existing eligible SRs.

3.3.3 Ongoing prospective comparative studies registered in online databases

Thirty ongoing studies registered on online databases were identified as potentially suitable. After screening, 22 studies were excluded: 16 were single-arm case series, 4 concerned salvage FT, one had an inappropriate comparator and one had n<50 patients per arm. Eight prospective comparative studies were eligible for inclusion; Table 4 summarises their baseline characteristics. (40-47) Seven are RCTs and one is a prospective NRCS. Two large RCTs from the UK (PART [n=800] and CHRONOS [n=2,450]) compare FT with radical treatment (RP or EBRT or brachytherapy).(40, 41) An RCT in China (n=438) compares focal IRE to RP.(42) The RCT in Sweden (n=250) compares HIFU to RP (43). Two RCTs compare FT to AS; in the USA, vascular-targeted PDT vs AS (n=400), (44) and in France focal HIFU vs AS (HIFUSA) (n=130).(45) The RCT from The Netherlands compares focal IRE (NanoKnife) vs extended hemi-ablation with IRE (NanoKnife) (n=200).(46) The NRCS from Israel compares 3 different FT arms: focal HIFU, CyberKnife, and focal cryotherapy (n=1000).(47) All studies are due to complete by 2030.

3.4 Discussion

3.4.1 Principal findings

This SR was commissioned to evaluate the evidence base for FT for clinically localised PCa in comparison with established standard management options, so that appropriate recommendations can be issued to guide clinical practice, and to identify gaps in the evidence base and provide recommendations for further research. Our review of primary studies identified one RCT and three retrospective matched cohort studies, reporting on different types of FT. The RCT compared PDT versus AS, and found that PDT was associated with a statistically significantly lower rate of treatment failure at 2 years. There were no differences in functional outcomes, but PDT was associated with worse transient adverse events. A retrospective, matched-pair study comparing focal HIFU with robotic RP

found no significant differences in treatment failure at 3 years, with focal HIFU having better continence and erectile function recovery. Two retrospective SEER-based, propensity-matched cohort studies compared focal laser ablation (FLA) against RP and EBRT, reporting statistically worse overall survival for FLA on adjusted analysis. The overall data quality and applicability of the primary studies were limited due to poor external validity, significant clinical heterogeneity, RoB and confounding, lack of long-term data and use of inappropriate outcome measures.

Overall, the evidence in support of FT as a feasible alternative to either AS or radical interventions for localised PCa is limited. Data regarding oncological effectiveness of FT compared with standard options were mixed and inconsistent. There was low certainty data showing FT had transiently worse functional and QoL outcomes compared with AS but better functional outcomes than radical prostatectomy. The vast majority of primary studies were small and uncontrolled; others were comparative studies with serious methodological flaws with extremely low internal and external validity. Most studies had significant clinical heterogeneity, with poorly defined populations, interventions (e.g. intermingling of whole-gland and FT as a single index intervention), different definitions of re-treatments with different intervals, different imaging and follow-up schedules, with only some involving repeat prostate biopsies, different comparators, outcome measures with different definitions of treatment failure measured at different time points, and a lack of long-term data. The overview of SRs confirmed our findings, with no SR showing high certainty evidence regarding the oncological effectiveness of FT in the long-term. Crucially, the conclusions of SRs ultimately depend on the nature and strength of the primary data. Low certainty data are highly unlikely to lead to recommendations which influence clinical decision-making.

The only RCT eligible for inclusion compared FT using Padeliporfin-based PDT versus AS in men with very low-risk localised PCa. (12, 13) The study found a lower progression rate, reduced need for radical therapy and a higher negative biopsy rate with FT after a median follow-up of 2 years. However, as the assessments of RoB, confounding and external validity demonstrated, the study had several limitations. The attrition rate in the study was relatively high, with a rate of missed biopsy at 2-years of 42% for the AS group. More patients in the AS arm chose to undergo radical therapy without a clear clinical indication, and this introduces confounding bias. The AS arm also had an unusually high disease progression rate (58% in two years), which is not typically observed in contemporary practice. For instance, the ProtecT Trial, which assessed an earlier, less stringent form of surveillance (i.e. active monitoring), demonstrated a 10-year progression rate of 20.6%.(2) Contemporary AS protocols, such as Tosoian et al.(48) reported 10-year reclassification rates of under 50%. The Padeliporfin RCT showed >50% of FT patients continued to have biopsy-proven PCa, with a third (32%) having Gleason score ≥3+4=7 disease at 2 years. However, we acknowledge that the majority of patients in the Tosoian et al. cohort included patients with very low risk disease.

AS is primarily aimed at reducing over-treatment of low-risk PCa, due to its very favourable prognosis. AS provides a means of deferring curative treatment until a point if and when it becomes clear the cancer is progressive. Accordingly, any trial comparing FT with AS needs to consider very carefully clinical care pathways, and measure end-points which are clinically meaningful to both arms to facilitate comparative analysis. The RCT chose treatment failure (defined as histological progression or death) and histological absence of cancer as co-primary endpoints. These outcomes are less meaningful in AS cohorts, since histological progression should trigger reclassification which is an expected outcome for 25-50% of men at 10 years; it should not be considered as treatment failure. Histological absence of disease is also an inappropriate outcome for AS, because the premise of AS is that the disease remains untreated. The study found at 2 years, more than half of FT-treated patients may have had persistent disease, of which 50% occurred in-field. FT was associated with adverse events and pain, and patients had transient reductions in urinary and sexual function. Based on the results of the PDT trial, as the population had low-risk disease, these findings compel us to re-examine the rationale of treating such patients, which was to reduce the risk of progression compared with AS (which should normally be very low), at the risk of: (1) over-treatment; (2) transient adverse events and reductions in function and quality of life; (3) persistent disease (50% risk at two years); and (4) still needing radical treatment (28%). This leads to the fundamental question: Is it appropriate to treat all men with low-risk disease, many of whom will not benefit but will have transient side-effects, in order to reduce the proportion of men needing more invasive treatment in the future? Based on current data, it may be very difficult for FT to improve either overall or cancer-specific survival in an AS population due to the very good prognosis with no treatment. Nevertheless, we acknowledge that these conclusions are based on the PDT trial alone, since it is the only RCT published on FT. It is possible that other FT modalities, especially newer technologies, may yield better oncological and quality of life outcomes; consequently

clinicians and researchers must be prepared to review and re-appraise the evidence base when new data emerge.

3.4.2 Implications for clinical practice and further research

The findings of our SR have shown that there is insufficient high-certainty evidence to endorse FT as an oncologically effective and durable treatment modality which compares favourably with AS or radical treatments for the management of patients with localised PCa. Consequently, its routine use in clinical practice is currently not recommended; its use should ideally be restricted to a clinical trial or prospective comparative study involving comprehensive data capture using standardised definitions and appropriate outcome measures.

In terms of further research, several key flaws and gaps in the evidence base have been identified. Firstly, there is a predominance of retrospective, highly flawed, uncontrolled studies in the current evidence base. Future studies must be prospective and protocol-driven in nature, with clearly specified hypothesis and supported by robust power calculations and statistical analysis plans. Collaborative databases and online registries such as the Study of Prostate Ablation Related Energy Devices Coordinated Registry Network (49) and High Intensity Focused Ultrasound Evaluation and Assessment of Treatment Registry (50) provide a platform for sharing data and should be encouraged, although it has to be acknowledged that prospectively collected data from registries and databases are fundamentally retrospective in nature; such data are at best exploratory and should be used for hypothesis-generating rather than hypothesis-testing purposes. Consequently, careful attention must be paid to the study design; whilst RCTs are preferable, the problems associated with conducting surgical RCTs are well documented and include lack of equipoise amongst surgeons and patients resulting in poor uptake and accrual, highly specialised nature of FT resulting in limited centres being able to conduct studies, time needed to measure long-term outcomes, heterogeneity of treatment definitions and thresholds, high costs and evolving landscape of the technology and imaging. Consequently, it is also important to conduct prospective non-randomised comparative studies with clear inclusion and exclusion criteria applying to both arms. Comprehensive capture of prospective data regarding patient characteristics, treatment, monitoring and follow-up schedules and outcomes is essential. In this regard, the framework outlined by the IDEAL Collaboration should be followed.(51) Novel study designs, such as cohort-embedded RCTs, should be encouraged and supported.(52) It would be imperative to use standardised criteria and validated thresholds in terms of patient eligibility, definitions of interventions, imaging modalities during treatment and monitoring, repeat treatments within a pre-defined timescale, biopsy schedules during follow-up, and outcome measures measured at appropriate intervals and follow-up duration, since there is significant heterogeneity regarding FT.(53, 54) The use of patient-reported outcome measures (PROMS) to measure functional and quality of life outcomes should be encouraged.

It would be critically important to position FT appropriately in the clinical care pathway for managing localised PCa. The appropriate comparator can then be identified along with the measurement of meaningful outcome measures applicable to all study arms. An understanding of the main clinical aim of each comparator is crucial. For instance, AS is primarily designed to avoid over-treatment for many patients, whilst providing a means of identifying those at risk of unfavourable oncological outcomes to allow curative treatment at a subsequent point in the future. The main drawback is a small risk of metastatic progression (i.e. 'missing the boat' for curative treatment), clearly demonstrated in earlier studies incorporating less stringent versions of AS.(2) Patient anxiety may also be a reason for reclassification, with 5-13% of men being reclassified due to anxiety or patient choice rather than disease progression.(55, 56) However, there is good evidence that men on AS have relatively low levels of anxiety and a decrease in anxiety over time. (57-59) Contemporary AS protocols have improved patient selection, risk classification and stringency of follow-up via regular clinical monitoring, more accurate imaging and repeat biopsy schedules, which means the risk of metastatic progression should be significantly minimised.(60) Conversely, curative interventions are designed to eradicate the cancer completely, to minimise the probability of adverse oncological outcomes including progression and death, at the risk of adverse functional and QoL outcomes. Some proponents of FT have argued that FT should be positioned mid-way between AS and curative interventions within the clinical care

pathway.(50) This would be difficult because AS and curative interventions lie at different ends of the spectrum, each with contrasting objectives. It would be challenging placing FT within the low-risk disease setting, considering the priority for the majority of patients is to avoid over-treatment. FT is likely to exaggerate the problem of over-treatment of localised low-risk PCa, especially since it is associated with adverse events and harms. If compared with AS, pragmatically FT would need to demonstrate a reduction in metastatic progression in the first instance. This will be difficult to measure because its incidence in this cohort is likely to be low. Hence the number of patients needed for recruitment to detect any potential differences would be unfeasibly high. Given such difficulties, perhaps it is not surprising to find the lack of robust evidence supporting the use of FT in the low-risk disease setting. The real challenge in managing low-risk disease lies in improving contemporary AS protocols, by refining and standardising criteria, definitions and thresholds in order to reduce heterogeneity.(61) There is very little incentive and even less clinical need in exploring a treatment for low risk-disease which is likely to worsen the problem of over-treatment, cause adverse events and adversely impact on function (albeit transiently), and yet struggle to match the oncological superiority of radical treatments in patients who need curative intervention. Nevertheless, if patients with low-risk disease still insist on being treated with FT after being carefully counselled regarding the lack of reliable evidence and major uncertainties regarding its long-term effectiveness and harms, they could still be offered treatment as part of a clinical trial or prospective comparative study. We acknowledge that in spite of the uncertainties, some patients may still choose to undergo FT followed by continuation of AS, but involving less intensive monitoring strategies, because AS conventionally involves stringent monitoring policies including repeat prostate biopsies which are associated with adverse events. FT may also be particularly attractive to some patients because of the perceived benefits in terms of functional and quality of life outcomes over radical therapy. In addition, there may be some situations whereby FT may be desirable; for instance when radical treatments are clinically indicated but patients are contraindicated due to co-morbidities or existing conditions, FT may be the only means of providing adequate local oncological control or delaying androgen deprivation therapy or systemic therapy. Given that data are currently lacking in this situation and clinical trials are unlikely given the relative scarcity of patients fulfilling these criteria, prospective studies with robust data capture are required.

The future of FT as a treatment option for localised PCa therefore may lie in the intermediate-risk disease setting, or in the setting of reclassification within an AS protocol. In either scenario, clinical trials would need to compare FT against radical treatments. Whilst FT may achieve more favourable functional and QoL outcomes, ideally it needs to achieve parity or acceptable non-inferiority margins in terms of oncological outcomes. The thresholds of non-inferiority would need to be carefully defined within a consensus framework involving multiple stakeholders including patients. Any measure of functional or QoL benefit must consider whether subsequent whole-gland salvage treatments incur additional morbidity compared with upfront radical therapy. A recent large, single-arm case series assessing focal HIFU in patients with intermediate-risk disease has provided some low-level evidence in this setting.(62) Under such circumstances, the index lesion must be carefully defined, and following treatment, patients must be cautiously monitored via regular imaging and repeat biopsies. Criteria and thresholds regarding how the index lesion should be defined remain heterogeneous, and there are uncertainties regarding how sensitive repeat imaging and biopsy schedules are in detecting clinically significant residual or recurrent cancer foci.

Our review of ongoing prospective comparative studies showed that there are at least eight, well-powered studies on FT which may yield moderate to high certainty data in the future, but most are not expected to report until at least 2027. Nevertheless, the vast majority of ongoing prospective studies (80% of potentially eligible studies identified) are either single-arm case series or involve low patient numbers.

Finally, we recommend that any evidence synthesis endeavour (i.e. SRs and meta-analyses) must also be protocol-driven and adhere to PRISMA guidance. The AMSTAR template should also be followed to maintain methodological rigour. Meticulous attention must be paid to assessments for RoB, confounding and clinical and methodological heterogeneity. SRs must specify clearly their PICO elements, and clear distinctions must be made between whole-gland, partial gland and lesion-targeted therapy, and subgroups should be defined *a priori*.

3.4.3 Strengths and limitations

This work is strengthened by being based on an *a priori* protocol and by adhering to PRISMA guidelines. The PICO elements were developed in conjunction with a multi-disciplinary panel (EAU PCa Guideline Panel) who also helped to interpret the findings and framed the resulting recommendations. We used a comprehensive and robust approach to appraise the evidence base, by reviewing primary and secondary studies and ongoing prospective trials, and undertaking RoB and confounding and AMSTAR assessments. Limitations include the use of stringent inclusion criteria for primary studies, incorporating only comparative studies with ≥50 patients per arm. The exclusion of single-arm case series can be considered a limitation. This was done to enhance the certainty of the evidence base. Studies with small sample sizes (i.e. trials with <100 patients per arm) are extremely susceptible to small study effects and bias.(63) Sample size or statistical precision is widely considered to be the best single proxy for the combined effect of different sources of bias in clinical trials.(64) There is an inherent danger that SRs which include small, heterogeneous studies may reach erroneous and misleading conclusions. Such findings are highly unlikely to change nor guide clinical practice. Nevertheless, the inclusion of SRs allowed us to compensate for the exclusion of single-arm case series, since the majority of SRs included them. We chose a threshold of n≥50 patients per arm instead of n≥100 to retain pragmatism. It was not possible to assess for publication bias, due to the narrative nature of our review. The limited availability of robust clinical effectiveness data renders the risk of publication bias less relevant. GRADE assessment was not possible due to extreme clinical heterogeneity affecting index interventions, comparisons and outcome measures. Nevertheless, given the limited quality of the primary data, GRADE assessment is unlikely to alter the conclusions. Our evidence synthesis also only applies to primary treatment of treatment-naïve localised CaP; salvage treatment was not considered. Finally, the review was hampered by the lack of high quality and reliable data, which limited our ability to make conclusive judgements regarding the efficacy of FT.

4. Conclusions

Based on a systematic, comprehensive and robust review of the evidence base, we conclude that the overall certainty of the evidence regarding the clinical effectiveness of FT for oncological outcomes in comparison with standard management options for the primary treatment of localised PCa was low and contained significant uncertainties. There are insufficient data to support the application of FT in routine clinical practice. Consequently, until higher certainty evidence emerges from robust prospective comparative studies measuring clinically meaningful outcomes at long-term time points in a standardised manner, for now we recommend that FT should ideally be performed within clinical trials or well-designed prospective cohort studies.

References

1.Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. 2020 [updated Apr. Available from: https://uroweb.org/guideline/prostate-cancer/.
2.Neal DE, Metcalfe C, Donovan JL, Lane JA, Davis M, Young GJ, et al. Ten-year Mortality, Disease Progression, and Treatment-related Side Effects in Men with Localised Prostate Cancer from the ProtecT Randomised Controlled Trial According to Treatment Received. European urology. 2020;77(3):320-30.
3.Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med. 2009;361(17):1704-6.
4.Bates A LT, Ayers J et al. Systematic review of benefits and harms of focal ablative therapy for clinically localised prostate cancer compared with standard therapies [CRD42019152178] International prospective register of systematic reviews 2019.
5.Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed). 2009;339:b2535.
6.Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2019.

7.Cochrane CENTRAL database. Available from: https://www.cochranelibrary.com/central [online]. Accessed 12th July 20208.Reeves BC, Deeks JJ, Higgins J. 13 Including non-randomized studies. Cochrane handbook for systematic reviews of interventions. 2008;1:391.
9.Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. Health technology assessment (Winchester, England). 2003;7(27):iii-173.
10.GRADE working group. Website available from: https://www.gradeworkinggroup.org/ [online]. Accessed 12th July 2020.
11.Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ (Clinical research ed). 2017;358:j4008.
12.Azzouzi AR, Vincendeau S, Barret E, Cicco A, Kleinclauss F, van der Poel HG, et al. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. Lancet Oncol. 2017;18(2):181-91.
13.Gill IS, Azzouzi AR, Emberton M, Coleman JA, Coeytaux E, Scherz A, et al. Randomized Trial of Partial Gland Ablation with Vascular Targeted Phototherapy versus Active Surveillance for Low Risk Prostate Cancer: Extended Followup and Analyses of Effectiveness. The Journal of urology. 2018;200(4):786-93.
14.Albisinni S, Aoun F, Bellucci S, Biaou I, Limani K, Hawaux E, et al. Comparing High-Intensity Focal Ultrasound Hemiablation to Robotic Radical Prostatectomy in the Management of Unilateral Prostate Cancer: A Matched-Pair Analysis. Journal of endourology. 2017;31(1):14-9.
15.Zheng X, Jin K, Qiu S, Han X, Liao X, Yang L, et al. Focal laser ablation versus radical prostatectomy for localized prostate cancer: survival outcomes from a matched cohort. Clinical Genitourinary Cancer. 2019;17(6):464-9. e3.
16.Zhou X, Jin K, Qiu S, Jin D, Liao X, Tu X, et al. Comparative Effectiveness of Radiotherapy versus Focal Laser Ablation in Patients with Low and Intermediate Risk Localized Prostate Cancer. Scientific Reports. 2020;10(1):1-8.
17.Valerio M, Ahmed HU, Emberton M, Lawrentschuk N, Lazzeri M, Montironi R, et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. European urology. 2014;66(4):732-51.
18.Ramsay CR, Adewuyi TE, Gray J, Hislop J, Shirley MD, Jayakody S, et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health Technol Assess. 2015;19(49):1-490.
19.Baydoun A, Traughber B, Morris N, Abi Zeid Daou M, McGraw M, Podder TK, et al. Outcomes and toxicities in patients treated with definitive focal therapy for primary prostate cancer: systematic review. Future Oncol. 2017;13(7):649-63.
20.Golan R, Bernstein AN, McClure TD, Sedrakyan A, Patel NA, Parekh DJ, et al. Partial Gland Treatment of Prostate Cancer Using High-Intensity Focused Ultrasound in the Primary and Salvage Settings: A Systematic Review. The Journal of urology. 2017;198(5):1000-9.
21.Wang L, Yang H, Li B. Photodynamic therapy for prostate cancer: a systematic review and meta-analysis. Prostate Int. 2019;7(3):83-90.
22.Tay KJ. Prostate focal therapy: the rule or exception? Curr Opin Urol. 2018;28(6):512-21.
23.Albisinni S, Mélot C, Aoun F, Limani K, Peltier A, Rischmann P, et al. Focal Treatment for Unilateral Prostate Cancer Using High-Intensity Focal Ultrasound: A Comprehensive Study of Pooled Data. Journal of endourology. 2018;32(9):797-804.
24.Ahdoot M, Lebastchi AH, Turkbey B, Wood B, Pinto PA. Contemporary treatments in prostate cancer focal therapy. Current opinion in oncology. 2019;31(3):200.
25.Tourinho-Barbosa RR, Wood BJ, Abreu AL, Nahar B, Shin T, Guven S, et al. Current state of image-guided focal therapy for prostate cancer. World J Urol. 2020.

26.Ziglioli F, Baciarello M, Maspero G, Bellini V, Bocchialini T, Cavalieri D, et al. Oncologic outcome, side effects and comorbidity of high-intensity focused ultrasound (HIFU) for localized prostate cancer. A review. Annals of Medicine and Surgery. 2020.
27.Loblaw A, Pickles T, Crook J, Martin A-G, Vigneault E, Souhami L, et al. Stereotactic ablative radiotherapy versus low dose rate brachytherapy or external beam radiotherapy: propensity score matched analyses of Canadian data. Clinical Oncology. 2017;29(3):161-70.
28.Scheltema MJ, Van Den Bos W, de Bruin DM, Wijkstra H, Laguna MP, de Reijke TM, et al. Focal vs extended ablation in localized prostate cancer with irreversible electroporation; a multi-center randomized controlled trial. BMC cancer. 2016;16(1):1-9.
29.Mendez MH, Passoni NM, Pow-Sang J, Jones JS, Polascik TJ. Comparison of outcomes between preoperatively potent men treated with focal versus whole gland cryotherapy in a matched population. Journal of endourology. 2015;29(10):1193-8.
30.de Cerqueira M, Laranja W, Sanches B, Monti C, Reis L. Burden of focal cryoablation versus brachytherapy versus active surveillance in the treatment of very low-risk prostate cancer: a preliminary head-to-head comprehensive assessment. European journal of cancer care. 2015;24(6):929-37.
31.Aoun F, Limani K, Peltier A, Marcelis Q, Zanaty M, Chamoun A, et al. High intensity focused ultrasound versus brachytherapy for the treatment of localized prostate cancer: a matched-pair analysis. Advances in urology. 2015;2015.
32.Barret E, Ahallal Y, Sanchez-Salas R, Galiano M, Cosset J-M, Validire P, et al. Morbidity of focal therapy in the treatment of localized prostate cancer. European urology. 2013;63(4):618-22.
33.Barreras SG, Sanchez-Salas R, Sivaraman A, Barret E, Secin FP, Redondo C, et al. Prospective comparative analysis of oncologic and functional outcomes between focal therapy and robotic radical prostatectomy. American Society of Clinical Oncology; 2017.
34.Kamrava M, Chung MP, Kayode O, Wang J, Marks L, Kupelian P, et al. Focal high-dose-rate brachytherapy: A dosimetric comparison of hemigland vs. conventional whole-gland treatment. Brachytherapy. 2013;12(5):434-41.
35.Vainshtein J, Abu-Isa E, Olson KB, Ray ME, Sandler HM, Normolle D, et al. Randomized phase II trial of urethral sparing intensity modulated radiation therapy in low-risk prostate cancer: implications for focal therapy. Radiation oncology. 2012;7(1):82.
36.Langley S, Uribe J, Uribe-Lewis S, Franklin A, Perna C, Horton A, et al. Hemi-ablative low-dose-rate prostate brachytherapy for unilateral localised prostate cancer. BJU international. 2020;125(3):383-90.
37.Lei Y, Zanker P, Yildiz S, Hancke K, Seidl D, Koch O, et al. Non-Whole-Gland High-Intensity Focused Ultrasound vs Whole-Gland High-Intensity Focused Ultrasound for Management of Localized Prostate Cancer: 1-Year Oncological and Functional Outcomes. Journal of endourology. 2019;33(2):100-6.
38.Bahn D, de Castro Abreu AL, Gill IS, Hung AJ, Silverman P, Gross ME, et al. Focal cryotherapy for clinically unilateral, low-intermediate risk prostate cancer in 73 men with a median follow-up of 3.7 years. European urology. 2012;62(1):55-63.
39.Tourinho-Barbosa RR, Sanchez-Salas R, Claros OR, Collura-Merlier S, Bakavicius A, Carneiro A, et al. Focal Therapy for Localized Prostate Cancer with Either High Intensity Focused Ultrasound or Cryoablation: A Single Institution Experience. The Journal of urology. 2020;203(2):320-30.
40.Reddy D, Shah TT, Dudderidge T, McCracken S, Arya M, Dobbs C, Emberton M, Fiorentino F, Day E, Prevost AT, Staffurth J. Comparative Healthcare Research Outcomes of Novel Surgery in prostate cancer (IP4-CHRONOS): A prospective, multi-centre therapeutic phase II parallel Randomised Control Trial. Contemporary Clinical Trials. 2020 Apr 14:105999.
41.Hamdy FC, Elliott D, le Conte S, Davies LC, Burns RM, Thomson C, Gray R, Wolstenholme J, Donovan JL, Fitzpatrick R, Verrill C, Gleeson F, Singh S, Rosario D, Catto JW, Brewster S, Dudderidge T, Hindley R, Emara A, Sooriakumaran P, Ahmed HU, Leslie TA. Partial ablation versus

radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. Health Technol Assess. 2018 Sep;22(52):1-96. doi: 10.3310/hta22520. PMID: 30264692; PMCID: PMC6187111.
42.ClincialTrials.gov [Internet]. US national library of medicine; [updated 2020 February 20; cited 2020 February 20]. Available from: https://clinicaltrials.gov/ct2/show/NCT04278261 NCT04278261 CgI. Comparison of Irreversible Electroporation and Radical Prostatectomy in Treating Prostate Cancer 2020
43.ClinicalTrials.gov [Internet]. US national library of medicine; [updated 2020 March 10; cited 2018 September 12]. Available from: https://clinicaltrials.gov/ct2/show/NCT03668652NCT03668652 Focal Prostate Ablation Versus Radical Prostatectomy (FARP) 2020
44.ClinicalTrials.gov [Internet]. US national library of medicine; [updated 2020 March 17; cited 2020 January 13]. Available from: https://clinicaltrials.gov/ct2/show/NCT04225299 NCT04225299 CgI. An Evaluation of the Efficacy of Partial Gland Ablation (PGA) With TOOKAD® Vascular Targeted Photodynamic Therapy (VTP) Versus Active Surveillance for Men With Intermediate Risk Localized Prostate Cancer 2020
45.ClinicalTrials.gov [Internet]. US national library of medicine; [updated 2019 September 17; cited 2018 May 21]. Available from: https://clinicaltrials.gov/ct2/show/NCT03531099 NCT03531099 CgI. Phase 3, Multicenter, Randomized Study, Evaluating the Efficacy and Tolerability of Focused HIFU (High Intensity Focused Ultrasound) Therapy Compared to Active Surveillance in Patients With Significant Low Risk Prostate Cancer (HIFUSA) 2020
46.ClinicalTrials.gov [Internet]. US national library of medicine; [updated 2020 March 10; cited 2018 September 12]. [Available from: https://clinicaltrials.gov/ct2/show/study/NCT01835977. Multi-Center Randomized Clinical Trial Irreversible Electroporation for the Ablation of Localized Prostate Cancer
47.ClinicalTrials.gov [Internet]. US national library of medicine; [updated 2020 March 10; cited 2018 September 12]. ClinicalTrials gov identifier NCT03982706. Available from: https://clinicaltrials.gov/ct2/show/ NCT03982706 HIFU v NanoKnife v Cryotherapy
48.Tosoian JJ, Mamawala M, Epstein JI, Landis P, Macura KJ, Simopoulos DN, et al. Active Surveillance of Grade Group 1 Prostate Cancer: Long-term Outcomes from a Large Prospective Cohort. European urology. 2020;77(6):675-82.
49.Gross MD, Sedrakyan A, Bianco FJ, et al. SPARED Collaboration: Patient Selection for Partial Gland Ablation in Men with Localized Prostate Cancer. J Urol. 2019;202(5):952-958. doi:10.1097/JU.0000000000000357
50.Lovegrove CE, Peters M, Guillaumier S, et al. Evaluation of functional outcomes after a second focal high-intensity focused ultrasonography (HIFU) procedure in men with primary localized, non-metastatic prostate cancer: results from the HIFU Evaluation and Assessment of Treatment (HEAT) registry. BJU Int. 2020;125(6):853-860. doi:10.1111/bju.1500452.
51.Hirst A, Philippou Y, Blazeby J, Campbell B, Campbell M, Feinberg J, et al. No Surgical Innovation Without Evaluation: Evolution and Further Development of the IDEAL Framework and Recommendations. Ann Surg. 2019;269(2):211-20.
52.Neves JB, Cullen D, Grant L, Walkden M, Bandula S, Patki P, Barod R, Mumtaz F, Aitchison M, Pizzo E, Ranieri V. Protocol for a feasibility study of a cohort embedded randomised controlled trial comparing NEphron Sparing Treatment (NEST) for small renal masses. BMJ open. 2019 Jun 1;9(6):e030965.
53.Van Den Bos W, Muller BG, Ahmed H, Bangma CH, Barret E, Crouzet S, et al. Focal therapy in prostate cancer: international multidisciplinary consensus on trial design. European urology. 2014;65(6):1078-83.
54.Lebastchi AH, George AK, Polascik TJ, Coleman J, de la Rosette J, Turkbey B, et al. Standardized Nomenclature and Surveillance Methodologies After Focal Therapy and Partial Gland Ablation for Localized Prostate Cancer: An International Multidisciplinary Consensus. European urology. 2020.

55.Bokhorst LP, Valdagni R, Rannikko A, Kakehi Y, Pickles T, Bangma CH, et al. A Decade of Active Surveillance in the PRIAS Study: An Update and Evaluation of the Criteria Used to Recommend a Switch to Active Treatment. European urology. 2016;70(6):954-60.
56.Van Hemelrijck M, Ji X, Helleman J, Roobol MJ, van der Linden W, Nieboer D, et al. Reasons for Discontinuing Active Surveillance: Assessment of 21 Centres in 12 Countries in the Movember GAP3 Consortium. European urology. 2019;75(3):523-31.
57.Dickey SL, Grayson CJ. The Quality of Life among Men Receiving Active Surveillance for Prostate Cancer: An Integrative Review. Healthcare (Basel). 2019;7(1).
58.Naha U, Freedland SJ, Abern MR, Moreira DM. The association of cancer-specific anxiety with disease aggressiveness in men on active surveillance of prostate cancer. Prostate Cancer Prostatic Dis. 2020.
59.Bellardita L, Valdagni R, van den Bergh R, Randsdorp H, Repetto C, Venderbos LD, et al. How does active surveillance for prostate cancer affect quality of life? A systematic review. European urology. 2015;67(4):637-45.
60.Peter-Paul M. Willemse TL, Nicolas Mottet, Cathy Yuan, Karin Plass, James Donaldson, Niall Davis, Paolo Dell'Oglio, Christian Fankhauser, Nikos Grivas, Alexandre Ingels, Michael Lardas, Matthew Liew, Karl Pang, Catherine Paterson, Imran Omar, Fabio Zattoni, Tim Buddingh. . Systematic review of deferred treatment with curative intent for localised prostate cancer to explore heterogeneity of definitions, thresholds and criteria and clinical effectiveness 2018 [Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018071780.
61.Lam TB, MacLennan S, Willemse P-PM, Mason MD, Plass K, Shepherd R, et al. EAU-EANM-ESTRO-ESUR-SIOG prostate cancer guideline panel consensus statements for deferred treatment with curative intent for localised prostate cancer from an international collaborative study (Detective study). European urology. 2019;76(6):790-813.
62.Guillaumier S, Peters M, Arya M, Afzal N, Charman S, Dudderidge T, et al. A multicentre study of 5-year outcomes following focal therapy in treating clinically significant nonmetastatic prostate cancer. European urology. 2018;74(4):422-9.
63.Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. BMJ (Clinical research ed). 2010;341:c3515.
64.Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000;53(11):1119-29.