

MINI-REVIEW

Focal therapy for prostate cancer: Challenges with patient selection, treatment modalities, and follow-up

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Abstract

Prostate cancer (PCa) remains the most common malignancy among men. Historically, the standard treatments for localized, clinically significant PCa have been radical prostatectomy or radiation therapy. However, the need to achieve optimal oncological outcomes while maintaining quality of life has led to the development of focal therapy (FT) as a novel treatment modality. At present, FT is performed using different types of energy sources: (i) cryotherapy, (ii) irreversible electroporation, (iii) high-intensity focused ultrasound, (iv) transurethral ultrasound ablation, (v) focal laser therapy, (vi) bipolar radiofrequency ablation, and (vii) photodynamic therapy. The role of FT in PCa is highly debated for several reasons, mainly because the disease is multifocal in most cases, and long-term outcomes from prospective clinical trials are still lacking. Nevertheless, it has been suggested that focal treatment of the index lesion is sufficient, as this lesion is believed to drive metastatic spread. Therefore, FT is considered a potential treatment option for patients with organ-confined, intermediate-risk PCa as an alternative to whole-gland treatments. Although FT generally preserves voiding and sexual functions, its effectiveness in cancer control needs to be validated through high-quality comparative trials. The aim of this article is to discuss the challenges of patient selection and review the various FT modalities and follow-up strategies after treatment.

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1. Introduction

Prostate cancer (PCa) remains the most frequently diagnosed malignancy in men (excluding skin cancer) and is the second most common cause of cancer-related death in the United States. Most men with PCa present with localized disease at the time of diagnosis.¹ Historically, the standard treatments for patients with clinically significant cancer and a life expectancy of >10 years have been radical prostatectomy (RP) or radiation therapy (RT).²

However, the need to achieve optimal oncological results while maintaining quality of life has led to the development of focal therapy (FT) as a new treatment option.³ FT aims to minimize harm to the neurovascular bundles, urethra, urethral sphincter, and

rectum. According to American Urological Association and American Society for Radiation Oncology guidelines, patients with intermediate-risk, organ-confined PCa may be candidates for FT if they are fully informed regarding potential side effects, recurrence risks, need for follow-up, lack of high-quality comparative data between ablation outcomes and those from RP or RT, and the possibility of needing additional therapy.⁴

In the past decade, FT has undergone technological refinements, including improved patient selection and post-ablation follow-up protocols, resulting in better outcomes with these treatment modalities. At present, FT is performed using different types of energy sources: (i) cryotherapy (CRYO), (ii) irreversible electroporation, (iii) high-intensity focused ultrasound (HIFU), (iv) transurethral ultrasound ablation (TULSA), (v) focal laser therapy (FLA), (vi) bipolar radiofrequency ablation (RFA), and (vii) photodynamic therapy (PDT). The aim of this article is to discuss the challenges in patient selection, review FT modalities, and examine follow-up strategies.

2. Patient selection

One of the keys to optimal oncological and functional success in FT is appropriate patient selection. Before the implementation of multiparametric prostate magnetic resonance imaging (mpMRI), recognition of the index lesion and differentiation of unifocal versus multifocal or unilateral versus bilateral tumors were challenging. It has been suggested that in multifocal PCa, FT to the index lesion (*the lesion with the highest cancer grade*) is sufficient because other non-index sites of disease harbor insignificant, low-grade PCa and are unlikely to contribute to disease progression.⁵

Klotz *et al.*^{6,7} described the feasibility of active surveillance (AS) in low-risk patients and demonstrated a 10- and 15-year cancer-specific survival (CSS) of 98.1% and 94.3%, respectively. Among patients with low-risk disease, FT can be considered for selected cases involving men diagnosed with radiographically evident, larger-volume, and low-grade PCa at a young age who are unwilling to accept conservative management.⁸ However, this approach remains controversial.

Tan *et al.*⁹ reported that FT might be indicated for patients discontinuing AS due to a unilateral focus on PCa grade group (GG) 2 as an alternative to whole-gland treatment. At present, the ideal candidate for FT is those who do not fulfill the inclusion criteria for AS and have single or multiple, unilateral, well-delineated, and mpMRI-visible lesions with target biopsy results consistent with clinically significant PCa GG 2. In addition, it is crucial to evaluate the location of the lesion to ensure that the

procedure can be performed with a treatment margin that minimizes the risk of injury to the neurovascular bundle, urethra, urethral sphincter, and rectum.⁹ Regarding PCa GG 3, FT is a viable strategy when the tumor can be completely ablated or for patients who refuse to accept conventional definitive management¹⁰ (Table 1).

3. Local therapy modalities

3.1. CRYO

Gao *et al.*¹¹ reported no differences in terms of overall survival (OS) when comparing CRYO to RP and RT, although RP showed better relapse-free rates (Table 2). Likewise, Ramsay *et al.*¹² demonstrated that there is no difference in terms of OS and relapse-free survival when comparing CRYO to patients treated with RP and/or external beam RT (EBRT), but CRYO demonstrated less functional adverse effects, mainly erectile dysfunction and urinary incontinence. Valerio *et al.*¹³ reported in a meta-analysis and systematic review an OS and disease-specific survival (DSS) of 100% in both analyses and pad-free continence and erectile function preservation were achieved in 100% and 81.5%, respectively. In contrast, it showed a presence of significant and insignificant cancer of 5.4% and 13%, respectively, and a probability of transition to secondary local treatment of 7.6%.¹³

3.2. Irreversible electroporation

Van den Bos *et al.*¹⁴ reported an infield recurrence and an out-of-field recurrence rate of 16% and 24%, respectively. No high-grade adverse events occurred, with bowel and urinary quality maintained at 6 months postoperatively. However, the median sexual quality of life score decreased from 66 to 54 at 6 months ($P < 0.001$).¹⁴ On the other hand, Kiełbik *et al.*¹⁵ reported an erectile function preservation of over 90% in most series. Valerio *et al.*¹³ reported in a meta-analysis and systematic review the presence of significant and insignificant cancer in 13.4% and 32.4%, respectively, and the probability of transitioning to secondary local treatment was 11.9%. The OS and DSS were 100% in both analyses, and pad-free continence and erectile function preservation were achieved at 100% and 90%, respectively.¹³

3.3. HIFU

Alkhorayef *et al.*¹⁶ evaluated patients treated with the Ablatherm and Sonablate devices and discovered a biochemical recurrence-free survival rate of 77% and 45% to 84%, respectively. Both systems had similar complication rates, although the Ablatherm device tends to result in a higher urethral stricture rate and fewer sexual adverse effects. Guillaumier *et al.*¹⁷ reported that 19% of patients required at least two retreatments. Failure-free survival

Table 1. Patient selection

National Comprehensive Cancer Network	Disease factors	Diagnostic approach	Biopsy	Patient factors
Favorable or unfavorable intermediate risk	(i) Localized (ii) Unifocal/Multifocal (iii) Unilateral (iv) PSA <10 (v) PCa GG 2 or 3	mpMRI/TRUS fusion+systematic biopsy	Transrectal or transperineal	(i) Informed consent (ii) Well motivated (iii) Willing to undergo close follow-up with PSAs, prostate MRIs and re-biopsies. (iv) Willing to undergo retreatment. (v) Understand the lack of long-term data and randomized controlled trials in this space

Abbreviations: PSA: Prostate-specific antigen; mpMRI: Multiparametric MRI; TRUS: Transrectal ultrasound; PCa GG: Prostate cancer grade group.

Table 2. Ablation energy sources

Therapy	Ablation energy and route of delivery	Mechanism	Intraoperative monitoring	US FDA clearance date
Cryotherapy	Freezing transperineal	Protein denaturalization and dehydration; cellular; membranes rupture; thrombosis of the microvasculature; and apoptosis	TRUS	Cleared for prostate tissue ablation in 1997
Irreversible electroporation	Electrical current transperineal	Electrical current within the target tissue leading to pore formation in prostate cell walls that result in cell apoptosis	TRUS	Cleared for soft-tissue ablation in 2015
High-intensity focused ultrasound	High-intensity ultrasound energy transrectal	Coagulative necrosis due to extreme temperatures and internal cavitation due to the interaction between water and ultrasound	TRUS	Cleared for prostate tissue ablation in 2015
Transurethral ultrasound ablation	High-intensity ultrasound energy transurethral	Thermal coagulation	MRI-thermometry	Cleared for prostate tissue ablation in 2019
Focal laser therapy	Heat transperineal	Coagulative necrosis	MRI-thermometry	Various laser systems with different clearance dates
Bipolar radiofrequency ablation	Heat transperineal	Protein denaturalization and dehydration; cellular and apoptosis	TRUS, CT, and MRI	Cleared for soft-tissue ablation in 2001
Photodynamic therapy	Laser plus intravenously administration of light-sensitive drugs transperineal	Vascular thrombosis; necrosis; and apoptosis	TRUS	cleared for other indications, not specifically for prostate

Abbreviations: CT: Computed tomography; MRI: Magnetic resonance image; TRUS: Transrectal ultrasound; US FDA: United States Food and Drug Administration.

and a metastasis-free survival rate after a 5-year follow-up were 88% and 95%, respectively. The main complications after 2 years of treatment were urinary incontinence (3%), urinary tract infections (8.5%), and recto-urethral fistulae (0.32%).¹⁷ Valerio *et al.*¹³ reported in a meta-analysis and systematic review the presence of significant and insignificant cancer of 0% and 23.3%, respectively, and the probability of transitioning to secondary local treatment of 7.8%. The OS and DSS were 100% in both analyses, and pad-free continence and erectile function preservation were 100% and 88.6%, respectively.¹³

3.4. TULSA

The TULSA feasibility was assessed in a prospective Phase I study with up to a 5-year follow-up.^{18,19} Recently, Dora

*et al.*²⁰ reported in a systematic review a prostate-specific antigen (PSA) decline of 54 – 97% and a salvage treatment rate after one TULSA treatment between 7% and 17%. The continence and erectile function preservation rates were from 92% to 100% and from 75% to 98%, respectively. Finally, Grade III adverse events were observed in 6% of patients, with no rectal injury/fistula, or Grade IV complication.²⁰

3.5. FLA

Feller *et al.*²¹ described the largest study with FLA and reported 23% of the in-field cancer recurrence rate; however, there is no long-term oncologic follow-up. No statistically significant changes in the International Prostate Symptom Score or sexual health inventory for

men scores at 12 months were observed, and no serious side effects were observed.²¹

3.6. Bipolar RFA

Zlotta *et al.*²² evaluated focal RFA before RP, but no details on the study population were available, and other oncological and functional outcomes could not be extrapolated either. A residual tumor was found in all men, although there was no intention to treat this group in this study.²²

3.7. PDT

A Phase III randomized controlled trial (RCT) comparing PDT versus AS in patients with low-risk PCa has been conducted^{23,24}. In 2017, Azzouzi *et al.*²³ reported early results of the trial, focusing on adverse events. These adverse effects were more common in the treatment arm, with erectile dysfunction and urinary incontinence rates reaching 38% and 27%, respectively, compared to 11% and 7% in the control arm. In 2018, Gill *et al.*²⁴ reported that 50% of patients in the treatment arm had no detectable cancer in the prostate, with 25% having residual cancer within the treatment field at a 2-year follow-up. Metastasis-free survival was identical in both groups (99% vs. 99% at 4 years), and the conversion rate to radical therapy was 24% in the PDT group versus 53% in the AS arm.²⁴

4. Follow-up strategies

Appropriate follow-up surveillance protocols are another key issue in managing patients after FT. Early FT series lacked standardized post-ablation follow-up protocols due to the absence of long-term follow-up data. Nonetheless, there was general agreement that patients should be followed with strict strategies similar to those used in AS. Van den Bos *et al.*²⁵ proposed a post-ablation follow-up protocol that included PSA testing every 3 months in the 1st year, every 6 months in the 2nd year, annually in the 3rd year, and then at the physician's discretion. In addition, a systematic biopsy was recommended between 6 and 12 months post-treatment.

At present, with the advent of the mpMRI of the prostate, most specialized FT centers follow the protocol described by Lebastchi *et al.*,²⁶ which includes PSA testing every 3 months in the 1st year, followed by every 6 months

thereafter. MpMRI is conducted at 6 months, 12 months, and then annually. A targeted biopsy of the ablation zone, as well as a systematic biopsy, is performed between 6 and 12 months after treatment. Further repeat biopsies are recommended if triggering factors such as rising PSA levels, MRI abnormalities, or abnormal findings on a digital rectal examination are present²⁶ (Table 3).

5. Discussion

The tumor microenvironment (TME) in PCa comprises not only neoplastic cells but also stromal, endothelial, neural crest, and immune cells, along with various soluble factors, such as interleukin (IL)-6 and receptor activator of nuclear factor kappa-B ligand. These components release substances such as chemokines, cytokines, extracellular matrices, and enzymes that degrade the matrix and result in a pathogenic entity.^{27,28} The TME creates an environment that circumvents the immune system and suppresses antitumor immunity, which results in disease progression. FT can stimulate the immune response through various mechanisms: induction of CD3+ and CD4+ levels in cells and the CD4+/CD8+ ratio, activation of T-cells, promotion of neutrophil recruitment, activation of macrophages, secretion of IL-1, IL-6, IL-8, IL-10, IL-12, thromboxane, and prostaglandins, regulation of cytotoxic T lymphocyte and natural killer cell migration, and an increase in CD8+ T-cell infiltration, among others.²⁹ Therefore, FT plays a fundamental role in breaking this favorable microenvironment, playing an immunomodulatory effect that can favor or inhibit tumorigenesis.³⁰

Increased understanding of the TME has led to the exploration of combining intratumoral immunotherapy with other treatments. Immunotherapy for the treatment of solid tumors, including the use of intratumorally injected immunotherapy instead of systemically administered immunotherapy, has shown a good response for specific tumor types. In PCa, the role of immunotherapy is debatable and limited to specific populations with advanced disease. The use of intratumoral immunotherapy as an adjunct to thermal ablation offers the potential to elicit a systemic and long-lasting immune response to cancer-specific antigens, leading to a synergistic effect of the combined therapy, whereas FT causes immunological

Table 3. Follow-up strategies

PSA	mpMRI	Biopsy	Re-biopsy
Every 3 months in the 1 st year and every 6 months thereafter	6 months, 12 months, and yearly	Ablation zone+systematic biopsy between 6 and 12 months after treatment	Triggering factors (i) rising PSA (ii) mpMRI abnormalities (iii) abnormal DRE

Abbreviations: DRE: Digital rectal exam; mpMRI: Multiparametric MRI; PSA: Prostate-specific antigen.

activation against prostate tissue. The combination of thermal ablation and immunotherapy is currently in the early stages of investigation for the treatment of several types of solid tumors.³¹

Understanding the tumorigenesis of PCa is at the root of the attempt to enhance the results of each therapy, since the TME, through an interconnected network, offers conditions for the survival, evolution, and metastasis of the tumor.³²

The role of FT in PCa is highly debated for several reasons, mainly because the disease is multifocal in more than 80% of cases. However, the logic supporting FT is based on some important aspects, including the concept of the index lesion, which seems to be related to the risk of disease progression. Therefore, its treatment would prevent the spread of tumor cells. Low-grade tumors have a tendency to present indolent behavior, so the risk of progression seems to be low, and the advent of mpMRI and target fusion biopsy allows the detection of the index lesion, a more accurate biopsy, and a safer patient follow-up. These arguments allowed FT to be considered in carefully selected patients as a potential treatment modality.³³⁻³⁵

The concept of success and failure in FT is controversial. It is important to distinguish between the success of the overall strategy (disease control rate and absence of secondary salvage treatment) and the success of the specific FT technique (negative biopsy in the post-ablation area). Furthermore, the risk of adverse effects is directly related to the location of the lesion to be treated. Therefore, several aspects need to be debated before further discussing results or deciding the best FT modality.

First, FT was considered an alternative to AS, with some series including men with what are now classified as low-risk diseases. Furthermore, post-ablation surveillance protocols have improved over the years, affecting study outcomes.³⁶ Second, although recent definitions of FT focus on the ablation of the index lesion, there were differences in the ablation techniques, with many early series using hemiablation or whole-gland ablations.⁷ Third, most FT studies are focused on evaluating the safety, feasibility, and both functional and oncological outcomes related to a specific type of energy modality. Finally, heterogeneity in study design prevents a reliable comparison among the different sources of energy and between FT and standard therapies such as RT and RP.

Although several modalities of FT are available, CRYO and HIFU have been the most studied sources of energy so far in terms of number of studies and length of follow-up. The decision between CRYO, HIFU, or other FT modalities

should be based on clinician experience and tumor characteristics since comparative studies are scarce.³⁷

Overall, FT rarely causes significant morbidity and seems to have a small impact on quality of life, although the oncological outcomes in the long-term follow-up need to be further evaluated.¹³ There is a predominance of retrospective and uncontrolled studies in the current literature that compare these results with standard therapies.

Albisinni *et al.*³⁸ conducted a retrospective study, comparing focal HIFU to robot-assisted laparoscopic RP in low-risk and intermediate-risk disease and reported no significant differences in treatment failure at 3 years, while focal HIFU had better recovery of continence and erectile function preservation. Zheng *et al.*³⁹ performed a retrospective study to compare FLA with RP using surveillance, epidemiology, and end results (SEER) data and showed that FLA had higher any-cause mortality, although CSS did not significantly differ between the arms. The same group⁴⁰ performed a similar retrospective study using the SEER database and compared FLA to definitive radiotherapy (EBRT) and described a significantly worse OS with FLA.

Zheng *et al.*³⁹ investigated the oncologic outcomes of FLA and compared them with those of RP, suggesting that FLA had a higher risk of all-cause mortality but an insignificantly lower risk of cancer-specific mortality. In contrast, Bates *et al.*⁴¹ conducted a systematic review comparing different modalities of FT management options. An RCT comparing PDT with AS found a significantly lower rate of treatment failure at 2 years with PDT, and there were no differences in functional outcomes.²³ A retrospective study comparing focal HIFU with robotic RP reported no significant differences in treatment failure at 3 years, with focal HIFU having better functional results.³⁸ Two retrospective cohort studies using SEER data compared FLA with RP and EBRT, reporting significantly worse oncological outcomes for FLA.^{13,40}

Some RCTs to compare partial ablation versus RP in intermediate-risk PCa are in progress, such as the PART RCT and a UK-based RCT (Comparative healthcare research outcomes of novel surgery in prostate cancer).^{42,43} Furthermore, a separate multi-arm, multi-stage RCT comparing FT alone to FT with neoadjuvant finasteride or bicalutamide is expected. Therefore, new prospective studies with longer follow-up periods are needed so that we can safely carry out these comparisons.

6. Conclusion

FT is emerging as a potential treatment for patients with organ-confined intermediate-risk PCa as an alternative

to whole-gland treatments. It offers the advantage of minimizing harm to voiding and sexual functions compared to standard therapies. While initial results are encouraging, they need validation through high-quality comparative effectiveness and prospective randomized trials; however, the heterogeneity in terms of therapeutic and follow-up protocols complicates the comparison of different FT approaches. Finally, it is important to emphasize that the success of treatment depends not only on the FT modalities but also on patient selection and optimal follow-up strategies.

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Conflict of interest

The authors declare that they have no competing interests.

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Not applicable.

Availability of data

The data of this study are available from the corresponding author on reasonable request.

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