Ablative options for prostate cancer management

Rafael R. Tourinho-Barbosa[1,2,3], Lucas Teixeira Batista[3], Xavier Cathelineau[1], Javier Sanchez-Macias[4], Rafael Sanchez-Salas[1]

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ABSTRACT

This review provides an overview of the available ablative options for prostate cancer (PCa) management. It contemplates the ablative concepts and the role of prostate ablation in different settings, from primary treatment to repeat ablation, and as an alternative to radiorecurrent disease. Improvements in prostate imaging have allowed us to ablate prostate lesions through thermal, mechanical, and vascular-targeted sources of energy. Partial gland ablation (PGA) has an emerging role in the management of localized PCa because toxicity outcomes have been proven less harmful compared with whole-gland treatments. Although long-term oncological outcomes are yet to be consolidated in comparative studies, recent large series and prospective studies in PGA have reported encouraging results. A second ablation after disease recurrence has demonstrated low toxicity, and future studies must define its potential to avoid radical treatments. PGA is an attractive option for PCa management in different scenarios because of its low-toxicity profile. As expected, recurrence rates are higher than those seen in whole-gland procedures. Long-term oncological outcomes of primary and salvage options are required to endorse it among the standard treatments.

Keywords: Ablation techniques; cryotherapy; focal therapy; high-intensity focused ultrasound therapy; prostate cancer.

[1]Department of Urology, Institute Mutualiste Montsouris, Université Paris-Descartes, Paris, France
[2]Department of Urology, Faculdade de Medicina do ABC, Santo André, Brazil
[3]Department of Urology, Hospital Cardiopulmonar, Salvador, Brazil
[4]Department of Urology, Hospital Clinic de Barcelona, Universidad de Barcelona, Barcelone, Spain

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Corresponding Author: Rafael Sanchez-Salas
E-mail: rafael.sanchez-salas@imm.fr

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Introduction

In recent years, prostate cancer (PCa) has been diagnosed in earlier stages as a result of widespread screening strategies. Although radical approaches, such as radical prostatectomy (RP) and external beam radiation therapy (EBRT), are considered the standard therapies for low- to intermediate-risk patients, a rising debate about overtreatment has led clinicians to seek less morbid alternatives.[1] Standing in the middle ground between active surveillance and radical approaches, partial ablation of the prostate aims to treat PCa while sparing the structures essential to preserve the genitourinary function.

Improvements in multiparametric magnetic resonance imaging (mpMRI) were key for disease localization and biopsy guidance.[2,3] Once tumoral lesions are reliably visualized by imaging, targeting for ablation becomes feasible. In addition, the development of ablative devices has allowed us to tackle the tumor foci while preserving the surrounding structures. Therefore, partial gland ablation (PGA) has emerged as an alternative to the radical procedures, considering the optimal selection of patient, the ideal source of energy, and the most appropriate treatment template are yet to be determined.[1,4]

Ablative energy sources (AESs) for PCa management include high-intensity focused ultrasound (HIFU), cryotherapy, vascular-targeted photodynamic therapy (VTP), irreversible electroporation (IRE), focal laser ablation (FLA), radiofrequency ablation, microwave ablation, and brachytherapy.[5] In this nonsystematic review, we perform a critical analysis of the recent literature to better understand the prostate ablation concept along with the use of available AESs in different templates and scenarios.

Clinical and research consequences

Ablative principles

PCa is a multifocal disease in 70% of patients; however, in most cases, an index lesion harbors

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the highest histologic tumor grade, which drives the PCa behavior.[6,7] Aggressive clones that lead to lethal metastatic disease seem to originate from the index lesion, whereas low-grade satellite lesions are unlikely to metastasize.[8,9] Therefore, a clinically significant index lesion should be treated in its early stages to avoid disease progression.[10]

In comparing mpMRI with whole-mount pathology, mpMRI can detect more than 80% of the index lesions.[11] In the Prostate Magnetic Resonance Imaging Study (PROMIS), mpMRI outperformed the traditional transrectal ultrasound (TRUS) systematic biopsy in the detection of clinically significant lesions with sensitivity of 93% vs 48%.[2] Combining both target and systematic biopsies presents the highest detection rates for clinically significant PCa; therefore, this combination became the new standard of prostate biopsy.[12] However, regarding PCa focus measures, mpMRI underestimates the tumor boundaries by about 10 mm compared with histopathology.[11] Therefore, some authors propose an 8- to 10-mm treatment margin surrounding the visible PCa focus to ensure adequate ablation during focal ablation, which is roughly a hemiablation for small prostates.[13]

Regarding the ablative modalities, a shift from whole-gland ablation (WGA) to PGA has been demonstrated in recent years, especially in the primary setting of PCa management.[5,14] PGA ranges from hockey-stick field ablation to hemiablation and quadrant or focal ablation (Figure 1). The best template for PGA is yet to be determined; however, hemiablation has been the most common template in HIFU, cryotherapy, and VTP studies, whereas focal ablation has been the goal for IRE, FLA, and brachytherapy in most recent studies.[15]

PGA has been widely proposed as a treatment for ISUP 1-3 PCa, but there is no consensus on whether higher grade lesions can be safely ablated.[16] Some authors have reported focal HIFU and cryotherapy as safe procedures in the selected high-risk patients.[17,18] Nevertheless, these patients have a higher risk of recurrence and are not considered the ideal patients for PGA thus far.

Main Points:

- Several ablative energy sources are available for PCa management, including high-intensity focused ultrasound, cryotherapy, vascular-targeted photodynamic therapy, irreversible electroporation, focal laser ablation, radiofrequency ablation, microwave ablation, and brachytherapy.
- PGA can be delivered in different templates, such as hockey-stick ablation, hemiablation, quadrant ablation, or focal ablation.
- PGA directed to the PCa index lesion is a safe procedure with consolidated midterm oncological outcomes.
- Additional ablative procedures after ablation failure are feasible and safe, but mid- to long-term outcomes are warranted.
- Prostate ablation is a safe alternative to morbid radical procedures in the radiorecurrent setting.

Description of available ablative modalities

HIFU

Currently, HIFU is the most studied AES applied for PCa management. Using a spherical transducer, the ultrasound waves converge at a focal point with consequent hyperthermia (80°C–100°C) and cavitation, which lead to irreversible coagulative necrosis and tissue destruction.[19] Fusion of mpMRI and ultrasound images improves accuracy for lesion localization and preservation of functional structures, such as the neurovascular bundles. The transrectal transducer allows real-time monitoring of the ablation area, and the operator should make pauses and readjustment to avoid prostate edema and vaporization. A major limitation of HIFU is the treatment of anterior lesions, especially in large prostates.[20] The ultrasound waves dissipate through the prostatic tissue, decreasing the intensity with a distance greater than 40 mm. HIFU is the only true noninvasive AES currently available.

Cryotherapy

Cryotherapy ablates the prostate lesions through at least 2 freeze-thaw cycles, causing both immediate and delayed cell destruction.[21] Transperineal needles are inserted in the prostate, guided by TRUS to actively freeze (argon gas) and thaw (he-

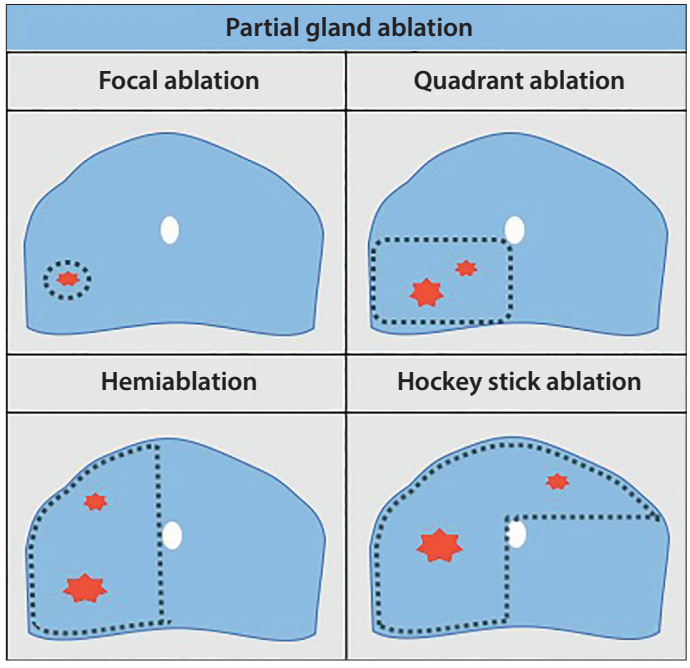

Figure 1. Partial gland ablation templates for prostate cancer management: focal ablation, quadrant ablation, hemiablation and hockey-stick ablation

lium gas) the prostate tissue. Temperatures under –40°C must be achieved, creating an ice ball that leads to intracellular crystallization, protein denaturation, and cellular apoptosis and necrosis.[22] Because cryoneedles are inserted transperineally, cryotherapy can target PCa in all the prostate locations, including anterior lesions. Thermal control is performed through the sensors placed near the rectum and within the treatment area, and a urethral warming catheter is used during the procedure to avoid urethral damage. Treatment can be monitored by TRUS in real time.

VTP therapy

VTP is a nonthermal AES based on the interaction between the light-diffusing fibers inserted transperineally and the intravenous photosensitizing agents. The most frequently studied photosensitizer is padeliporfin (WST11). The activation of a vascular photosensitizer within the ablation area leads to the production of reactive oxygen species, thrombosis, vessel obliteration, and cell destruction.[23]

IRE

IRE is a nonthermal AES that uses transperineal electroneedles to deliver high-voltage, low-energy electric current. The electric field produces nanopores and modifies the cell membrane permeability, leading to apoptosis. The determinants of irreversible cell injury are duration, frequency, and intensity of the electric field.[24] A major advantage of IRE is its ability to preserve the structures adjacent to the tumor tissue. General anesthesia and full muscle paralysis are required to avoid needle displacement induced by electrical impulses and reflex movements.

FLA

In FLA, an MRI-compatible trocar is inserted under MRI guidance directly around a prostate lesion in either transperineal or transrectal approach. The laser-diffusing fiber within a cooled catheter system is advanced to the ablation area and activated after reconfirming the fiber position. When activated, the fiber delivers high-energy laser light, producing hyperthermia and coagulative necrosis. FLA causes interstitial damage and is also referred to as laser interstitial thermotherapy.[25]

Radiofrequency ablation and microwaves

The 2 other AESs are radiofrequency and microwaves.[26,27] Monopolar or bipolar needles are transperineally inserted in the prostate. Medium-frequency radiowaves are delivered, causing frictional heating over 60ºC that leads to the denaturation of proteins, cell membrane damage, and tissue necrosis. The evidence about radiofrequency and microwaves is still insufficient to recommend them as a PGA modality.[4]

Focal brachytherapy

Brachytherapy is already established as a whole-gland treatment; it can also be focally applied. Focal brachytherapy is performed through transperineal implantation of radioactive I^{125} seeds. High-dose radiation is focally delivered within the target area. When used for PGA, brachytherapy should not be combined with external beam radiation.[28]

PGA for primary PCa

Several different AESs are available for prostate ablation, but there is no comparative study to determine what would be the best choice thus far (Table 1). PGA instead of ablating the whole prostate has been proposed for patients with focal lesions, providing similar oncological outcomes and less genitourinary toxicity.[29,30]

Studies comparing PGA to the standard radical approach are still lacking in the literature. Meanwhile, most part of PGA data comes from retrospective and more recent prospective series, mainly about HIFU and cryotherapy.[15] Heterogeneity among those studies goes beyond the source of energy. Different methods of patient selection, extension of ablation, follow-up schedule, definition of treatment failure, and outcome measures preclude us to generalize the findings of these studies.

Follow-up strategies relying only on prostate-specific antigen (PSA) and MRI do not seem to be appropriate after PGA. Several recent studies have demonstrated that routine biopsy after PGA provides better accuracy to detect recurrent PCa.[31] The utility of biochemical recurrence definitions after PGA is still a matter of debate. Nadir PSA and PSA kinetics after ablation might guide the clinicians along with MRI findings, but biopsy confirmation of recurrence is advocated.[32]

Recurrence in the treatment has been heterogeneously reported, ranging from 4.5% to 33% of patients.[15] Recurrence rates are even higher when biopsy is routinely performed during the follow-up irrespective of PSA or MRI findings.[31] In addition, positive biopsies out of the treatment area occur in more than 10% of patients. Out-of-field disease is associated with the multifocal nature of PCa and with mpMRI/prostate biopsy limitations to rule out early-stage cancer at initial evaluation.

Although long-term oncological outcomes are yet to be consolidated, the safety profile of ablative procedures is noticeable. Most series of PGA have reported pad-free rates over 95% and erection sufficient for penetration in more than 80% of patients, regardless of the AES.[17,33,34] Complications of PGA are few and mild compared with those of radical treatments. Severe complications have been reported in less than 5% of patients after PGA, of which acute urinary retention is the most common. Less than 2% of patients develop urethral stricture, whereas rectourethral fistula is rarely reported.[17,35,36]

When comparing WGA with PGA, some authors found that PGA is associated with better sexual function, early recovery

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Table 1. Characteristics of the currently available ablative modalities for prostate cancer

Ablative modality	Energy source	Prostate access	Mechanism	Characteristics
HIFU	Ultrasound waves	Transrectal probe	-Hyperthermia -Noninvasive -Ideal for posterior lesions	- Largest series of PGA - Only truly noninvasive ablative option - Limitations for treatment of anterior and apical lesions - Damage to the surrounding structures - Cooling system avoids thermal injuries to the rectal wall - Safe; midterm oncological outcomes are available - Increasing studies in salvage setting (after PGA or EBRT recurrences)
Cryotherapy	Cryoneedles	Transperineal cryoneedles	-Freeze-thaw cycle -Temperatures below –40°C	- Ablative option with longest follow-up - Damage to the surrounding structures - Transurethral warming catheter reduces urethral injury - Accessibility to various locations of PCa, including anterior lesion - Safe; midterm oncological outcomes are available - Available studies in salvage setting (after PGA or EBRT recurrences)
VTP	Photosensitizers	Transperineal laser fibers	Activation of photosensitizer through laser light -Reactive oxygen species generation, local thrombosis, and vessel obliteration -Nonthermal	- Photosensitizers: oral or intravenous; most frequent agent: padeliporfin - Recent series template: hemiablation - Phase III randomized study available comparing VTP with active surveillance - Most of treated patients with GG1; further research in intermediate-risk patients is required - Special care: patients are kept under dimmed light for 6 h and should avoid exposure to sunlight for 48 h
IRE	Electric pulses	Transperineal electroneedles	-High-voltage, low-energy electric pulses -Nanopores in cell membrane -Nonthermal	- Preserves structures adjacent to the tumor, potential benefit for salvage prostatectomy - General anesthesia and full-muscle paralysis are required to avoid contractions - Short procedure time - Initial prospective series reporting focal ablation with low toxicity in primary treatment - Few reports in salvage setting

Table 1. Characteristics of the currently available ablative modalities for prostate cancer (Continued)

Ablative modality	Energy source	Prostate access	Mechanism	Characteristics
FLA	Laser fibers	Transperineal or transrectal laser fiber trocars	Pulsed waves lead directly to cell damage by shockwaves -Thermal necrosis	-Can be performed under MRI guidance with periprostatic nerve block - More complicated setup - Limited clinical data - Initial prospective series reporting focal ablation with low toxicity in primary treatment
RFA and microwaves	Radiowaves	Transperineal monopolar or bipolar needles	-Medium-frequency alternating current -Local heat	-Very limited data on applying RFA before radical prostatectomy -Insufficient data to recommend RFA for prostate ablation
Brachytherapy	Radiation seeds	Transperineal radiation seed insertion	-DNA damage by directly and indirectly ionizing radiation	- Established whole-gland treatment - Focal brachytherapy should not be associated with external beam radiation - Good clinical outcomes as local salvage therapy for radiorecurrent disease - Avoids thermal energy in apical lesion

EBRT: external beam radiotherapy; FLA: focal laser ablation; GG: Gleason grade group; HIFU: high-intensity focused ultrasound; IRE: irreversible electroporation; MRI: magnetic resonance imaging; PCa: prostate cancer; PGA: prostate gland ablation; RFA: radiofrequency ablation; VTP: vascular-targeted photodynamic therapy

of urinary continence, and fewer complications, especially a reduction in acute urinary retention. These findings endorse the general concept that the extension of ablation matters and PGA has a less detrimental effect on the genitourinary function than more extensive templates.[30,37]

Approximately 15%–30% of all patients who undergo PGA need salvage local treatment in a midterm follow-up.[15] Salvage treatment options available in such scenarios are reablation, EBRT, or RP.[38]

Repeat or additional ablation after primary ablation failure

Primary PGA failure may occur within the treated area or in the untreated prostate (i.e., selection failure), requiring a repeat ablation or an additional ablation, respectively. Whether the need of an additional ablation should be considered a treatment failure or only part of the care line is still a matter of debate. Repeat ablation is supported by some authors depending on their own experience; however, evidence remains scarce in this field.[39] When applying repetitive ablations to treat PGA recurrences, approximately 90% of patients remain free from the radical treatments.[33,40]

Only HIFU and cryotherapy have been evaluated as repeat ablation options, almost exclusively after WGA. A review of salvage local treatments found only 5 studies reporting repeat ablation, of which only 1 assessed the outcomes after PGA.[38] Repeat ablation has been associated with low complication rates and good functional outcomes, whereas cancer control should be evaluated in a longer period of time before drawing any conclusion.

A recent study reported outcomes from second ablation in patients who underwent PGA using HIFU or cryotherapy as the primary treatment.[41] Among 15 patients who received HIFU and 11 who received cryotherapy, 96% repeated the same energy modality after a median time of 21 months from the primary treatment. The authors found that the recurrence-free survival after the second ablation was much longer in patients who needed additional ablation because of the out-of-field recurrence than in those who needed repeat ablation after in-field recurrence (89% vs 35% at 2 years, p=0.02, respectively). In this series, all the patients were continent, and no major complication was reported after the procedures.

Salvage ablation for radiorecurrent disease

Biochemical recurrence is found in nearly one-third of patients after EBRT.[42] Androgen deprivation therapy has been applied to many of those patients who would be ideal candidates for local salvage treatments, withholding the opportunity for cura-

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tive intent treatments.[43] One of the main issues associated with salvage local treatment for radiorecurrent PCa is the possibility of significant genitourinary toxicity. Therefore, ablative therapies can be applied for these patients, aiming to reduce treatment harms. The most studied AESs in this setting are HIFU, cryotherapy, and brachytherapy.[44,45]

Severe gastrointestinal and genitourinary side effects have been limited to a maximum of 5%–10% of patients after salvage ablation, although toxicity might be underreported because of the retrospective nature of available studies.[45] Recent studies report incontinence rates of 5%–49% depending on the AES applied and incontinence definition.[44] Erectile dysfunction rates after salvage ablation remain high ranging from 60% to 100%; however, many of these patients have pre-existent erectile dysfunction due to primary EBRT.

In a meta-analysis of observational studies about salvage ablation, the prevalence of biochemical control was 58%, 60%, and 69% in the studies assessing salvage HIFU therapy, cryotherapy, and brachytherapy, respectively; however, the follow-up time was highly variable among the studies.[44] Longer follow-up times are warranted to assess the ability of salvage ablation to delay metastasis and increase survival.

Conclusion

Improvements in imaging have allowed us to tackle the PCa-dominant lesions with clearly reduced toxicity compared with whole-gland treatments. Different ablative modalities have been proven safe in this field, but the optimal AES and treatment template are yet to be determined. Reliable evidence on PGA provides encouraging midterm oncological outcomes, but long-term comparative studies are expected. Repeat ablation after primary treatment failure must be the key to avoid radical treatments, but further research in this setting is required. AES is also an option to reduce the morbidity related to salvage therapies for radiorecurrent PCa.

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