Review article

Focal therapy of prostate cancer: energies and procedures

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Abstract

**Purpose:** Over the last years, focal therapy has emerged as an intermediate management technique between radical approaches (radical prostatectomy, external beam radiation, and brachytherapy) and watchful waiting to manage some early stage prostate cancers (CaP). Different energy modalities are being developed. The aim of this study is to review these energy modalities and their indications.

**Materials and methods:** We reviewed the literature to concentrate on the practical aspects of focal therapy for CaP with the following key words: photodynamic therapy, high intensity focused ultrasound (HIFU), cryotherapy, focal laser ablation, electroporation, radio frequency, external beam radiation, organ-sparing approach, focal therapy, CaP, and then by cross-referencing from previously identified studies.

**Results:** Prostatic tumor ablation can be achieved with different energies: freezing effect for cryotherapy, thermal effect using focalized ultrasound for HIFU, and using thermal effect of light for focal laser ablation (FLA) and activation of a photosensitizer by light for PDT, among others. Radio frequency and microwave therapy have been tested in this field and demonstrated their usefulness. Electroporation is currently being developed on preclinical models. External beam radiation with microboost on neoplastic foci is under evaluation. HIFU and cryotherapy require the use of sophisticated and expensive machines and, consequently, the procedure is expensive. Laser techniques seem to be less onerous, with the added advantage of size.

**Conclusions:** Several energy modalities are being developed to achieve the trifecta of continence, potency, and oncologic efficiency. Those techniques come with low morbidity but clinical experience is limited regarding to oncologic outcome. Comparison of the different focal approaches is complex owing to important heterogeneity of the trials. In the future, it seems likely that each technique will have its own selective indications. © 2012 Elsevier Inc. All rights reserved.

**Keywords:** Prostate cancer; Focal therapy; HIFU; Cryotherapy; Photodynamic therapy; Focal laser ablation

1. Introduction

Prostate cancer (CaP) is the most common cancer among men over 50 years in industrialized countries in terms of incidence. It represents the second cause of cancer-related death [1]. At present, radical approaches, such as surgery, external beam radiation, and brachytherapy remain the gold standard. Those treatments, however, come with a high incidence of morbidity, including on average: 50% chance of impotence, 10% chance of incontinence, and 10% chance of rectal toxicity [2–4]. Furthermore, systematic radical approaches lead to overtreatment with an absolute survival benefit at 15 years of only 1% among a PSA-screened population [5]. Also, the European Screening Study revealed that 1,410 men have to be screened and 48 diagnosed to avoid 1 CaP-related death over a 9-year interval [6]. With PSA screening, development of new prostate biopsies protocols, and magnetic resonance imaging (MRI), the accuracy of detection and localization has increased. As a corollary, a growing number of small-volume and low-grade cancer foci are diagnosed in young healthy men.

For part of these low risk localized CaP, active surveillance is another viable option of management [7]. In the literature, the most accomplished active surveillance study is the one reported by Klotz et al. [7] on 450 patients. The overall survival was 78.6% and specific survival was 97.2% at 10 years. After a median follow-up
of 6.8 years, only 30% of patients were treated surgically. However, only 1 prospective randomized trial compared radical prostatectomy and active surveillance on respective cohorts of 347 and 348 patients with a median follow-up of 12.8 years. The results showed a gain of 6.1% specific survival at 15 years in favor of radical prostatectomy and a relative risk of death with surgery significant of 0.62 [8]. This result underlines the potential shortfalls of active surveillance. Moreover, it induces important psychological stress for patients, and it is often difficult for clinicians to propose this management option to young men with long life expectancies.

Focal therapy is an emerging alternative treatment option, which offers great hopes in terms of cancer control and decreased morbidity for localized CaP. The challenge of current focal therapy modalities is to treat only localized tumors, sparing the rest of the prostate, especially near the neurovascular bundles and the urethral sphincter, to minimize the potential morbidity.

The concept of focal therapy remains controversial among the urological community because CaP is frequently multifocal. Multifocality was reported in 50%–87% cases in contemporary series of radical prostatectomy [9–11]. However, Stanford University group showed that in case of multifocal localizations, only the volume of the index lesion itself (i.e., the main lesion) is predictive of progression [10,12,13]. A threshold volume of 0.5 ml is currently held to discuss clinically significant lesion size. This volume corresponds to a 10% risk of extraprostatic extension [14]. In addition, CaPSURE group showed that the proportion of patients with unilateral cancer of small volume and low risk was increasing with a percentage of 29.8% in 1989–1992 against 45.3% in 1999–2001 [11]. More recently, Mouraviev et al. [15] reported unilateral and/or unifocal disease in 13%–67% of patients.

Although the idea of focal treatment is simple, the application for CaP met some difficulties: criteria of patient’s selection for focal therapy, precise localization, visualization, and characterization of significant cancer foci, accurate guidance of ablative energy into the area to be targeted, oncologic efficacy evaluation, and finally surveillance modalities.

Different energy modalities are experienced and some preliminary results are being published. Further prospective trials are needed to highlight the full potential of each technique. Thus, it is still too soon to compare the efficacy of these approaches. Practical aspects, such as length of the procedure, cost-effectiveness, equipment size, . . . are important factors that could, in the future, promote one technique above the others.

In this article, a description of the principles of each energy modality as well as information on their practical use is provided to help understanding the different techniques and compare them.

2. Focal cryotherapy

2.1. Principles

Cryotherapy consists in cellular destruction by freezing. The prostate cooling is obtained by introducing transrectal ultrasound (TRUS)-guided needles using a transperineal approach. A temperature of −40°C is reached at the central part of the prostate and the surrounding area using argon based probes. This technique relies on pressurized gas that can freeze (argon gas) and actively warm (helium gas) through the Joule-Thompson effect in which different gases undergo unique temperature changes when depressurized according to unique gas coefficients. The introduction of thermocouples for systematic temperature monitoring and use of a urethral warming device have substantially contributed to a reduction in cryotherapy-associated morbidity. Thermal control is ensured at the urethral sphincter, prostatic apex and close to the neurovascular bundles by inserting monitoring probes. A warming Foley catheter is inserted to protect the urethra, and the rectum can be protected by injection of a saline solution in the interprostatorectal space.

Two cycles were completed in the procedure initially described by Onik et al. [16]. The two parameters that correlate with the likelihood of cell destruction are the cooling rate during freezing and the lowest temperature reached. Temperatures lower than −40°C are required to completely destroy cells and a double freeze-thaw cycle results in more extensive tissue damage and cell death than a single cycle.

Cryosurgery destroys cancer cells by brutal and repeated freezing of the prostate. The treatment leads to cell death by denaturing cellular proteins by dehydration, rupture of the cell membranes by ice crystals, ischemia related to vascular stasis, and micro thrombi [17].

Cryotherapy procedure can be monitored with TRUS by visualization of the ice ball front. An experimental MRI-compatible robot used to insert needles into the prostate was recently developed and should soon allow for MRI-real time monitoring [18]. This relies on the development of MRI-compatible cryoprobes currently used for liver and kidney cancer treatment [19].

2.2. Pros and cons

- Focal cryotherapy is not yet a validated management option for localized CaP. Several studies have been reported with median follow-up of 12–70 months and biopsy proven recurrence rates of 4%–23%. Regarding functional outcome potency and continence were preserved in, respectively 65%–90% and 95%–100% [20–26].
- This TRUS-guided treatment mobilizes expensive and bulky equipment, such as argon and helium gas bottles.
- The ice ball front can be monitored during treatment using ultrasonography and allows for real-time monitoring of the procedure.
Intraprostatic needle insertion requires transperineal access. This percutaneous approach is attractive but the inability to reach the anterior part of the prostate because of the conflict with rigid structures (such as the pubic bone) is a major drawback.

Clinical and radiologic follow-up after focal therapy may be complicated from prostate morphologic modification.

In case of treatment failure, radical prostatectomy remains a feasible option but the procedure becomes more technically difficult because of tissue rehandling.

Pros and cons of focal cryotherapy are summarized in Table 1. Clinical results are presented in Table 2.

3. Focal HIFU

3.1. Principles

HIFU produces ultrasound waves generated by a spherical transducer. The ultrasonic energy is focused on a fixed point. Ultrasound waves deposit energy as they travel through tissues. During imaging and exploration modes, this deposited energy is insignificant. By increasing the intensity of the waves and focusing them on a single point, HIFU allows for the deposition of a large amount of energy into tissue, resulting in its destruction through cellular disruption and coagulative necrosis [27]. Two mechanisms of tissue damage are involved: thermal effect and cavitation [28]. The thermal effect relies on the absorption of ultrasonic energy by the tissue and its conversion into heat. In adequate conditions, the temperature within sonicated tissue will raise to a sufficient level to induce irreversible damages. Damages are classified into three groups: hyperthermia that can destroy malignant cells in with low temperatures (41 to 49°C) during

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Advantages and disadvantages of focal cryotherapy</th>
</tr>
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<tbody>
<tr>
<td><strong>Pros</strong></td>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>- Real time monitoring with trans rectal ultrasonography (visualization of the ice ball)</td>
<td>- Biopsy proven recurrence rate: 4%–23%</td>
</tr>
<tr>
<td>- Perspective of real time monitoring with MRI</td>
<td>- Median follow-up: 12–70 mo</td>
</tr>
<tr>
<td>- Possibility of secondary radical treatment in case of failure</td>
<td>- Secondary radical treatment possible in case of failure but more difficult</td>
</tr>
<tr>
<td>- Short hospital stay (2–3 d)</td>
<td>- Anterior fibro-muscular stroma is a complex region to reach</td>
</tr>
<tr>
<td>- Less morbidity than radical approaches: Potency: 65%–90% Continence: 95%–100%</td>
<td>- Modification of prostate morphology: clinical and radiological follow-up more complex</td>
</tr>
<tr>
<td>- Procedure cost: €2,500 for 5 needles, 1 urethral warming catheter, and 2 thermal monitoring probes €160 for argon gas bottle per procedure</td>
<td>- Preoperative hormone therapy in 0%–92% of cases</td>
</tr>
<tr>
<td>- Overcrowding of the operating room</td>
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</table>
an extended period (>10 min), coagulation which consists in necrosis of tumor tissue without immediate ablation (level of protein denaturation 57 – 60°C) and vaporization inducing tissue necrosis and charring (temperature >100°C) (Fig. 1). Cavitation is the result of the interaction of ultrasound and microbubbles of water. This interaction may lead to oscillation of these microbubbles, violent collapses and dispersion of energy enhancing tissue ablation.

This technique provides the advantage of a transrectal treatment with prostate destruction while sparing the rectum itself. By combining precise control over the position of the transducer within the rectum and active cooling of the rectal mucosa, the risk of rectal injury is minimized. Two devices are available for the treatment of CaP with HIFU: Sonablate and Ablatherm.

3.2. Pros and cons

- Focal HIFU is not yet a validated management option for localized CaP. Several studies have been reported with median follow-up of 12–120 months and biopsy proven recurrence rate of 8%–23%. Regarding functional outcome, data were inconsistently reported but potency and continence were preserved, respectively in 89%–95% and 90–100% [29,30–33].
- It is the least invasive technique requiring only intrarctal probe insertion.
- It relies on bulky, expensive, and difficult to transport equipment. This treatment modality is not available in every institution.
- Tumor location is also an important parameter. To avoid urethral lesions, tumor located near the prostatic apex or near the midline should not be treated using this energy modality. Also, HIFU cannot reach anterior tumors, located too far away from the energy source.
- This treatment can be repeated in case of primary failure but with an increased risk of side effects [34]. As with focal cryotherapy, radical prostatectomy remains a potential option in case of failure but is to be more difficult than usual because of tissue rehandling. Also, follow-up might be more complicated than after radical treatment.
- Prostate size is a limiting factor and preoperative transurethral resection of the prostate (TURP) is frequently proposed to reduce the size of the gland.

Pros and cons of focal high intensity focused ultrasound (HIFU) are summarized in Table 3. Clinical results are presented in Table 4.

4. Focal photodynamic therapy (PDT)

4.1. Principles

Raab [35] and Tappeiner et al. [36] initially described PDT at the beginning of the 20th century. PDT is based on the interaction between light brought by a laser fiber, a photosensitive agent (PS) administrated orally or intravenously, and oxygen present in tissues: the absorption of a luminescent photon by the PS leads to a chain reaction inducing the release of singlet oxygen and antioxidant enzymes. This singlet oxygen can directly kill tumor cells by the induction of necrosis and/or apoptosis, or cause destruc-
be conducted in a darkened room to prevent cutaneous photosensitization.

4.2. Pros and cons

- Focal PDT is another technique requiring transperineal needle insertion. Its particularity relies on the administration of a photosensitizer that can be activated by light in the vasculature or in the tissue. Some photosensitizers have the advantage of being selective of neoplastic cells [43,44] but they can also induce side effects. Trials are very heterogeneous, using different photosensitizers and different ablative templates. Recently, 2 phase II trials using WST 11 were completed and oncologic results are expected. From a functional outcome standpoint, no change from baseline was observed when using IPSS and IIEF scores [45,46].
- This modality uses diode lasers as the energy source with all the advantages cited above.
- This treatment also alters prostate morphology and follow-up may be more challenging than usual. In case of a primary failure, a repeat treatment and radical approaches are 2 feasible options. (Azzouzi A-R, Emberton M: Results of Tookad soluble vascular targeted photodynamic therapy (VTP) for low risk localized CaP (PCM203), presented at the AUA 2011, Washington DC).
- Reliable treatment planning is still lacking and its elaboration relies on the integration of 3 variables: light distribution, photosensitizer distribution and oxygen present in tissues. This issue is still being investigated and a 2-mm precision can be achieved for Jankun et al. [47], while Betrouni et al. [48] reported an 84.89% correlation between simulated volumes and MRI-obtained volumes after swelling correction.
- PDT can be considered as an oxygen-dependent therapy like external beam radiation. Following this example, several teams reported that fractionated treatment might be more effective [49,50]. However, this raises the question of PDT efficacy for hypovascular or hypoxic prostate tumors [51–53].

Pros and cons of focal PDT are summarized in Table 5. Clinical results are presented in Table 6.

5. Focal laser ablation (FLA)

5.1. Principles

FLA was initiated in the 1970s [54]. Its applications typically uses neodymium-yttrium-aluminum-garnet (NdYAG) lasers at 1,064 nm or diode lasers at 830 nm. The Nd-YAG laser has deeper penetrating abilities, but it is bulkier and more expensive. The technologically more advanced 980-nm diode lasers are increasingly used.
Table 4
Summary of clinical studies on focal HIFU

<table>
<thead>
<tr>
<th>Ablative template</th>
<th>N° pts</th>
<th>Mean preoperative PSA (ng/ml)</th>
<th>Follow-up</th>
<th>Cancer diagnosis modality</th>
<th>BDFS or RFS</th>
<th>RP specimen analysis</th>
<th>Biopsy proven recurrence</th>
<th>Potency</th>
<th>Continence</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madersbacher 1995</td>
<td>True focal</td>
<td>10</td>
<td>24.5</td>
<td>NA</td>
<td>NA</td>
<td>Unilateral echoic lesion and histology proven</td>
<td>NA</td>
<td>3 Complete destruction of the tumor and 7 partial destructions (mean 53%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Muto 2008</td>
<td>Posterior hockey stick</td>
<td>29</td>
<td>5.4</td>
<td>5–10</td>
<td>32 Months</td>
<td>MRI and TRUS-guided biopsy</td>
<td>ASTRO 2 years BDFS: LR: 83% IR: 54% HR: 0%</td>
<td>NA</td>
<td>At 6 mo: 3/28 (11%) At 12 mo: 4/17 (23%)</td>
<td>NA</td>
</tr>
<tr>
<td>Ahmed 2011</td>
<td>Hemiablation</td>
<td>20</td>
<td>7.3</td>
<td>4 + 3 or less</td>
<td>12 Months</td>
<td>MRI and 3D-mapping transperineal biopsy every 5 mm</td>
<td>NA</td>
<td>At 6 mo: 2/19 (11%) in the treated lobe</td>
<td>19/20 (95%)</td>
<td>18/20 (90%)</td>
</tr>
<tr>
<td>El Fegoun 2011</td>
<td>Hemiablation</td>
<td>12</td>
<td>7.3</td>
<td>3 + 4 or less</td>
<td>10 Years</td>
<td>TRUS-guided biopsy</td>
<td>RFS: 90% at 5 years 38% at 10 years</td>
<td>NA</td>
<td>At 1 year: 1/12 (8%)</td>
<td>NA</td>
</tr>
<tr>
<td>Ahmed 2012</td>
<td>Hemiablation or midline ablation or bilateral 2-areas ablation</td>
<td>41</td>
<td>6.6</td>
<td>4 + 3 or less</td>
<td>12 Months</td>
<td>MRI and 3D-mapping transperineal biopsy every 5 mm</td>
<td>NA</td>
<td>At 6 months: 9/39 (23%) of which 3/39 (8%) had significant cancer</td>
<td>31/35 (89%)</td>
<td>38/38 (100%)</td>
</tr>
</tbody>
</table>

ASTRO criterion = 3 successive rises in PSA level; BDFS = biochemical disease-free survival; GS = Gleason score; NA = not available; NVB = neurovascular bundle; Pts = patients; RFS = recurrence-free survival; RP = radical prostatectomy; UTI = urinary tract infection; HR = high risk; IR = intermediate risk; LR = low risk; MRI = magnetic resonance imaging.
Energy is delivered to the prostate using laser fibers inserted using a transperineal approach through needles. The thermal effects produced by the laser energy spread from the absorption zone and cause an increase in the temperature of surrounding tissues. Damages can be classified as described in Fig 1. Studies have shown that wavelengths between 800 and 1,100 nm have comparable effects [55,56]. The results obtained in vivo on canine model and cadavers demonstrated a good penetrating power and easy handling [56–58]. Penetration of the laser beam also varies according to optical and thermal properties of the target tissues. Monitoring of the procedure can be achieved by using fluoroptic thermometry that consists in handling [56 –58].

Penetration of the laser beam also varies according to optical and thermal properties of the target tissues. Monitoring of the procedure can be achieved by using fluoroptic thermometry that consists in handling [56 –58].

6. Other focal therapy modalities

6.1. Interstitial microwave thermal therapy

Microwave antennas launch electromagnetic waves in the frequency range of 300 MHz to 2,450 MHz into the surrounding tissue. The waves cause small electric currents propagating through tissue, causing it to heat up. Microwave applicators are inserted in the prostate through the perineum and each one is housed within a water-cooling jacket. Rectum and urethra are protected using thermocouples and cooling Foley catheter.

To the best of our knowledge, microwave thermal therapy has mainly been performed for recurrent cancer after external beam radiation, and no attempt of focal therapy is available in the PubMed database.

Sherar et al. [63] reported the feasibility and safety of this modality for radio-recurrent CaP.

Lancaster et al. [64] reported a whole-gland microwave thermal therapy on 1 patient with a localized CaP. At 18 months, PSA was still undetectable and no complication arose.

Recently, Cheng et al. monitored successfully a procedure on a preclinical dog model using MRI and contrast-enhanced ultrasound [65].

Development of medical imaging and biopsy strategies makes possible the realization of focal microwave thermal therapy.

6.2. Radiofrequency interstitial tumor ablation (RITA)

The energy is produced by a radiofrequency (rf) generator that can reach 50 W with a frequency of 460 kHz. It is administered through a 15-gauge needle with monopolar triple-hook electrodes separated by a 120° angle, describing
<table>
<thead>
<tr>
<th>Ablative template</th>
<th>PS</th>
<th>N° pts</th>
<th>Light delivery path</th>
<th>GS</th>
<th>PSA</th>
<th>MRI results</th>
<th>PSA response</th>
<th>Remaining cancer on biopsy</th>
<th>Incontinence</th>
<th>Potency</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Windahl 1990</td>
<td>Hematoporphyrin derivative and photofrin</td>
<td>2</td>
<td>Transurethral Post TURP Post TURP remnant</td>
<td>NA</td>
<td>6 and 10</td>
<td>NA</td>
<td>Reduction from 10 to 2.5 and from 6 to 0.2</td>
<td>0/2</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Zaak 2003</td>
<td>5-ALA</td>
<td>6</td>
<td>- transperineal (2) - transurethral (3) - during RP (1)</td>
<td>5–8</td>
<td>4.9–10.6</td>
<td>NA</td>
<td>Reduction of 20%–70%</td>
<td>NA</td>
<td>None</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Moore 2006</td>
<td>Temoporfin</td>
<td>6 (10 procedures)</td>
<td>Transperineal Free hand insertion</td>
<td>3 + 3</td>
<td>1.9–15</td>
<td>Visible necrosis areas</td>
<td>Reduction in 8/10 procedures (14%–67%)</td>
<td>10/10</td>
<td>NA</td>
<td>3/5</td>
<td>- Sepsis (n = 1) - irritative voiding symptoms - recatheterisation (n = 2) - recatheterization (2)</td>
</tr>
<tr>
<td>Arumainayagan 2010</td>
<td>Padeliporfin (WST 11)</td>
<td>40</td>
<td>Transperineal</td>
<td>NA</td>
<td>NA</td>
<td>Visible necrosis areas</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Azzouzi 2011</td>
<td>Padeliporfin (WST 11)</td>
<td>85</td>
<td>Transperineal</td>
<td>NA</td>
<td>NA</td>
<td>87% necrosis in the treated lobe</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

GS = Gleason score; MRI = magnetic resonance imaging; PS = photosensitizer; pts = patients; RP = radical prostatectomy; TURP = transurethral resection of prostate.
a 2 cm volume sphere when they are deployed. These electrodes are introduced into the prostate using transperineal approach under TRUS guidance. Urethra can be cooled using saline serum irrigation. RITA permits an irreversible destruction of live tissue by generating temperatures around 100°C that induce a coagulative necrosis in the tumoral area, without any evidence of venous thrombosis or significant hemorrhages at the tumoral borders [66].

Studies have shown that TRUS-guided RITA treatment is feasible, safe, and reproducible for the treatment of previously untreated patients with clinically localized CaP, yielding predictable lesion sizes [66,67]. Shariat et al. [68] reported the RITA procedure on 11 patients (8 after radiation failure and 3 primary treatments). Before the RITA treatment, systematic sextant and 6 laterally directed biopsies were used to map the local extent of the disease. Only areas of biopsy-proven cancer were focally ablated.

Overall, 90% of the patients experienced a decrease in serum PSA superior to 50%, and PSA doubling time after RITA was longer than that before RITA (mean 37 ± 22 vs. 14 ± 13 months). At 1-year biopsies, 55% of patients were free of cancer. Minor adverse effects occurred with hematuria (n = 2), bladder spasms (n = 1), and burning sensation during urination (n = 1). Continence and erectile function are not mentioned. Two procedures had to be interrupted because of increase of temperature measured by the rectal probe.

RITA is a suitable modality for organ-sparing treatment. Further studies are needed to evaluate its full potential.

6.3. External beam radiation, brachytherapy, cyberknife, proton therapy

Radiotherapy techniques using photons are widely used in the management of CaP [69,70]. Several pilot studies in which a microboost is delivered to the dominant tumor region have been conducted with external beam radiation [71–73] and brachytherapy [74]. The highest dose was delivered in a feasibility study by Singh et al. [75] who treated 3 patients with an ablative dose of 95 Gy to the macroscopic tumor within the prostate with no severe toxicity. Tumor localization was performed by using MRI [71–73], sestant biopsies [74], or both [75].

In these trials, no severe toxicity was observed, and Mirabel et al. reported 98% of 5-year biochemical disease-free survival.

A single blind randomized clinical trial comparing standard external beam radiation to standard external beam radiation associated to an additional integrated microboost to the macroscopic tumor of 95 Gy has recently begun with already 50 patients included [76]. Proton therapy appears to be another viable option for the focal treatment of CaP but the cost-effectiveness ratio is currently not favorable to that method [77].

Cyberknife is a promising technique offering equivalent oncologic control and less morbidity than standard external beam radiation or brachytherapy. To the best of our knowledge, no clinical trial is available on the PubMed database. However, some trials are presently recruiting.

6.4. Electroporation

Irreversible electroporation (IRE) is a new nonthermal ablation modality that uses short pulses of DC electric current to create irreversible pores in the cell membrane, thus, causing cell death.

In a preclinical canine model, Onik and colleagues [78] reported the feasibility and efficiency of this procedure for the treatment of CaP. One of the disadvantages of this technique is the risk of reflex movements induced by the electrical impulse that could induce needle displacement and thus cause damage to healthy structures.

6.5. Nanoparticle thermotherapy

It is a novel method of interstitial heating of tumors following direct injection of magnetic nanoparticles. Its feasibility and good tolerability was shown in 2 phase I clinical trials for whole-gland treatment of localized CaP. However, this new approach is limited by patient discomfort at high magnetic field strengths and irregular intratumoral heat distribution [79].

7. Discussion

Focal therapy for CaP remains to become a validated management option for localized CaP owing to a lack of evidence regarding oncologic efficacy [80]. This assessment is applicable to all energy modalities. More data with longer follow-up are available for HIFU and cryotherapy but it
remains insufficient to recommend those treatment modalities outside of a clinical trial. For FLA and PDT, data are more recent with short follow-up and phases II and III clinical trials are ongoing.

For all these therapies, clinical studies involved a small sample with short follow-up. Preliminary data on oncologic outcomes is encouraging but lasting cancer control can only be demonstrated with extended follow-up of larger patient cohorts. Furthermore, there is still no consensus on what patient eligibility criteria for focal therapy should be.

Though focal therapy is now understood to be indicated for low risk localized CaP [81], different diagnosis strategies are being used to adequately map cancer foci among the prostate. The aim is to adequately identify and localize clinically significant tumor inside the prostate.

For some authors, only transperineal saturation biopsies can now enable an accurate mapping of the locations, dimensions, and uni- or multifocal tumor lesions [82-84]. However, this technique comes with high cost and possible biopsy-related complications. For others, the couple MRI/TRUS-guided biopsy would allow for detection of the index lesion. Villers et al. have shown that it is possible to detect tumor sites >0.33 ml using multiparametric MRI [85]. Furthermore, real-time MR-guided intervention has recently become available for prostate biopsy, supported by integrated technology that utilizes a robotic-assisted needle delivery system [86]. MRI may also enable guidance of transrectal biopsy to increase the sensitivity and specificity of detection (especially for anterior fibromuscular stroma cancers). Emerging TRUS technologies, including contrast-enhanced ultrasound, Doppler ultrasound, elastography, and fusion MR-ultrasound imaging should further enhance diagnostic accuracy.

In the presented trials, patient selection was heterogeneous between studies. Gleason score and mean preoperative PSA were not comparable. Some authors proceeded to the tumoral mapping using TRUS-guided biopsies while others used only transperineal saturation biopsies. Ablative templates were different from 1 study to another.

Defining treatment success or failure often relies on PSA level. Biochemical standards for defining treatment success or failure have not been established for focal therapy. Astro (3 successive PSA rises) or Phoenix criteria (PSA nadir + 2 ng/ml) are usually used but their validation applies only to external beam radiation, and no evaluation has been made regarding their pertinence for FT. Once again, there is no standardization between studies in the use of these criteria. Moreover, using PSA nadir after FT is difficult because this treatment leaves in place a variable portion of the prostate that can still produce PSA.

Relying on PSA levels alone to assess the efficiency of FT seems insufficient because there is no hard proof that biochemical disease-free survival is related to overall or specific mortality.

As for TRUS-guided biopsy or imaging methods on their own, they are at present unreliable due to lack of sensitivity. Once again, emerging TRUS technologies (contrast-enhanced ultrasound, Doppler ultrasound, elastography, and fusion MR-ultrasound imaging) should be evaluated in this indication.

In the presented trials, assessment of oncologic efficacy was performed using random TRUS-guided biopsies and multiparametric MRI in the most recent studies. Follow-up of FT procedures was mainly performed using PSA levels. As previously discussed, these modalities lack sensitivity. Retargeting devices allowing to rebiopsy the previously identified tumoral area (Urostation System - Koelis, La Tronche, France) should be able to increase detection rate of treatment failure [86].

However, all clinical data available on focal therapy regarding functional outcome are promising, with better continence and potency rate than with radical approaches. However, functional data were inconsistently reported in the different series, leading to a potential bias.

In the hypothesis of oncologic control equivalence and comparable morbidity of each energy modality, the potential advantages and disadvantages of these different organ-sparing approaches should be reported.

Repeatability of FT procedure and possibility of secondary radical treatment in the case of failure are advantages shared by all energy modalities. However, clinical and radiologic follow-up can be more complex and less reliable due to the modification of prostate morphology after treatment. Another advantage of all FT procedures is the shorter hospital stay than with radical approaches leading to decreased economic impact.

Real-time monitoring is an important parameter allowing control of adequate progress of the procedure and precise delivery of the energy on cancer foci. Currently, MR-thermometry can be used to monitor tissue temperature during FLA. Transrectal ultrasound can be used to monitor focal cryotherapy by revealing the ice ball front [87].

Also, MRI is a valuable asset, allowing real-time guidance of needle insertion but it remains a complex procedure requiring expensive compatible equipment [86].

HIFU relies on a bulky device, difficult to transport as cryotherapy relies on argon and helium gas bottles leading to an overcrowding of the operating room. Technological improvement of diode laser sources now led to the development of very light lasers (between 2 and 5 kilos) that are easily transportable and with a very long life expectancy, reduced maintenance requirements, and storage cost. HIFU appears to be a less invasive procedure but risks of rectal lesions cannot be excluded.

Transperineal insertion of the needles is used for FLA, PDT, and cryotherapy. This approach makes access to anterior tumors difficult from the conflict with the pubic arch. Robotics development permitting automated mechanical delivery of the intervention needle through different angles may provide a solution.

Prostate volume is another limitation of HIFU frequently requiring transurethral resection of prostate (TURP) before
HIFU. By contrast, FLA and PDT can be performed initially.

Currently, energy modalities available for FT have different advantages and disadvantages and none can be preferred based on practical aspect. In the future, it is likely that each technique will have its specific indications based on tumor and patient characteristics. Prospective trials are still lacking to confirm the oncologic efficacy of focal therapy.

8. Conclusions

Focal therapy is emerging as an intermediate option between radical approaches and watchful waiting in the management of low-risk CaP in carefully selected patients. As it remains to be validated by scientific societies, its application must be confined to clinical research.

Several energy modalities are being developed to achieve the trifecta of continence, potency, and oncologic efficacy. Those techniques carry a low morbidity but clinical experience is limited to define the oncologic outcome.

Comparison of the different focal approaches is complex owing to important heterogeneity of the trials. Each energy modality has its own advantages and disadvantages, and currently none has proven to be superior to the others. Selection of the most suited organ-sparing approach must be decided with the patient, depending on the tumor characteristics.

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