REVIEW ARTICLE

Focal therapy for prostate cancer. Alternative treatment

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Received 13 December 2013; accepted 19 December 2013
Available online 18 June 2014

KEYWORDS
Prostate cancer;
Focal therapy;
Diagnosis;
Treatment

Abstract

Context: The great controversy surrounding the treatment of localized prostate cancer is related with its possibilities of radical treatment or active surveillance. The objective of this paper is to analyze the rationale selection among current focal therapy modalities regarding tumor and patient selection.

Evidence acquisition: Current articles about advantages and disadvantages on the treatment of localized prostate cancer as well as information about focal therapy regarding tumor selection, characteristics and indications cited in MEDLINE search were reviewed.

Summary of evidence: Focal therapy standardized criteria must be: low risk tumors, PSA < 10–15, Gleason score ≤ 6, and unilateral presentation all supported by image-guided biopsy and nuclear magnetic resonance (NMR). There are doubts about the suitability of focal therapy in cases of bilateralism or in those with Gleason score 3 + 4 or PSA > 15.

Conclusions: Focal therapy is an alternative for localized prostate cancer treatment. However, some aspects of their diagnosis and selection criteria should be defined by prospective studies which should provide knowledge about the indication for focal therapy.

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PALABRAS CLAVE
Cáncer de próstata; Terapia focal; Diagnóstico; Tratamiento

Terapia focal en cáncer de próstata. Alternativas de tratamiento

Resumen

Contexto: Los tratamientos radicales o de seguimiento activo son alternativas en el manejo del cáncer de próstata localizado, ambos no exentos de riesgos y efectos secundarios. El objetivo de este trabajo es analizar las diferentes posibilidades de la terapia focal en sus diferentes opciones para tratar el cáncer de próstata localizado.

Adquisición de evidencia: Realizamos una revisión en Medline de las diferentes posibilidades de tratamiento focal desde el punto de vista técnico, desarrolladas en la actualidad con atención a los estudios prospectivos aleatorizados, así como las formas de seguimiento y evolución de resultados.

Síntesis de evidencia: Diferentes técnicas en este momento están disponibles para realizar terapia focal, básicamente aquellas mínimamente invasivas—terapia vascular fotodinámica (TVF), crioterapia, braquiterapia, ultrasonido focalizado de alta intensidad (HIFU), láser intersticial—que permiten acceso directo y dirigido a la glándula. Los resultados preliminares de los estudios actuales demuestran una buena aceptabilidad de las técnicas con escasos efectos secundarios y buenos resultados oncológicos. La biopsia junto con la resonancia magnética nuclear (RMN) son las guías de seguimiento en estos pacientes, siendo el papel del antígeno prostático específico (PSA) menos definido.

Conclusiones: La terapia focal es en la actualidad una alternativa con técnicas disponibles para una buena ejecución. Los datos actuales apuntan a una escasa morbilidad y buenos resultados oncológicos que hacen de la terapia focal una posible alternativa de tratamiento en los tumores localizados, a la espera de los resultados de más estudios aleatorizados.

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Introduction

The high incidence of patients with overdiagnosis of prostate cancer based on prostate-specific antigen (PSA) reaches up to 53%, and a therapeutic approach based on active surveillance has been adopted. This approach aims to prevent iatrogenesis and the sequelae that active treatments cause in this group of patients, whose cancer would never have generated any clinical problem or affected their survival. In a survey of low-risk patients only 10% acceptance of active surveillance was reached in patients with low-risk prostate cancer. This poor acceptance is due to the lack of reliable parameters which define patients with indolent tumors; hence, the patient is going to need intensive surveillance and require certain diagnostic procedures, especially prostate biopsies in 30% of patients.

We asked ourselves which treatment would be the most appropriate one for patients who refuse active surveillance. An alternative would be to eliminate only the tumor, preserving a significant proportion of the gland and the neurovascular and sphincter structures. In this context, focal therapy (FT), which can satisfy both objectives: destroy the tumor and cause minimal or no harm to the patient, was strongly introduced. Recently re-evaluated data related to the dominant tumor-related lesion (index lesion) have raised new therapeutic expectations which show that, although uni- or bilateral satellite microfoci may remain, they do not pose any life-threatening risk for the patient.

At present, with the combined help of imaging techniques, basically nuclear magnetic resonance (NMR) and properly targeted biopsies, we are able to define index lesions better in order to determine which patients can be candidates for FT.

Cryotherapy and laser

Cryotherapy

Cell freezing and warming lead to cytolysis, due to both the creation of intracellular crystals and intracellular dehydration, pH changes, and endothelial alterations at a microvascular level. Its use has already been approved by the clinical guidelines of both the European and the American Urology Associations in the radical treatment of prostate cancer.
Freezing therapy techniques started as early as in the 19th century, but it was basically in the 1990s when it was checked that this technology was safe enough for its expansion in the treatment of organ-confined prostate cancer (Fig. 1).

With this technological development, the urologist, by using 2 freeze cycles and 2 heating cycles, is able to preserve the surrounding tissue without damaging it. With these principles, and based on the possibility of treating only the prostate areas where the existence of a tumor is proven, the first results of focal cryotherapy were published in 2006.14

Tissue ablation with interstitial laser, named focal laser ablation (FLA), is based on a photothermal effect as a result of the absorption of radiant energy by the surrounding tissue, inducing really high temperature in a very short time15; this rise in temperature produces irreversible cell damage.

Since there is laser absorption, both aqueously and through hemoglobin, the ideal wavelengths which should be used are around 590 and 1064 nm.

The extension of thermal damage is measured both by the temperature reached and the heating time. Protein denaturation occurs at temperatures over 60 °C and, macroscopically, well-defined areas of necrosis appear, surrounded by a small hemorrhagic ring.16

The use of cryotherapy in the field of focal prostate therapy is relatively recent,14 but its results are promising enough to increasingly take them into consideration.

Although the technological development has succeeded in drastically reducing complications, the occurrence of prostate-rectal fistulae and urinary incontinence being exceptional, erectile dysfunction is still frequent as a consequence of the radical nature of the treatment.17 That is why the studies on FT with cryotherapy do not only emphasize cancer-control programs, but also achieve, with high probability, the preservation of sexual functioning as well as urinary continence.

In that regard, a study published this year on 1160 cases treated with FT between 1997 and 2007 showed that the rate of patients free of biochemical progression after 36 months was 75.7% and only 14.1% of them had a positive biopsy. Along with this, complete continence was achieved in 98.4% of cases and spontaneous erection reached 58.1%.18

In a study with a 3.7-year follow-up by Bahn et al.,19 on 73 patients treated with focal cryotherapy, complete continence and enough potency for intercourse were documented in 100 and 86% of patients, respectively. Out of those patients who underwent biopsy, only an 81-year-old man showed positivity in the treated area. Out of the other 11 patients who had positive biopsies in untreated areas, 8 (73%) had low-grade and small-volume tumors, so no complementary treatment was indicated.

The technique can be performed in a more traditional way or with a template; the more knowledge we have about the location of the tumor, the more precise the use of the template will be in the area to be destroyed.

Nowadays, we have solid data to consider FT with cryotherapy a safe alternative, with a very low complication rate and good medium-term cancer control, when selecting unilateral tumors, with a low tumor burden and with a low- or intermediate-risk profile.

**Laser**

The first data with laser therapy date back to 1993, when its effectiveness was shown in the treatment of locally recurrent prostate cancer after radiotherapy.20 Clinical trials were not developed until the year 2009.21

In order to carry out the treatment, it is necessary to perform computerized dosimetric planimetry where the distribution of light energy is calculated, have a laser energy source (usually Nd:YAG, although since 2011 there has also been a diode laser which reaches a wavelength of 1064 nm) and a fiber-optic system with a diameter of around 300 and 600 µm.

Side effects are rare, the most frequent ones being perineal pain and hematuria in 25 and 16% of patients respectively, with no sexual function and continence.
impairment being found. The few oncolgical results showed
67% of negative biopsies in the treated area after 6 months.15

Patients can return home 3 h after treatment.12

Clinical studies are few, with significant clinical variability
being detected in them, basically because the technique
has not been standardized yet and both the energy source
and the temperature reached, as well as the use of probes
to limit the temperature, are very different between the
groups working in this field.

Cryotherapy is becoming a reality in the focal treatment
of prostate cancers in those patients who are considered
candidates for it, and there are more and more works con-
firming its safety, as well as its low- and medium-term
oncological effectiveness although, for the moment being,
clinical guidelines only regard it as a choice within clinical
trials.12

FT with laser is still at a developmental and investiga-
tional stage, so once the technique has been systematized,
a larger number of studies with longer follow-up will be
needed.

Vascular photodynamic therapy

While VPT was initially used more than 100 years ago for skin
lesions, the technical difficulties to deliver light to deeper
organs limited its use to skin diseases. The evolution of
the technique and the development of optic fibers gradu-
ally enabled the use of VPT for deeper organs such as the
retina,23 tumors of the head,24 neck25 and the pancreas.26

To perform VPT, we need the combined reaction of 3
components: a photosensitive drug, light with specific wave-
length for each drug and tissue or vascular oxygen.26 The
drug is orally or intravenously administered to the patient
in its inactive form, taking precautions to avoid the light.27

When the drug receives light stimulation, its biochemical
features change to an active form, which causes the appear-
ance of superoxide and hydroxide radicals. Free radicals
cause tissue and endothelial damage with thrombosis and
rapid vascular occlusion and subsequent necrosis of the
lesion to be treated.28-30 The patient’s immunity also plays
a role in tissue necrosis.31

The first 2 patients who underwent this type of therapy
due to prostate cancer date back to 1990. After 2 resections
of the prostate in each patient, VPT was performed using a
drug with tissue distribution, light being delivered through
an intraurethral optic fiber. The subsequent biopsies were
negative in the 2 patients.22

The current technique uses transparent-needle pricking
through the perineum, a brachytherapy template also being
able to be used.33,34 Optic fibers of a determined size are
put inside the needles, delivering light at a specific wave-
length. Tissue penetration by the fiber is less than 5 mm
(Fig. 2).35,36

Several VPT drugs and procedures for prostate cancer
have been described. The most commonly used drug with
tissue distribution has been temoporfin. It shows a time dis-
tribution of 2–5 days13 and a long elimination time; patients
required up to 6 weeks of light protection.31 It was used in
patients with post-radiotherapy recurrence, but also as a
primary treatment. There was a low success rate, primar-
ily as initial treatment, where in all patients’ tumor presence
was found in the post-procedure biopsy.33

Aminolevulinic acid was also used in prostate VPT. It
has a tissue distribution with a clear trend toward accumu-
lating itself in prostate neoplastic cells, while respecting
benign stromal and epithelial cells.37 5 treated patients
were reported, but follow-up only with PSA did not reflect
the efficacy of the drug.37

Motexafin (MLu8, LuTex®) is a drug with a mainly vascu-
lar distribution; it was used in 17 patients with recurrent
prostate cancer after radiotherapy. Negative biopsies were
recorded in 3 out of 14 patients. No control through imaging
techniques was used in the study.38-40

The more recently developed agents are padoporfin
(WST-09) and padeliporfin (WST-11). WST-09 (Tookad®, Steba
biotech, Luxembourg) was used in phase I and II stud-
ies in patients with post-RDT recurrence, but also as a

Figure 2  Puncture technique with transparent needles. (A and B) Central multichannel and laser optical fibers. (C) Placement of
needles. (D) Control MRI after treatment with area of necrosis.
### Table 1  Ongoing clinical trials on TF for the treatment of prostate cancer.

<table>
<thead>
<tr>
<th>Focal therapy</th>
<th>Center-hospital</th>
<th>Phase of the study</th>
<th>IC</th>
<th>MAC</th>
<th>EPI</th>
</tr>
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<tbody>
<tr>
<td>Cryotherapy</td>
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</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>and oncologic efficacy</td>
<td></td>
</tr>
<tr>
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<td></td>
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<td></td>
<td>Univ. College London Hospitals (UK)</td>
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<tr>
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<td></td>
<td>Univ. College London Hospitals (UK)</td>
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<td>Negative prostate biopsy</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Progression of the disease to intermediate or high risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ecternal radiotherapy</td>
<td>UMC (Holland)</td>
<td>Phase III</td>
<td>Localized intermediate-high risk PCa for modulated intensity radiotherapy</td>
<td>Absence of disease during the 5 years of biochemical follow-up</td>
</tr>
</tbody>
</table>

**PB:** prostate biopsy; **TUGPB:** transrectal ultrasound guided prostate biopsy; **PCa:** prostate cancer; **IC:** inclusion criteria; **cyl:** cylinders; **MAC:** main assessment criterion; **EPI:** estimated patients included; **Gl:** Gleason pattern; **HIFU:** high-intensity focalized ultrasound; **MRI:** magnetic resonance imaging; **VPT:** targeted vascular photodynamic therapy.
primary treatment, being considered safe from the point of view of photosensitivity. The side effects (hypotension) of its combined administration with a solvent (Cremophor®) prompted the development of a soluble version, WST-11.41

WST-11 (Tookad® Soluble) proved to be safe from the surgical and photodynamic point of view in a first study with dogs42 and in completed phase I and II studies (Table 1). In 2 international, multicenter, phase II studies, 85 patients received treatment, 83% of those who received optimal doses had a negative follow-up biopsy after 6 months.63 8 (9.3%) important side effects were reported but without threatening their withdrawal from the study. There was no decrease in the sexual function in the 6 months following the procedure. An international, multicenter, phase II clinical trial is currently ongoing, where the functional and oncological results are being analyzed in patients treated with VPT (Tookad® Soluble) versus active surveillance.52,64

As in all focal therapies for prostate cancer, one of the most controversial points is the definition of failure and the follow-up form for patients. All the studies have shown that PSA is not a useful tool for follow-up after VPT. NMR and possibly contrast ultrasound are more valid alternatives, along with prostate biopsy.65-67 One of the weaknesses of VPT is still the effective control of the procedure and the monitoring of the real administered dose. It has been proven that each of these 3 essential elements for VPT (drug, light and oxygen) can show an heterogeneous distribution in the prostate.68-70 Feedback systems in real time are currently being developed, but their practical implementation could take some time.71,72

Several modifications have been proposed to improve the efficiency of the technique, for instance fractionated light administration, alternating with short periods of inactivity to enable the restoration of drug and oxygen concentrations in the prostate73 or metronomic VPT, that is, simultaneous but very slow drug and light administration to increase the selectivity of tumor cell destruction.74

The selectivity of the drug for tumor tissue also represents a field where improvements have been proposed. The association of monoclonal antibodies seems to be an interesting but limited solution due to the low photosensitivity of the drug/antibiotic complex and the heterogeneity of prostate tumor tissue.55,56 Another possibility of improving its administration would be to associate the drug with serum proteins such as albumin, lipoproteins or even folate to achieve diffusion inside the cell instead of the drug being left in the organ vasculature.75,76 VPT has the ideal characteristics of any ablation technology for the focal treatment of prostate cancer. It has been shown that it can perform selective therapy of prostate areas up to the complete ablation of the gland. Its future will depend on the capacity to develop control systems of the procedure in real time and to improve the sensitivity of the drugs for tumor tissue.

**High-intensity focused ultrasound**

The technique of high-intensity focused ultrasound (HIFU) is an ablation method which consists of applying sound waves to tissues causing cell death. Ultrasounds are originated from high-frequency vibrations generated in a transducer. Cell death occurs at temperatures between 80 and 100 °C produced at the focus point, through processes of coagulation necrosis and cavitation.77 It was not until the 1990s when this technology was clinically applied to the prostate.78 Its capacity as a tissue ablation technique can be considered a therapeutic alternative to standard radical therapy for the treatment of localized prostate treatment.79

There are 2 available HIFU systems currently marketed: Ablatherm® (Edap-Technomed, France) and Sonablate® 500 (Focus Surgery, USA); both of them have been recently assessed in large, multicenter series with medium-term results. Japanese and European groups showed oncological results comparable to standard radical treatment with a follow-up of 5–8 years, disease-free survival rates of 75–84%, 63–72% and 49–68% in low-, medium-, and high-risk patients.61,62 The safety results showed a favorable preservation of erectile function of around 70% and continence rates of about 1–2%. The stenosis rates obtained after applying whole-gland HIFU vary between 0 and 40%, although urethral catheterization to suprapubic with early urethral voiding, or prior to transurethral resection, seems to have a lower incidence.63

Focal therapy with HIFU was initially used in clinical practice by Muto et al. on the basis of series of primary treatment of the gland.84 Patients with unilateral disease (n = 41), according to the standard 12-cylinder TRUS biopsy, received focal treatment by ablation of the bilateral surrounding area and of the unilateral transitional area. The short-term oncological control rates, assessed through postoperative biopsy after 12 months, were similar (84.4% cancer-free rate for the whole gland and 76.5% for focal treatment). However, there was no significant benefit among the groups related to urinary symptoms.

The results of our experience with focal HIFU have been recently published in 2 prospective studies which were approved by a research ethics committee. These trials assessed focal treatment within the Innovation, Development, Exploration, Assessment, Long-term (IDEAL) guidelines.85 Remapping through transperineal biopsy and multiparametric-imaging NMR (T2-enhanced images, diffusion-weighted imaging, improved dynamic contrast) were used in order to apply a precise diagnosis to the detection, localization, and characterization of cancer (Fig. 3).
In the first phase I/II studies, 20 patients received semi-glandular treatment for any identifiable disease (Gleason ≤ 7). Absence of clinically significant disease was achieved in all patients (19 out of 19 biopsied patients) in the treated area which underwent TRUS biopsy at month 6. On the other hand, 95% of the 20 patients preserved erectile function and continence with no protection during a follow-up period of 12 months. The second study focused on a more focal therapy, with a treatment aimed at a uni- or bilateral disease through biopsy remapping. A trifecta rate was reached (absence of clinically significant disease, preservation of erectile function and complete continence without using any protector) in 89% of the 41 patients treated during a 12-month follow-up.

As in other solid-organ cancers, the dominant tumor lesion or index lesion was considered the main prognostic factor. To date, the lack of medium- and long-term published data causes restrictions by health authorities (in particular, the lack of approval by the FDA) for the introduction of HIFU in clinical practice, both in the whole gland (primary and preserved) and in the parameters of FT. Along with that, the recommendations made by the NICE (RU) are that HIFU should be exclusively applied in clinical trials or in association with the recording of prospective results. Therefore, it is clear that prospective trials are required so that HIFU could be established as a standard therapeutic choice.

HIFU is an ideal treatment platform, which allows for focal ablation in daily practice, with a minimally invasive procedure, using established and clinically available technology. We are waiting for obtaining results from long-term studies.

Brachytherapy

Brachytherapy (BT) allows us to treat partial volumes with a high gradient-dose, which enables us to administer low doses to adjacent structures with adequate cancer control. This makes BT an alternative adapted to the concept of FT. There are three scenarios where BT can be used as FT:

1. Treatment with curative intent of localized, low-risk tumors with an identifiable index lesion (biovolume), as pure FT.
2. Overdose treatment of the index lesion in medium- and high-risk tumors, since most local relapses occur at the location of the pre-treatment dominant lesion (concept of differential therapy).
3. Salvage of local recurrences after external radiotherapy or BT, or even surgery.

The main contribution so far was made in a multidisciplinary consensus of European experts which took place in 2010, its main objectives being the definition of suitable patients for this procedure.

Defining which patients are subsidiary to FT is an area of the utmost importance. It is considered that eligible patients should have a significant, unilateral tumor ≤ 0.5 ml, clinical stage ≤ T2b, Gleason ≤ 3 + 4 and PSA ≤ 15 ng/ml.

After BT, 2–3 years are required to prove the histological absence of a tumor in the biopsy, which makes establishing the disease situation more difficult, since there may exist a biologically inactive residual tumor.

NMMP studies have the same limitations, since the studies published showed greater atrophy over time, reaching a maximum level of atrophy coinciding with histological negativization at approximately 24 months. The data recently published in a pilot study with 21 patients and 34% of treated prostate volume, D90 183 Gy, showed less local toxicity when compared to those where the whole gland had been treated.

In future studies, it will be essential to use validated questionnaires evaluating the effect of FT in the genitourinary and rectal field and in the overall quality of life.

An overdose with FT in the dominant tumor, combined with a lower dose in the rest of the gland, may increase the focal control of the disease, reduce the metastasis rate, and increase survival. This approach would eliminate the doubts arising from the multifocality of prostate cancer when considering a focal approach.

Two studies with low-rate BT as overdosage (boost) in tumor subvolumes showed no differences in acute or chronic toxicity with a dose reduction in the urethra. High-rate BT (192Ir) as overdosage after external radiotherapy (64 Gy) was examined in 77 patients by Shick et al., showing in a subgroup of 20 patients that the application of a unilateral boost does not go hand in hand with grade IV toxicity and a free-disease survival rate of 80% at 5 years.

From the year 2000 to the present, data of more than 250 patients, who had been salvaged with whole-gland BT after recurrence following external radiotherapy or BT, have been published, with a 5-year biochemical control rate of approximately 50% (20–87%) and acceptable toxicity data.

Several studies with NMMP showed that practically all recurrences are located in the pre-treatment dominant tumor lesion. The experience of focal BT in untreated cold areas or in areas suspicious of recurrence at the time of NMR analysis has been minimal to date, although it is of great interest given the toxicity associated with global salvage treatments such as surgery or cryotherapy. The University of San Francisco experience on 15 patients with salvage focal BT, NMMP-guided following BT with curative intent, showed a good tolerance profile with no grade 3 or 4 genitourinary toxicity, and only 13% of refractive erectile dysfunction. Today, the image fusion system for NMMP and ultrasound remains unresolved due to the different positioning of the patient in both techniques. Nor is there an appropriate definition of macroscopic tumor + areas of non-significant subclinical disease (CTV). There are studies where FT is understood as hemi-ablation of the gland (Zelefsky) and others which consider it as ultra-focal therapy (Gustav Roussy group). The same problem arises in the context of differential therapy (Fig. 4).

With regard to the administration technique, a real-time technique is recommended with dynamic dose calculation prior to NMMP fusion, with the lesion being geographically located through transrectal ultrasound. The use of linked seeds is recommended because of the displacement or migration of seeds, in the case of ultra-focal therapy, it may have a greater impact on the deposited dose, and thus on tumor control.
Focal prostate treatment with BT is possible with lower theoretical toxicity and probable with similar cancer control. Multicenter studies are essential, if possible with a significant volume of patients, which may enable a response to these issues of local control and toxicity.

Ongoing studies

The interest in focal therapies has increased and several clinical trials have been started to further investigate this field. In this review, we describe the phase II and III clinical trials which are currently being conducted. Table 1 shows phase I, II and III trials.

Follow-up criteria after treatment with focal therapy

A possible solution could go hand in hand with FT, although there are several fundamental aspects which remain unresolved, one of the most controversial ones being the parameters and tools to be used in follow-up and to define oncological effectiveness.

The European consensus group on focal therapies for PCa has determined that the best way to assess oncological effectiveness was the performance of a template-guided transperineal prostate biopsy after 6 and 12 months of treatment, with ambulatory TRPB-E being accepted as a valid alternative in order to reduce costs and morbidity. With regard to follow-up, the same group of experts recommended the use of PSA measurements every 3 months during the first year and then every 6 months. The difficulty of using kinetics for monitoring partially treated prostates suggests that, in the near future, imaging techniques such as multiparametric NMR or contrast ultrasound and the new biomarkers might be a better alternative for the follow-up of these patients. For all these reasons, FT should be considered an experimental therapy.

Conclusions

FT as a treatment technique is an option which has been tested in different forms, always within the context of minimally invasive transperineal approaches.

The aim is always to define with an appropriate selection those lesions to be treated through imaging techniques and biopsies, destroying the lesions with a minimal impact on healthy tissues and adjacent structures.

The characteristics of the different alternatives may display oncological and functional results, although we are not able to differentiate them with the available data.

The results obtained show good tolerance from the point of view of the side and oncological effects.

The ongoing studies will help us to better define the role of each technique, as well as to contemplate treatment from an oncological, functional, and a cost-effectiveness perspective.

Conflict of interest

The authors declare that they have no conflict of interest.

References


