REVIEW ARTICLE

Focal therapy for prostate cancer. Rationale, indications and selection

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Received 13 December 2013; accepted 19 December 2013
Available online 13 April 2014

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;
Background and rationale

To date, the therapeutic strategies employed for clinically localized prostate cancer (CLPC) consist of proposing active treatments such as radical surgery. Although these procedures have been shown to be highly effective in achieving high rates of healing in CLPC, they do involve significant morbidity and reduced quality of life.\(^1\)\(^2\)

To avoid the morbidity associated with the overdiagnosis and subsequent radical overtreatment of CLPC, a noninvasive therapeutic option known as active surveillance has emerged during the last decade.

Between these 2 strategies lies focal therapy (FT) in CLPC, a therapeutic modality that seeks to treat the prostate gland under the principle of organ preservation. The effect is achieved by eliminating the major focus of the tumor (tumor index), which determines the total prostate tumor volume, the Gleason tumor grade and the tumor’s biological aggressiveness.

The main limitations that urologists face nowadays when indicating FT for low to intermediate risk CLPC concern the location of the tumor, the understaging of the disease and oncologic safety when implementing a technique.

Only the scientific knowledge gained from the experience and results of various published series can answer these questions and put FT in its proper place.

Urologists should deepen their knowledge on the following aspects:

1) The type and characteristics of patients who can benefit from FT.
2) Which imaging techniques and minimal diagnoses should be required for its correct indication.
3) How to properly assess the information provided by biopsies to define the tumor index.

Urologists should be well versed in this type of information and should consider it when proposing this alternative to their patients. They should inform their patients properly about the therapy’s advantages and disadvantages, as well as the quality of life that the therapy will maintain. If FT achieves quality of life, we will be witness to a paradigm shift in the local management of this prevalent disease.

The objective of this review is to develop and analyze the published studies that provide an overall view of the relevance of FT and the diagnosis and selection of patients who could be considered candidates for FT.

Rationale and biopsy methods for focal therapy

FT has gained special interest in the last 5 years as a paradigm shift in treatment, placing it in the middle ground between surveillance and radical therapy.\(^3\)\(^4\) However, there is still no consensus on which patients are candidates for this therapy.\(^4\)\(^5\) A number of authors consider that FT is an alternative to active surveillance,\(^6\) while others argue that FT should be considered an alternative to radical therapies.\(^7\)\(^8\) The arguments for performing FT exclusively on patients who are candidates for active surveillance include the following:

1) Reduced psychological morbidity (emotional burden) that not undergoing cancer treatment represents.
2) Reduced cancer progression rate in approximately 1/3 of patients who require late intervention within the subsequent 5 years. Up to 10% of patients who underwent active surveillance elected to undergo surgery within 5 years, even in the absence of histological progression.\(^9\)\(^10\)

The application of FT can be seen as a strategy to reduce the adverse reactions associated with conventional therapy on the full gland. Even when patients are at a high-risk stage of the disease, the evidence indicates that the benefits of radical therapies in terms of controlling the cancer and preventing death are seen only after 10 years.\(^11\)\(^12\)

A strategy that treats the cancer and carefully monitors the tissue unaffected by de novo cancer can prevent the need for future radical therapy (or delay it a few years). Patients can therefore benefit from the lack of adverse reactions related to radical therapy.
The risk of progression and death after radical therapy increases when the Gleason score is \( \geq 7 \). Therefore, a Gleason score of 7 is excluded in most active surveillance protocols, but the Royal Marsden criteria allow a Gleason score of 3 + 4 (nondominant).\(^{13}\)

At present, we can assume that patients can be categorized in a risk scheme in which not only a Gleason score of 6 but also a Gleason score of 7 (3 + 4), and depending on core lengths larger or smaller than 6 mm, are appropriate for FT as long as the tumor index is known.\(^{14}\)

The prognostic significance of stages T2a, T2b and T2c has recently been questioned, given that the progression rates show no significant differences in these groups. FT could therefore also be applied to patients with bilateral disease of low tumor volume, in whom a significant quantity of prostate tissue can be preserved and in those in whom a part of the neurovascular bundle can be preserved. The threshold at which tissue ablation using focal approximation becomes ineffective when compared to total ablation of the gland remains to be determined. A phase 2 clinical trial that assessed the HIFU method in patients with low-volume unilateral or bilateral disease required the preservation of approximately 50% of the gland, regardless of whether the disease was unilateral or bilateral, to reflect the degree of ablation obtained.\(^{15,16}\)

Transrectal ultrasound-guided systematic biopsy (TRUS biopsy) to determine whether patients are candidates for FT is inherently defective.\(^{17}\) TRUS is not useful for detecting unilateral cancer in 50% of men whose cancer would have been detected by a radical prostatectomy or by mapping through a prostate biopsy. Additionally, a third of patients are understaged as Gleason 6 despite presenting a Gleason score of 7.\(^ {10-21}\) The issue depends on whether all identified cancer foci require treatment or whether the treatment of the major focus is enough (tumor index), while monitoring those low-volume and low-grade lesions that are not treated.\(^{22}\) To this end, transperineal template-guided biopsy, alone or sectioned into several variants (combined with resonance magnetic nuclear and/or ultrasound fusion imaging), appears to be the most appropriate method for defining patients/tumors as potential candidates for FT, as this approach provides a better definition of risks (Fig. 1).

The role of magnetic resonance imaging in the diagnosis and selection of focal therapy

Recent advances in multiparametric magnetic resonance imaging (mpMRI) have enabled the identification of high-grade or high-volume prostate cancer lesions, which is considerably useful when attempting to selectively treat lesions that have a greater probability of becoming clinically apparent.

The anatomical sequences T1 and T2 have been shown to be useful when evaluating large or high-grade tumor regions, although the detection of lesions measuring 5 mm or less in diameter is limited.\(^{23}\) Therefore, it is standard practice to accompany mpMRI with functional sequences, such as contrast enhancement, diffusion weighting and spectroscopy.

The use of functional sequences significantly improves the detection rate for small lesions, especially those with a higher Gleason grade. The first functional sequence to be widely used was dynamic contrast, with agents such as gadolinium. Image analysis can be performed qualitatively or with the help of quantitative methods such as the wash in wash out curves. The rapid incorporation and elimination of contrast is indicative of abnormal vasculature in the cancer, while slower input and output are probably due to benign lesions. With the use of dynamic contrast, the detection rate for tumors measuring 0.2 cc is 77% and can reach 90% for tumors measuring 0.5 cc or more. The negative predictive value of mpMRI to rule out clinically significant tumor is 85% and 95% for slice volumes of 0.2 and 0.5 cc, respectively.\(^ {14}\)

The diffusion-enhanced image detects the random movement of water in the interstitial space. In the tumor tissue, these movements are restricted due to the high cell density. A high signal indicates that cancer is suspected. There is the option to calculate the apparent diffusion coefficient (ADC), which decreases as the Gleason score increases.\(^ {25-27}\) This appears to be the most promising modality for detecting high-grade lesions.

Magnetic resonance spectroscopy (MRS) evaluates the relative metabolic composition of voxels (units) of tissue, associating low citrate and high choline levels with the presence of cancer. MRS usually requires extended exposure times and can be a difficult technique due to the use of an endorectal coil and a 3 T magnet. The detection of the tumor using MRS also depends on the tumor volume and grade.\(^ {28,29}\) The employment of at least 2 parameters functional along with anatomic sequences can lead to rates of detection equivalent at employment of the 3 parameters functional.\(^ {30}\)

Currently, the energy sources employed to conduct the release of energy to the target are laser ablation,\(^ {31,32}\) transurethral HIFU,\(^ {33}\) brachytherapy with radioactive seeds,\(^ {34}\) high-dose brachytherapy\(^ {35}\) and hyperthermia with magnetic nanoparticles.\(^ {36}\) With the latter of these techniques, it is the magnet that activates the energy source, while the other techniques use the images simply to direct the energy source to the target.

The ideal moment for evaluating treatment response is during the energy release, so that the energy release can be modified according to the tissue response. This has been attempted through MRI thermometry of the lesions generated using laser ablation, within the magnet.\(^ {30}\) The real-time capture of images using other treatment modalities has been restricted to the placement of needles or fibers within the prostate in previously determined lesions. It is standard practice to use high-power magnets to obtain a high-quality image analysis and a less powerful magnet and open access for interventional procedures.

If the treatment response cannot be evaluated in real time, the most common time for monitoring the image of the prostate is 1 week after performing focal ablation therapy, but not if brachytherapy is performed. At that time, the ablation area can be seen as an area lacking relief (non-contrasted), with the tissue in relief (Fig. 2A and B).\(^ {37}\) The adverse effects of the treatment should also be checked at that time, for example in the rectum or sphincter. It is important to remember, however, that it is normal to observe small noncontrast areas of tissue beyond the treated region without causing clinical sequelae.\(^ {30,36}\) The noncontrast tissue volume in the MRI usually correlates with the histological volume of necrosis obtained.\(^ {18,39}\)
Figure 1  Transperineal biopsy regimen. Tumor sectors and information.
Focal therapy for prostate cancer: Rationale, indications and selection

Pathological criteria for the diagnosis and selection of patients

The function of the biopsy is to reach a diagnosis and help make decisions related to therapy. In conservative treatments such as FT, determining the exact topography of the lesion is essential for making decisions about therapy.

Prostate cancer is multifocal in a high percentage of cases (Fig. 3A and B), and there is disagreement in the literature as to whether multifocality is currently greater or less than before. However, this could be a secondary problem because focal treatments are not limited to the destruction of a nodule but can include large areas of the prostate. It is therefore likely to be more important to know whether the carcinoma is unilateral or not (Fig. 3B-D).

Some 19.2% of low to intermediate-risk carcinomas are unilateral, and therefore patients who have them are candidates for FT. However, how reliable is the unilaterality of the tumor established through biopsy? Only 35% of patients considered unilateral with the sextant biopsy and 40.4% of those with the biopsy extended to 12 cores are truly unilateral. The best biopsy regimen is therefore still to be determined, and other variables should probably also be taken into account.

In most cases, the extraprostatic growth starts in the primary node, and almost all studies indicate that the smaller or secondary nodules are not usually aggressive. The evolution of the carcinoma is therefore considered to be marked by the primary tumor.

When determining risk groups, the assessment of tumor grade according to the Gleason system is essential, but the reproducibility of the score obtained in the biopsy compared with that found in prostatectomy is low, depending on the initial regimen. Therefore, in 2005, the Gleason system was adapted, showing that the reproducibility between the grade of the biopsy and that of the prostatectomy went from 58% (with the classical method) to 72% (with the modified method). The interobserver reproducibility is improving thanks to a better definition of criteria and educational methods.

Topography determination

The vast majority of prostate carcinomas are located in the peripheral zone of the posterior area (Fig. 3A-C), preferentially toward the apex. The tumor is located exclusively in the transition area in only 2% of cases. It is worth noting the placement of the primary node in the anterior half of the prostate (Fig. 3D) in 15% of cases. This location can explain certain cases of discrepancy between the biopsy findings and what can be found in the prostatectomy specimen, and establishes the possibility of performing the prostate biopsy transrectally and transperineally at the same time.

For a patient who is a candidate for FT, a broad sampling of the prostate is necessary to determine the primary node. A number of authors have proposed a 3-dimensional transperineal mapping with more than 40 cores.

![Figure 2](http://www.elsevier.es) Areas of focal ablation. (A) A low signal can be seen in the left peripheral area. (B) The lesion in the left peripheral area shows early improvement with gadolinium.

![Figure 3](http://www.elsevier.es) Multifocal prostate carcinoma. (A and B) Bilateral tumor. (C and D) Unilateral tumor.
Table 1. Selection criteria for candidate patients for focal therapy.

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<th>Clinical</th>
<th>Biopsy</th>
<th>Image</th>
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<td>Clinical stage T1 or T2a</td>
<td>Minimum 12 cores</td>
<td>Single lesion with a maximum size: 12 mm</td>
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<tr>
<td>PSA &lt; 10 ng/mL</td>
<td>No Gleason grade 4 or 5</td>
<td>Maximum extent of capsular contact: 10 mm</td>
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<td>PSA density &lt; 0.15 ng/mL/cc³</td>
<td>Maximum percentage of tumor in each core: 20%</td>
<td>Absence of extraprostatic extension or invasion of seminal vesicles</td>
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<tr>
<td>PSA velocity &lt; 2 ng/mL annually for the year prior to the diagnosis</td>
<td>Maximum extent of tumor in each core: 7 mm</td>
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<tr>
<td></td>
<td>Maximum percentage of cores affected by the tumor: 33%</td>
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Selection of patients for focal therapy: which patients are candidates?

Patients in the low-risk group appear to be ideal candidates. In this context, Katz et al. used strict low-risk criteria with 56 patients who underwent FT and concluded that these criteria by themselves (Gleason score <7, PSA levels <10 ng/mL, T2b and 1 positive biopsy <80% of 1 nucleus with absence of perineural invasion) should not be used for selecting patients for this type of treatment. A second argument for not exclusively using clinical criteria is their lack of correlation with the pathological postprostatectomy criteria, where an understaging of 34% has been shown. An international expert consensus panel has suggested recommendations for selecting patients who are candidates for FT, such as those with low to moderate-risk prostate cancer. Patients with a clinical stage >T2b and with dominant Gleason grade of 4 should be excluded. Additionally, they recommend the performance of transperineal prostate biopsies, as well as the use of mpMRI to identify areas for biopsy and treatment. Eggener et al. proposed a number of selection criteria for patients who are candidates for FT based on clinical characteristics and imaging and biopsy results (Table 1). Currently, the European guidelines recommend limiting this type of treatment to patients with low to moderate-risk prostate cancer, with a clinical stage no greater than cT2a and a radiological stage less than or equal to cT2b.

The criterion of the presence of Gleason pattern 4, tumor burden in cores and the unilateral and bilateral nature of the tumor are subjects of discussion awaiting results and the implementation of randomized trials.

Conclusions

FT can be an alternative to the classical forms of radical treatment for managing localized prostate cancer.

At present and with the combined support of imaging techniques (primarily mpMRI and properly directed biopsies), we can better define the index lesions to determine which patients are candidates for undergoing FT.

Although the Gleason score remains a reference for the definition of aggressiveness, we need new markers that better define this characteristic.

Patients at low risk, with little tumor burden and unilateral involvement can be ideal candidates for FT, although it is possible that patients with intermediate-risk (or bilateral) tumors could also be candidates.

Advances in imaging techniques, new markers and prospective studies help us to better select candidates for FT, as well as other future possibilities.

Likewise, the progress of new imaging technology will dramatically help the development of this type of treatment.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References


