How will focal therapy fit in with existing treatments?☆

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Abstract
Context: The current management of localized prostate cancer is a therapeutic challenge with different options including active radicals or active follow-up. The aim of this paper is to analyze the feasibility and validity of the “Focal” active treatment versus the concept of active follow-up or Radical Treatment.
Evidence acquisition: We reviewed the literature on the various diagnostic methods, advantages, and difficulties of active follow-up and Radical Treatment, versus focal therapy with the possibilities of defining characteristics of aggressiveness and patient selection.
Evidence synthesis: The mesh biopsy techniques along with multiparametric magnetic resonance imaging and association of factors such as tumor size, length of affected cylinder and Gleason are parameters that allow us to define location and definition of clinically significant tumors and subsidiary of focal therapies.
Conclusions: The definition, location and aggressiveness of prostate cancer in low-intermediate risk tumors can be defined avoiding radical therapies with their side effects or the risks of underestimating tumors as in active follow-up without the minimum side effects.

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¿Cómo encajará la terapia focal en los tratamientos existentes?

Resumen

Contexto: El manejo actual del cáncer de próstata localizado supone un reto terapéutico con diferentes opciones, incluyendo las activas radicales o el seguimiento activo. El objetivo de este trabajo es analizar la posibilidad y validez del tratamiento activo -focal- frente al concepto de seguimiento activo o tratamiento radical.

Adquisición de evidencia: Realizamos una revisión de la literatura sobre los diferentes métodos diagnósticos, ventajas o dificultades del seguimiento activo y tratamiento radical frente a la terapia focal, con las posibilidades de definición de características de agresividad y selección de pacientes.

Síntesis de evidencia: Las técnicas de biopsia con rejilla junto con la resonancia nuclear magnética nuclear multiparamétrica y la asociación de factores como el tamaño del tumor, la longitud del cilindro afecto y Gleason son parámetros que nos permiten afinar en la localización y definición de tumores clínicamente significantes y subsidiarios de terapias focales.

Conclusiones: La definición, localización y agresividad del cáncer de próstata en tumores de riesgo bajo-intermedio puede ser definida evitando las terapias radicales con sus efectos secundarios, o los riesgos de subestimar tumores como en el seguimiento activo con los mínimos efectos secundarios.

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Puntos comunes: active surveillance and focal therapy

Active surveillance (AS) and focal therapy (FT)-directing therapy to cancer instead of to prostate-share a significant common denominator: the idea that men, given an acceptable cancer risk, they generally prefer to keep their prostate. Physicians recommend preservation strategies of tissues through AS and FT hoping to minimize some of the harms associated with overdiagnosis. While the diagnosis cannot be reversed, we can present to the newly diagnosed man a procedure associated with reduced levels of damage in a group of patients who probably have little opportunity to benefit from treatment. In recommending the preservation of tissues, the doctor gives one of the two strategies that the patient can consider as an alternative to whole-gland radical therapy in its many forms.

Strategy one

AS provides a containment strategy: "Mr. John, you have prostate cancer; but we are pretty sure that it is unimportant. I think that it is unlikely you will be affected if we do not touch it. We will survey it and will treat it in case we see changes."

Strategy two

FT provides a risk reduction strategy: "Mr. John, you have prostate cancer. We have identified the worse part of it. We should be able to treat the cancer and to preserve most of your prostate".

Both strategies overlap considerably; however, one of them focuses on the period final, and the other one on the beginning. Both try to refer men with low-risk prostate cancer, who can safely avoid a whole-gland radical therapy. AS procedure assesses over time the situation of low risk by submitting the patient to a test that lacks precision. After every review, some patients are newly classified because they exceed the upper level of risk and they leave the AS; usually whole-gland radical therapy is offered to them. Finally, a depurated group of patients with low-risk status, who have not been reclassified histologically, are considered free of "progression".

When offering FT, location, extent and risk (according to the cancer degree and the maximum length of the nucleus of cancer) have to be established in advance and in order to define the disease's topography. These three parameters determine the completion of treatment. In order to rule out cancer clinically important, accuracy is required not only in the therapy field (high specificity) but also in the volume of the tissue that has to be preserved (high sensitivity). Traditional diagnostic tests are not up to the job. Focal therapist must adopt a sampling strategy that could fulfill both requirements.

For the physician, recommending a strategy for preservation of tissue implies significantly different challenges from those that arise when treating the whole gland. The doctor treating the entire gland in the most basic level requires at least a diagnosis of prostate cancer. A Gleason of 3+3 mm is enough to decide to carry out the treatment. A question still remains: if the cancer is aggressive or lethal. This aspect is unimportant for the surgeon or for the radiation oncologist who plan patient's IMRT, because the treatment for the organ-confined disease does not depend on the size, the cancer grade and localization. For everyone the goal, in a certain manner, is the prostate, not the cancer.

When recommending AS, the physician requires more information. A strategy of prostate preservation will never
"clean" any excess of the disease that could have been overlooked initially. Therefore, as a lower threshold – the patient must have a diagnosis of prostate cancer – the application of an upper threshold of disease is also needed in AS. The question is: what is the worst disease this man has? Because of an inherent imprecision that is both systematic and random error, standard TRUS guided biopsies provide reliable information about the lower threshold exclusively. In other words, TRUS biopsy informs about the minimum amount of disease that might be present, not the maximum. The reason is that prostate cancers, in our diagnostic spectrum, occupy about 1/30% of prostate volume. As a result, a direct impact of a tumor focus is a rare event. Because either a failure or marginal take is most likely than a direct impact, the rule is that both the maximum core length of cancer such and the Gleason pattern will be underrepresented in an initial set of biopsies compared to what is really there. Therefore, it is difficult to define the upper limit of the disease with standard diagnosis PSA/TRUS biopsy. TRUS guided rebiopsy is used as a way to correct this sampling widely recognized deficiency. Some AS protocols suggest a verification biopsy by the time of hospitalization. In other words, the state of the low-risk patient has to be confirmed with a second set of biopsies in order to allow his entrance. As REDUCE and REDEEM,4 studies have proven, TRUS biopsy used over the time is not very reliable; therefore that strategy is meaningless. When combining a 20–30% sensitiveness with TRUS biopsy for a clinically significant disease – the target condition we are trying to rule out – the strategy is unlikely to be efficient.

Although a rebiopsy qualification is not a requirement, most physicians will recommend a deferred rebiopsy during first or second year of follow-up. Referred biopsy and immediate "confirmation" biopsy have the same limitations. Transrectal ultrasound biopsy lacks of specificity in order to discard clinically important disease. The reasons are technical, but they relate to the systematic sampling of certain portions of the prostate (some parts are never reached) and also to the divergent sampling strategy (lateral to midline) that the technique employs. The theoretical study developed by Kepner is a good model for improving tumor detection.5

In most of AS protocols TRUS rebiopsy deserves some attention. Obviously, redoing a test does not improve its overall accuracy. The retest will reduce some of the random errors inherent to the prostate parts routinely used in biopsy strategy. Systematic error will not be affected, unless a different needle guidance is used or prostate size is reduced, for example, by the effect of an inhibitor 5-alpha reductase, and made more accessible to the same needles. The reduction in the random error will be more evident in the peripheral area of the gland. Assuming that the original location of the needles has been preserved and assuming that no emergence of new types of cancer or any existing progression has resulted in the interval, two results are possible. The first one is the finding of small foci of pre-existing cancer that could have easily been lost in the first biopsy. The second is to reach more directly a pre-existing cancer, and as a result to obtain a different spectrum of the Gleason pattern. Taking into account the Gleason ground effect 3+3, the only difference that can be derived is an increased risk for increasing Gleason pattern even when no real change has taken place. The maximum core length of cancer can go either way as long as the first biopsy contains more than 1 mm of the disease. If the patient begins with only 1 mm of the disease is difficult to obtain less than this.

From a strictly oncologic point of view, the postponement of the control biopsy as it is traditionally done in AS, makes little sense. Low-risk cancers should not change very often, and if they do it should be for a very long period of time. If this is the case, why then plan biopsy intervals of 1–4 years as it is commonly made in the protocols of AS? Planning biopsy interval imposes two ideas that are both uncertain. The first idea is that the TRUS biopsy is a "good" test to rule out in clinically significant disease in if when actually present. It's not. The second one, which is probably spurious, is that the biopsy is done in the idea that if we wait even a short period of time in terms of prostate cancer, the cancer that was previously considered as low risk, may actually become more aggressive, and if it does we can identify.

Active surveillance, focal therapy and future

Fortunately, much of what we do for the men with prostate cancer risk and what has been done in men who have been diagnosed with prostate cancer will change. The key objective missed so far is the location of the tumor. Imagine for a second treating kidney, breast or liver cancer without an idea of where the tumor is. It would be impossible. It is frustrating and quite worrying to think that we diagnose and treat prostate cancer without knowing tumor location or extent. If you do not know where the cancer is, we have to look for it through our process of blind and partially random biopsy. If the patient has prostate cancer treatment should be directed to the organ, because we really do not know where the cancer is.

Diagnostic pathway is going to change

This change will be achieved by two ways. The first one is multiparameter magnetic resonance imaging (MRI). The second one is the imaging-guided biopsy. This requires that images have to be obtained before the biopsy, as in the others solid organ cancers, resulting in the following two consequences. Firstly, some men (probably around 1/3 of them) despite high PSA levels could avoid prostate biopsy. This is based in the results obtained in several papers in which MRI has demonstrated to have high sensibility (80–90%), negative predictive value (90–95%) and negative likelihood ratio (0.1–0.2), for clinically significant disease.7,8 Then, it is reasonable to assume that some men will decide to postpone the biopsy if the performance is enough reassuring for patients with high PSA and, even more for their urologist. However, in the current moment it is unknown the exact prevalence of "risk males" with normal magnetic resonances. Until prevalence figures are known,
only the proportion of men who can delay or avoid biopsy can be calculated with no doubt. Current studies suggest that 1/3 of the men could be classified as possessors of a “normal” MRI. These normal RMI are superimposed to those showed by men who either do not have prostate cancer or have microscopic volumes of well differentiated cancer.

By contrast, imaging-guided biopsy will be performed in those men whose MRI showed prostate lesions (low T2 signal and/or dynamic contrast-enhanced and emptying and/or low diffusion-weighted image). Numerous studies, most published in 2010 and 2011, have proved that strategy of targeted biopsies at MRI suspicious areas show very high sensitivities with positive predictive values for clinically significant prostate cancer (80–90%). These results represent an improvement over TRUS biopsy (30% of sensitivity for significant prostate cancer). High quality RMI will limit the use imaging-guided sampling. Probably, these data will change the current urological practice. Besides, patients will be capable of perceiving the great differences between both procedures, refusing to choose the current practice.

If it is approved, imaging-guided biopsy will have two main effects. According to current definitions, ratio of men with significant disease will increase significantly. At the same time, ratio of men with no significant disease will decrease. Although these two results (smaller number of men undergoing to biopsy with smaller number of biopsies) can make choosing imaging-guided biopsy, some caution must be maintained. All standard-risk definitions are based in a blind located randomized sampling. Under these circumstances, the cancerous biopsy lesion is a very unusual event. TRUS biopsy underestimates systematically both the tumor extent and the incidence. Thus, it is necessary to improve the current classification or to elaborate a new classification. Frequently, imaging-guided sampling involves a very long (sometimes alarmingly) maximum core cancer length, for lesions considered small. For example, lesions of 0.5 cm – Stamey’s threshold for significant volume – frequently will give rise to core cancer length of 10–12 mm (up to 70 or 80% of core). Thereby, patient is in low risk category as due to the use of common sense approach. By contrast, the same patient would not be in low risk category if we employ the current staging system. Therefore, the greater accuracy achieved makes necessary to elaborate more appropriate definitions of risk to specific strategy. Recently, we have proposed a new model based on both the volume and the degree. This model has been validated by prostate mapping simulations using a cohort of radical prostatectomy specimens for computer simulation. It provides an exhaustive method to stratify risk for men with localized prostate cancer that is limited to 3 risk definitions, representing each definition as a semaphore (Table 1). Green disease is limited to small foci of Gleason pattern 3.

Yellow disease is defined as tumor focus greater than 0.2 cm and smaller than 0.5 cm, (maximum length core cancer ≥4 mm). Alternatively, any secondary 4 pattern, appeared as minor finding of the cancer, is considered as yellow disease. Yellow disease is typically indeterminate. Today nobody can predict its development. Until we know the true potential of the lesions, active surveillance could be a reasonable option in elderly, while in youth, the treatment could be the most adequate alternative.

Red disease, characterized by higher length of core cancer (≥6 mm) and/or dominant Gleason pattern 4 in smaller lesion, is the type of disease that most of us would like to treat. Red disease meets or exceeds the volume threshold of 0.5 cc.

We have to take into account that at this stage these definitions are very conservative in order to be employed by the urological community. Recent studies from European Study of Screening for Prostate Cancer suggest that patients with tumoral volume index smaller than 1.3 cc and with Gleason pattern 3 can be considered significant tumor and, therefore, the patients do not have to be very worried.

A convergence of pathways

As consequence of how quickly the novelities are assumed and because many barriers remain, much of this study is speculative. One thing we can be sure of is that imaging tests are becoming increasingly significant tools in diagnostic route. These jointly with biopsy shall provide the precise tumor location (aspects that currently lack).

In this point the going gets rough. Remember, in general smaller number of men are biopsied. With current and perhaps modern criteria (according to radiological phenotype), men biopsied are more prone to develop significant disease. With the methodology described in our study, the number of men labeled as having prostate cancer will be smaller. This fact is, without doubt, important because if the label is correct there will be no clinical consequences. The decrease in the number of insignificant prostate diagnostics is due to two processes. Firstly, smaller number of men will be biopsied. Secondly, in men with lesions in RMI, randomized biopsies will evolve to targeted one. If the urologist develops both randomized and targeted sampling, the rates of clinically insignificant disease will become higher, although lower than now.

Therefore (fewer men diagnosed and fewer labeled with insignificant disease: green disease), AS will be a minor requirement in the future. The only thing that will test is a revaluation of our notion of risk. In all AS protocols, there are many men exceeding the upper risk threshold, but we do not know anything about them. It is possible that only yellow disease is perfectly acceptable to be observed in some men, because we can be 95%
sure that it does not coexist simultaneously with red disease. Only we need the data, but standardization process will take time. Even red disease could be acceptable in come men, especially if we know more about the tumor biology. The deep sequencing of these lesions – possibly only through representative pathology – is hoped that will assist in the more refined classification of the more “aggressive” lesions.

So what about focal therapy? Focal therapy, by definition, has always required a target. Well-defined and accurate targets will be the outcome of the new way based on imaging test. It is possible that focal therapy arrives sooner than currently – nowadays it is required that patient requests it – because patient and physician will know cancer location early, before biopsy. This, as it is done today (when available), provokes debate – often initiated by the patient – whether it is absolutely necessary to treat all the normal tissues.13

It follows that, with the time, an upper threshold for the disease will be established – either by impact or by location – above which tissue preservation is considered useless or undesirable. This is observed in kidney. In general nephron-sparing surgery is not usually performed on patients having tumors greater than 4–7 cm.14 In breast cancer, proven multicentricity is an indication for mastectomy instead of lumpectomy.

Currently, upper threshold for prostate cancer is Gleason pattern 4 in contralateral side, although many physicians prefer not having demonstrable disease in the untreated side (of course, this does not mean that the disease is not present). Inside treated area – or “in the field” – current upper limits are: disease limited to the organ and the absence of Gleason pattern 4+4 or the presence of any Gleason pattern scale 5.

Currently, either radical surgery or radiotherapy of whole gland must be offered to any patient who meets or exceeds these two upper limits.

All treatments fail by different ways. Moreover, the consequence of the failure depends on the type of treatment associated with this failure. Failed surgery entails radiotherapy or androgen suppression therapy. Failed radiotherapy has a number of available options. Focal treatments will also fail, probably much more frequently than the treatment of the whole gland. Like all treatments, focal therapy may fail for staging mistakes. Like radiotherapy, it can fail due to recurrence or residual disease within the field. This therapy can also fail in the same way in which active surveillance fails in some patients – by the progression of not treated lesion. Most focal therapies can be reapplied. It is necessary to define and to know the toxicity of retreatment as well as the toxicity/efficacy ratio of sequential therapy (focal therapy followed by whole gland therapy, either by surgery or radiotherapy). All this is work for the future, but it will be crucial if patients are able to take informed decisions about their therapeutic options.

**Conflict of interests**

The authors declare that they have no conflict of interest.

**References**

