

Focal therapy for prostate cancer

Focal therapy of prostate cancer is currently a concept rather than a therapeutic option. The controversy surrounding the concept addresses the theoretical rationale for focal therapy, not the actual results, as there are almost none. The major arguments against focal therapy can be classified under the broad headings of 'understaging' or 'unnecessary intervention'.

The understaging argument centers around the multifocality of prostate cancer. This argument highlights the importance of the occasional, but troublesome, finding of a large, extracapsular or high-grade tumor (Gleason score ≥ 7) in about a quarter of radical prostatectomy specimens removed from men initially classified as having a low-risk cancer (defined as tumor stage cT1c or cT2a, Gleason grade 3 + 3, and serum PSA level < 10 ng/ml). The unnecessary intervention argument asserts that any intervention is unnecessary in a man with a unifocal, low-risk cancer. This argument presumes that small, low-grade cancers rarely grow into large or high-grade tumors, and that cancers can be safely watched in an active surveillance program and treated effectively when progression is evident, but before metastases develop.

Indeed, 85% of all prostate cancers are multifocal, but the index or largest cancer makes up, on average, more than 90% of total tumor volume (Ohori, M. *et al.* abstract #1574, presented at the AUA Annual Meeting: 2006 May 20–25, Atlanta, GA, USA). The other foci tend to be very small: 80% are < 0.5 ml, and the median volume of these incidental cancer foci is 0.3 ml (Sartor, A. O. *et al.* *Urology* 72 [Suppl. 6], S14–S24 [2008]). These incidental foci are similar to the cancers found in a third of men over the age of 50 years. If the index cancer could be ablated, any remaining cancer is likely to pose little threat and can be monitored for progression.

The understaging argument points to the occasional large, aggressive cancer found in about a quarter of men with low-risk cancers, an observation that drives physicians to recommend immediate curative therapy. This concern can, however, be offset by additional testing: another biopsy (Berglund, R. K. *et al.* *J. Urol.* 180, 1964–1967 [2008]), especially a transperineal mapping biopsy (Barzell, W. E. & Melamed, M. R. *Urology* 70 [6 Suppl.], 27–35 [2007]), and MRI of the prostate. While MRI cannot delineate small-volume, low-grade cancers, a

normal or nearly normal MRI provides strong reassurance that a large, high-grade cancer was not missed (Shukla-Dave, A. *et al.* *BJU Int.* 99, 786–793 [2007]).

Does it make sense to treat prostate cancer focally, even if appropriate candidates can be identified? What is the advantage of focal ablation over active surveillance? Neither patients nor their physicians are enthusiastic about watchful waiting, an option chosen by only 6% of men (Harlan, S. R. *et al.* *J. Urol.* 170, 1804–1807 [2003]). Would ablating a small cancer reduce the risk of future progression and the need for radical therapy?

The technology needed to ablate small regions or sectors of the prostate harboring a known cancer is rapidly becoming available. Cryotherapy is already being used (unfortunately outside of formal clinical trials) and the preliminary data is encouraging, although the criteria for eligibility, the parameters of treatment, the length of follow-up, and the absence of patient-reported outcomes make these results hard to interpret.

Ultrasound-guided high-intensity focused ultrasound (HIFU), photodynamic therapy using newly developed light-sensitizing agents, and MRI-guided HIFU are all promising new tools that will place focal therapy easily within the grasp of the medical community.

In this issue of *Nature Reviews Urology*, imaging and biopsy techniques for improving the detection and characterization of tumors within the prostate are the subjects of a Review by Baris Turkbey *et al.* (page 191) and a News & Views commentary by Gerald Andriole (page 188). The issue of using focal therapy in patients with early-stage prostate cancer is examined by Vladimir Mouraviev and colleagues in their Review (page 205). The authors discuss the stage migration observed in prostate cancer, and pathologic factors that are important in selecting potential candidates for focal therapy. This Review, along with the other articles, highlights the importance of perfecting an image-guided technique and accurate characterization of tumors as being essential in the development of a focal therapy approach to the management of prostate cancer. Now is the time to plan the clinical trials that are essential if we are to determine whether focal therapy makes any sense and is of real benefit to our patients.

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Competing interests

The author has declared an association with the following company: Steba Biotech N.V. See the article online for full details of the relationship.