

There is no role for focal therapy in prostate cancer

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The increasing interest in focal therapy for prostate cancer derives from the paucity of prospective randomized studies to guide treatment for this disease, and the concern that the current therapies incur excessive patient morbidity. Radical prostatectomy, external beam radiotherapy and brachytherapy are the established standard treatments for locally confined prostate cancer. However, owing to a lack of data, we struggle with individual patients to decide which modality is best, and in many cases we do not even know if we are enhancing survival over observation alone. The Scandinavian Prostate Cancer Group demonstrated a modest improvement of survival in a cohort of nonscreened men who underwent radical prostatectomy compared with those who underwent no primary therapy.¹ With the advent of prostate-specific antigen (PSA) screening, however, we are detecting an increasing number of indolent cancers² and it is not certain whether the same survival advantage would be found in a screened population. Furthermore, with over-detection has come overtreatment, and overtreatment in turn gives rise to numerous associated adverse effects and potential impairment of quality of life.³

Focal therapy has arisen in this context as a treatment that can ablate prostate cancer with minimal collateral damage, thereby side-stepping some of the treatment dilemma. Focal therapy involves subtotal ablation of the prostate with one of several energy sources, including cryotherapy, high intensity focused ultrasound and photodynamic therapy. Targeting the tumour or one specific region of the prostate is done with the expectation of avoiding the adverse effects of total-gland therapy, especially incontinence and impotence.⁴

There is, however, little evidence to support the application of focal therapy. First, its efficacy remains unproven, and, second, it has yet to be demonstrated that it will reduce side effects of treatment. Furthermore, while we await clinical trials to answer these fundamental questions, there are significant conceptual difficulties with focal therapy.

The principal conceptual shortcoming of focal therapy is the fact that prostate cancer is often multifocal. Only about 20% of tumours are unilateral and unifocal.⁵⁻⁷ There are 2 ways around this issue of multifocality. Either one is able to identify each focus and treat each appropriately (or limit

focal therapy to unifocal prostate cancer), or one assumes that not each focus requires treatment. This latter argument is made frequently based on the idea that the largest tumour (the index lesion) is driving the potential progression of the disease, and the secondary lesions are indolent.⁵ Yet we know that prostate cancer, like most cancers, is a heterogeneous disease, and we do not know in all cases that these satellite lesions do not harbour a biologically significant focus of disease.⁸ This is currently a leap of faith, particularly since we are unable to monitor the growth of secondary lesions because of our inability to adequately image the prostate.

The inability to image foci of prostate cancer is the second principal conceptual difficulty with focal therapy. Improvements continue to be made especially in magnetic resonance imaging (MRI) of the prostate, but we are still far from being able to accurately identify every index lesion of prostate cancer on MRI, let alone secondary sites of disease.⁹ The alternative strategy is to map the cancer by systematic biopsy, but this too has unproven reliability.¹⁰⁻¹² Furthermore, saturation biopsies are expensive and they are not without complications.^{13,14} There are many anecdotal stories of subsequent difficulties with the posterior dissection and nerve-sparing at the time of radical prostatectomy.

A third shortcoming is the need to define outcome variables. These therapies are ablative, so that a threshold PSA appears most appropriate (e.g., PSA > 0.5 µg/L), but dynamic definitions as used for radiotherapy have also been proposed.^{15,16} This will need to be addressed with top priority if focal therapy is to be studied in a systematic fashion.

Conceptually, we should really be comparing focal therapy to active surveillance, since both are targeted at the same population of low-risk patients. Active surveillance

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itself is an unproven management strategy for prostate cancer, although it is currently being assessed in 2 prospective randomized trials, including the Surveillance Therapy Against Radical Treatment (START) Trial and the Prostate Cancer Intervention Versus Observation Trial (PIVOT), in addition to the Canary registry trial. We need to overcome the tendency for automatic treatment of every prostate cancer that is diagnosed — overdiagnosis does not have to lead to overtreatment.³ The principal obstacle to active surveillance is our limited ability to predict which cancers can be safely observed without subsequent disease progression — our concern for undertreatment. At the same time, it is difficult for both the treating physician and the patient to accept that a cancer has been diagnosed but is not being treated. If we were able to remove the uncertainty of active surveillance by being able to define risk better and detect progression reliably, then the interest in focal therapy would likely dwindle.

The experience with active surveillance should be instructive for focal therapy. A recent series from Memorial Sloan-Kettering Cancer Center, for example, found a high rate of higher risk disease in patients who fulfilled criteria for active surveillance but underwent radical prostatectomy.¹⁷ The investigators identified pT3 cancer in 11% and Gleason pattern 4 in 49% of patients. Five of 8 patients with no cancer shown on second biopsies went on to have Gleason pattern 4 cancer on radical prostatectomy. These findings reinforce that we are poor at assessing risk, which is the foundation of focal therapy.

The International Task Force on Prostate Cancer and the Focal Lesion Paradigm has been established and has published a position statement.⁴ This group refers to focal therapy as “attractive from a conceptual perspective” and suggests that “cases ... should be collected prospectively in a database for future analysis.” They readily acknowledge that criteria for patient selection have yet to be determined and summarize that “this procedure may fill a void in the therapeutic options available to men who are potential candidates for active surveillance who prefer therapy.” Is it reasonable to submit patients to an unproven therapy with poorly defined adverse effects just for the sake of “doing something”? Also, since focal therapy is currently aimed at lesions that we believe may not actually require therapy, it is going to be difficult to show the superiority of any treatment in this population.

There is currently no role for focal therapy in the management of localized prostate cancer. Our efforts should

focus on improving methods of screening, diagnosis and risk stratification to allow optimal identification of patients who are suitable for active surveillance, and those with more significant disease should go on to radical prostatectomy or radiotherapy — the established standard therapies.

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