Editorial

# The future of active surveillance

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Active surveillance (AS) consists of four elements, each of which is amenable to improvement and will likely change over the next decade. These are (I) the diagnostic algorithm leading to the initial finding of favorable risk prostate cancer; (II) establishing the indolent nature of the patient's known disease and ensuring there is no co-existent higher grade cancer; (III) identifying grade progression over time, and (IV) interventions to reduce the risk of disease progression.

The circumstances leading to diagnosis have been, for the last 25 years, an elevated prostate specific antigen (PSA) leading to a systematic biopsy of the prostate. This approach resulted in a controversial revolution in the diagnosis and management of prostate cancer. The PSA-biopsy approach is attended by the well-known risks of overdiagnosis and overtreatment. These risks led to the USPSTF assigning a 'D' recommendation to PSA screening in 2011 (1). Encouragingly, the widespread adoption of AS has led to a recent proposal to change the recommendation to 'C', or neutral, placing the onus on the patient to decide whether he wants the screening test. Diagnosis of favorable risk prostate cancer needs to be disaggregated from the decision to treat, and this was the key benefit of AS. However, surveillance alone has not solved the problem attendant to the PSA-transrectal ultrasound (TRUS) biopsy approach, including uncertainty about the optimal PSA threshold for biopsy, many negative biopsies, a significant urosepsis rate, pathologic miss of higher grade cancer, and a general reluctance by men to undergo this procedure.

The future of AS is likely to be influenced by the change in approaches to screening. It is very likely that the PSA-TRUS biopsy approach will be modified substantially to reduce these unwanted effects. In order to further stratify risk, an elevated PSA will be followed by a second biomarker test of plasma, serum, or urine. Current candidates are the 4K, Prostate Health Index (PHI), select MDx, and PCA3 tests. The pipeline is full of other 'liquid biopsy' assays, including the Mitomics assay (a circulating mitochondrial DNA deletion assay), Telo PC [a circulating tumour cell (CTC) telomere based assay], and others. The analogy is to following an elevated serum glucose with a Hb1ac test. Like the Hb1Ac, these tests assign a more precise risk of individual prostate cancer. For those found to be at risk, a magnetic resonance imaging (MRI) will be performed and a targeted biopsy carried out of abnormal areas on MRI.

It is unclear at the moment whether MRI is sufficiently accurate to allow the systematic biopsy to be avoided if the MRI is negative or if a targeted biopsy is being performed. In 2017, the best estimate of the negative predictive value (NPV) for a negative MRI is 85%. The NPV is lower amongst high risk cohorts (2). Thus, in patients who are at risk for significant cancer, a substantial number will have a false negative MRI. In my view, systematic biopsies will continue to be required in patients at risk for significant cancer based on clinical and molecular parameters.

As long as systematic biopsies continue to be performed, favorable risk prostate cancer will be diagnosed and AS play a major role in management. However, if systematic biopsies are replaced in most patients by MRI and only targeted biopsy, it is likely that the overdiagnosis of low grade cancer will diminish. In the absence of systematic biopsies, some patients will have Gleason 6 found on targeted biopsies, and be managed with AS.

Once the patient has a diagnosis of favorable risk prostate cancer, the next step is to confirm indolence and exclude co-existent higher grade cancer. The virtual complete absence of patients with surgically confirmed Gleason 6 cancer who have metastasized to either lymph nodes or bone means

that, in the absence of higher grade cancer, indolence can be assured. While about 10% of Gleason 6 cancers harbor significant molecular aberrations, these are usually present in prostates with co-existent higher grade cancer (3). It is unclear whether these occasional genetic aberrations (PTEN deletion, for example), in the absence of higher grade cancer, confers an increase in metastatic potential. The absence of cases of metastasis in 'pure' Gleason 6 cases suggests either that it does not, or that the cancers undergo grade dedifferentiation prior to metastasizing.

An exception is the patient with a germ line DNA repair mutation, i.e., BRCA1–2 or ATM. These patients develop a very high mutational load early in the course of disease (4). Patients with these germ line mutations have so much genetic instability that they should probably by treated aggressively, even with favorable risk disease. It is likely that other susceptibility genes will be defined over the next few years that provide a clear signal to treat or not treat.

Exclusion of co-existent higher risk disease is currently done with a confirmatory biopsy. This reliance on confirmatory biopsy is changing rapidly. The adoption of MRI into the management algorithm means that the misattribution of low grade cancer in the patient who harbors an aggressive high grade cancer missed on systematic biopsy (the Achilles Heel of surveillance), will be largely reduced.

Another approach is the use of tissue based molecular biomarkers, including Oncotype Dx, Prolaris, Promark, and Decipher, to predict which patients are likely to progress. The problem with these assays is that they were all validated just prior to the MRI era. Today, most AS patients who harbor occult co-existent higher grade cancer will have this identified on MRI and confirmed by targeted biopsy. Therefore the potential benefit of a genetic marker which predicts for the presence of higher grade cancer based on the genetic profile of a low grade cancer is more limited than it was even a few years ago, before the advent of multiparametric (MP) MRI.

There is a role for these markers in the equivocal cases. These include the young patient (< age 55) with extensive Gleason 6 cancer; patients with Grade group 1 but a high PSA density; the patient with a Gleason 3+4 cancer who is interested in surveillance as a management strategy; and the patient with restricted diffusion on MRI (Pirads 4 or 5) whose targeted biopsy is negative or shows only low grade cancer (5). However, the typical patient with a few microfoci of Grade group 1 cancer, a low PSA density, and a negative MRI is not likely to benefit from a tissue based molecular assay.

At the other end of the spectrum, there are clearly patients with intermediate risk cancer who are have indolent disease. In the Sunnybrook cohort, of 220 men with Gleason 7 managed with surveillance, the actuarial rate of metastasis at 15 years was 20% (6). (All of these were risk re-classified prior to developing metastases). While that proportion is high, and has resulted in a more restrictive approach to surveillance for intermediate risk patients, the glass is also half full; 80% did not metastasize. The Cleveland Clinic group has reported 98% metastasis free survival at 10 years in a small intermediate risk cohort (7). These favorable experiences present a tantalizing opportunity to better identify the intermediate risk patients who could be managed safely with surveillance using a combination of MRI and genetic tissue based analysis.

The common theme is more accurate risk assessment for a robust clinical end point, i.e., prostate cancer metastasis or mortality. We have come a long way in the last 5 years. MP MRI affords the opportunity to identify the large occult high grade cancers early (8). It is likely that these large missed cancers accounted for the majority of the 30 metastatic cases in the 993 patient Sunnybrook series. MRI has recently been incorporated into risk nomograms that extend the current nomograms based on clinical parameters to incorporate MRI findings. For example, a patient with no risk factors and a mildly elevated PSA, with an a priori risk of significant prostate cancer of 7%, whose MP MRI is normal, will be able to avoid biopsy altogether; this patient's risk of significant cancer is reduced to 1% (6). MRI, however, is not perfect. In the high risk patient, systematic biopsies are required despite a negative MRI.

The field of AS has come a long way since the initial publication in 2002. There are now more than 2,400 publications on the topic of 'AS in prostate cancer', and more than 20,000 patients reported on in prospective series from more than 15 centers all over the world. We have learned how to better select patients; which clinical parameters predict for co-existent higher grade cancer; the natural history of Grade Group 1; the limitations of PSA kinetics as a trigger for intervention; and benefit from the emerging role of MRI and biomarkers.

The controversies and unanswered questions in this field have moved from concept to application. Given the enormous amount of data from randomized trials [PIVOT (9), Protect (10)] and prospective series of conservative management, no informed individual would argue that the principle of conservative management for low

 

risk disease is misplaced. The questions are now related to who, how, when, and what. Future research questions cover a broad swath.

(I) Patient selection.
  (i) What are the molecular events and biomarkers that signal 'progression' of low grade disease? For example, PTEN deletion has been identified as a key step in the progression of prostate cancer, and is present in about 10% of Gleason 6 cancers. However, this deletion on its own may not be sufficient to induce a metastatic phenotype. We are just at the beginning of learning which genetic and epigenetic aberrations alter the behavior of prostate cancer cells. Many other tantalizing mechanisms have recently been identified; for example, the effect of circulating exosomes containing biologically active molecules, i.e., mRNA, shed by more aggressive cancer cells and incorporated into low grade cells resulting in more aggressive behavior. Another priority is determining whether patients with certain known germ line mutations, particularly involving defects in DNA repair, i.e., BRCA or ATM, are candidates for surveillance. We will learn much more about how these aberrant genetic pathways interact over the next decade.
  (ii) How to optimally identify the 'wolves in sheep's clothing'. Nomograms incorporating MRI and/or biomarker findings to predict the risk of co-existent higher grade cancer are needed urgently. Sorting out how to use these tests optimally will require further research. For example: how to manage the patient who has a Pirads 4 lesion whose targeted biopsy shows Gleason 6 cancer. Does the presence of restricted diffusion mean he has a biologically more aggressive cancer despite being Gleason 6; was a higher grade cancer missed; or does it signify nothing? The role of a genetic biomarker in this setting seems obvious, but there is little data on this situation. The field of radiomics, i.e., the molecular events associated with restricted diffusion and other MR abnormalities associated with cancer, is only beginning (11). Similarly, what is the best strategy for a patient with microfocal Gleason 6 cancer whose Prolaris or Oncotype Dx assay reveals a mildly elevated risk score? MRI with targeted biopsy also likely plays a role in this setting but there is little data. How to integrate MRI and biomarkers into treatment decision making is a major research priority.
  (iii) Which intermediate risk patients are candidates for surveillance? Many intermediate risk patients are candidates for surveillance; the key is to identify those with indolent disease accurately. Further studies using molecular biomarkers and MRI to select these patients are warranted.

(II) Ongoing management: once patients have been selected for surveillance, a host of research questions present themselves.
  (i) What interventions (diet, exercise, micronutrients, and pharmacologic agents) are warranted to reduce the risk of biological progression? This is a fruitful and important area for research. Many ongoing studies are evaluating the role of exercise, dietary modification, and naturally occurring micronutrients in men on surveillance. These patients are followed for many years; they are motivated; and a great deal of evidence suggests that prostate cancer progression is amenable to modification by dietary or other influences. Specific questions include the role of exercise; weight loss; reduction of animal protein or carbohydrate in the diet; and the use of natural dietary micronutrients, including Pomegranate, Capsaicin, Lycopene, etc. A host of other compounds have been suggested as being useful in the surveillance setting, so called 'Holistic Surveillance' (12).

  There is also a great deal of interest in the use of common drugs with metabolic or cardiovascular benefits, particularly statins and diabetic medications, i.e., metformin, which appear to inhibit progression of prostate cancer. Clinical intervention trials testing these agents are warranted.
  (ii) What is the most efficient and cost-effective way to follow patients longitudinally? Is serial biopsy still required, and in whom? Can risk stratification allow some patients to minimize the burden of follow up? This is both a

 

quality of life and economic question. An unmet need in the field is excessive reliance on serial biopsy. Can MRI, if negative, replace systematic biopsy; and can targeted biopsy alone (i.e., 2–4 cores) replace the 12–14 core systematic approach? Can patients with a negative molecular biomarker avoid or reduce the frequency of biopsies? Is the NPV of a negative MRI sufficiently high that a biopsy can be safely avoided; and how does the NPV vary according to patient risk? Aside from discontinuing surveillance because of short life expectancy, are there patients whose disease is so predictably indolent that no further follow up is required despite a 15–20 years life expectancy? How do we identify these?

Many national policy groups have recommended against PSA screening, largely due to the risks of overdetection and overtreatment. Can the widespread adoption of surveillance for low risk disease rehabilitate prostate cancer screening and satisfy policy makers and methodologists that the benefits outweigh the risks at an acceptable cost? This will require modeling studies based on recent data.

In summary, research is warranted at the molecular, epigenetic, epidemiological, radiologic, and clinical trials levels.

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## Footnote

*Conflicts of Interest*: The author has no conflicts of interest to declare.

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