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Active Surveillance for Low-Risk Prostate Cancer

Laurence Klotz

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Abstract There is ample evidence that low risk and many cases of low-/intermediate-risk prostate cancer, are indolent, have little or no metastatic potential, and do not pose a threat to the patient in his lifetime. Major strides have been made in understanding who these patients are and in encouraging the use of conservative management in such individuals. A component of conservative management is the early identification of those 'low-risk' patients who harbour higher risk disease, and benefit from definitive therapy. This represents about 30 % of newly diagnosed low-risk patients. A further small proportion of patients with low-risk disease demonstrate biological progression to higher grade disease. Men with lower risk disease can defer treatment, in most cases for life. Men with higher risk disease that can be localized to a relatively small volume of the prostate can undergo selective therapy. The results of active surveillance, embodying conservative management with selective delayed intervention for the subset who are re-classified as higher risk overtime based on repeat biopsy, imaging or biomarker results have shown that this approach is safe in the intermediate to long term, with a 3 % cancer specific mortality at 10–15 years. Further refinement of the surveillance approach is ongoing, incorporating MRI, targeted biopsies and molecular biomarkers.

Keywords Prostate cancer · MRI · Active surveillance · Molecular biomarkers

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L. Klotz (✉)
Division of Urology, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Ave. #MG408, Toronto, ON M4N 3M5, Canada
e-mail: Laurence.Klotz@sunnybrook.ca

Introduction and Background

In a recent special publication entitled '200 Years of Surgery', Atul Gawande concluded 'If the past quarter century has brought minimally invasive procedures, the next may bring the elimination of invasion' [1••]. This observation is nowhere more apt than in the management of localized prostate cancer. The field of prostate cancer treatment is rapidly transitioning towards tissue conserving approaches, including active surveillance and focal therapy. Progress in these areas will be reviewed in this chapter.

PSA testing was widely embraced in North America and many countries in Western Europe beginning in 1989 and continued unabated until 2012, when the US Preventive Services Task Force published a level D recommendation against PSA screening http://www.uspreventiveservicestaskforce.org/uspstf12/prostate/prostateart.htm, followed by ambivalent recommendations by several other respected national health policy organizations https://www.auanet.org/education/guidelines/prostate-cancer-detection.cfm. This remains a topic of intense controversy and disagreement. However, the result has been a steady decline in the rate of PSA testing and referral for biopsy over the last few years.

In areas with high PSA testing, a remarkable phenomenon occurred. Over a 5-year period, there was a threefold increase in the annual age-adjusted incidence of prostate cancer, followed by a gradual decrease. This was accompanied by a steady and dramatic decrease in the median volume of cancer in newly diagnosed men. This was a typical instance of stage migration of cancer, occurring as a result of a new diagnostic test which detects cancer that was previously undiagnosed but prevalent. The new test resulted in the almost immediate diagnosis of hundreds of thousands of men who harboured preclinical prostate cancer; as these prevalent cases were identified and treated, the incidence gradually returned towards

baseline levels (although remained higher than baseline), reflecting the 'true' incidence of the disease.

The USPSTF recommendation against PSA screening was largely due to the risks of overdiagnosis and overtreatment of non-life threatening disease http://www.uspreventiveservicestaskforce.org/uspstf12/prostate/prostateart.htm. Prior to this time, most cases of prostate cancer were treated by either radical prostatectomy or high-dose radiation treatment. However, the task force recommendation, bolstered by substantial evidence regarding the indolent nature of low-grade disease and the favourable outcome with conservative management, has resulted in a widespread re-consideration of these therapies, and an emerging consensus regarding the use of conservative management for low risk, and selected intermediate-risk patients.

The Rationale for Surveillance

Prostate cancer is part of the ageing process and develops 'normally' with age in men from all races and regions. In Caucasians and Blacks, the chance of harbouring prostate cancer is approximately the same as one's age, thirty percent of men in their 30s, 40 % in their 40s and so on [2]. Most of these are microfoci only (<1 mm^3) and low grade. The high prevalence of microfocal prostate cancer has been confirmed in autopsy studies of Caucasians, Asians and other racial groups going back more than 50 years. A recent autopsy study in Japanese and Russian men who died of other causes showed that overall 35 % of both groups had prostate cancer, and 50 % of the cancers in Japanese men aged >70 were Gleason score 7 or above [3]. In Japanese men under 60, the prevalence was lower than that in Caucasians, but there was no difference in men older than 60. This finding suggests that, particularly in men over 70, microfocal Gleason 3+4 might also represent 'overdiagnosis'.

Genetic Features of Low-Grade Prostate Cancer

Genetic analyses comparing Gleason 3 and 4 patterns, the two most common histologic patterns of prostate cancer, have found that the molecular hallmarks of cancer differ profoundly between them. The hallmarks of cancer, described by Hanahan and Weinberg, provide a framework for comparing the degree of malignancy of these subtypes of prostate cancer [4, 5••, 6•].

The six original hallmarks of cancer include unlimited replicative potential, sustained angiogenesis, local tissue invasion, insensitivity to antigrowth signals, metastasis and replicative self sufficiency. The update in 2011 added two more: deregulating cellular energetics and evasion of immune destruction. The genetic pathways responsible for these hallmarks of malignancy have been worked out with precision and in detail (Table 1). The Gleason score has an uncanny and remarkable ability to segregate prostate cancer between genetically normal and abnormal cells (It is rumoured that Don Gleason, the pathologist who described the eponymous grading system, thought that Gleason pattern 3 or less should not be called cancer, but was unsuccessful in convincing his colleagues of this). There are many examples of this distinction. Proliferation pathway-associated genes, including Akt and HER2neu, are expressed normally in Gleason 3 and abnormally in Gleason 4 (Table 1). Genetic pathways mediating apoptosis resistance, angiogenesis and the development of other pro-angiogenic factors, genes involved in regulating cellular metabolomics, and metastasis and invasion processes, are similarly overexpressed in Gleason 4 and normal in 3 [7–16, 19, 20]. There are exceptions; in particular, both phosphatase and tensin homolog (PTEN) [18, 21•] and TMPRSS2-ERG [22, 23], commonly upregulated and present respectively in most Gleason 4s, have been reported to be altered in a proportion of Gleason 3. Given the limits of histology, this is not surprising. However, these isolated genetic alterations do not appear to translate into an aggressive metastatic phenotype.

Table 1 Gleason 3 lacks the hallmarks of cancer

Characteristic of cancer	Gleason 3	Gleason 4
Expression of pro-proliferation embryonic, neuronal, haematopoietic stem cell genes, EGF, EGFR [7]	Not present	Overexpressed
AKT pathway [7]	Not present	Aberrant
HER2neu [8]	Not present	Amplified
Insensitivity to antigrowth signals such as cyclin D2 methylation, CKDN1β [9, 16]	Expressed	Absent
Resistance to apoptosis: DAD1 [12]	Negative	Strong expression
BCL2 [12]	Mostly negative	Upregulated
Absence of senescence: [13]	Normal	Increased
Sustained angiogenesis: VEGF [14]	Expression low	Increased
Other pro-angiogenic factors and microvessel density [15]	Normal	Increased
Tissue invasion and metastasis markers (CXCR4, others) [19]	Normal	Overexpressed
PTEN [18][a]	Present (7 % deleted)	Deleted
TMPRSS2-ERG translocation [22, 23]	Present 45 %	Present 50–60 %
Clinical evidence of metastasis and mortality [24••, 26]	Virtually absent	Present

Metastatic Potential

While some cancers are aggressive, others have little or no metastatic potential and may even involute spontaneously [13]. Several large clinical series have reported a rate of metastasis for surgically confirmed Gleason 6 (where there is no possibility of occult higher grade cancer lurking in the prostate) that approaches zero [24••]. A natural limitation of the conservative (no treatment) management series is that, since the diagnosis is based on needle biopsy, there is no way to exclude the possibility that the patients who progress to metastasis had occult higher grade cancer at the time of diagnosis. This occurs in about 25 % of men initially diagnosed with Gleason 6 on biopsy, and these plausibly are responsible for most of the prostate cancer deaths reported in series of conservative management.

An alternative explanation for the rate of metastasis of surgery for Gleason 6 cancer is that the intervention is highly successful and alters the natural history of the disease. A possible analogy is the surgical management of basal cell carcinomas of the skin, which are almost universally cured by surgical resection, and yet may become lethal if neglected. However, if this analogy holds, one would have expected a few of the Gleason 6 cancers to have micrometastasized prior to surgery or to have a local recurrence with subsequent metastasis. This is rarely seen, if ever. Further, if resection of a small basal cell carcinoma of the skin had the same effects on quality of life as a radical prostatectomy, it is plausible that dermatologists would also be proposing conservative management in the 'low-risk' cases!

One multicentre study of 24,000 men with long-term follow-up after surgery included 12,000 with surgically confirmed Gleason 6 cancer [24••]. The 20-year prostate cancer mortality was 0.2 %. About 4000 of these were treated at MSKCC; of these, one died of prostate cancer; a pathological review of this patient revealed Gleason 4+3 disease [25]. A second study of 14,000 men with surgically confirmed Gleason 6 disease found only 22 with lymph node metastases; the review of these cases showed that all had higher grade cancer in the primary tumour. The rate of node-positive disease in the patients with no Gleason 4 or 5 diseases in their prostates was therefore zero [26] (A limitation of this study was that patients had, in most cases, a limited node dissection; but given the large cohort size, the message is still clear).

Gleason grading is not perfect, and occasional genetic mutations that confer an aggressive phenotype may be prehistologic or may occur as a result of transformation of normal or low-grade cancer cells. A recent genetic analysis of multiple metastatic sites from a patient who had extensive Gleason 4+3 pT3a N1 disease resected at age 47, and died 17 years later of metastatic CRPC, reported that the metastatic lesions appeared to derive from a microfocus of Gleason pattern 3 disease, rather than, as expected, from the high-grade cancers elsewhere in the prostate [27]. A second case report from the same group described a patient on active surveillance with 12 annual biopsies that were negative or showed Gleason 6 cancer only. Biopsies were discontinued for 5 years, until a repeat biopsy performed for a rise in PSA showed Gleason 9 cancer, which had metastasized. Molecular characterization of the biopsies in this patient showed no homology at all between the earlier low-grade cancer and the high-grade cancer [28•]. These case reports are a challenge to the view that Gleason pattern 3 does not behave like a malignancy. It is fair to say in response that (a) biology is complex, dynamic and not 100 % predictable, (b) these are single case reports and should be viewed in that context and (c) it is possible that histological Gleason pattern 3, particularly when it coexists with higher grade cancer, can harbour pre-histological genetic alterations that confer a more aggressive phenotype. This is the conceptual basis for genetically based predictive assays that disaggregate low-grade cancer into low and higher risk groups. Importantly, these cases should be balanced against the extensive clinical evidence supporting the absence of metastatic potential in the vast majority of pure Gleason pattern 3 cancers. Some have proposed that Gleason 3 cancer may evolve as a differentiated clonal offspring of a higher grade cancer that had metastasized, resulting in a shared genetic phenotype [29].

Biomarkers

Several new biomarkers have recently been approved by the FDA based on their ability to predict progression in low-grade prostate cancer patients. These include the Prolaris assay [30] (Myriad Genetics), which looks for abnormal expression of cell cycle-related genes and the Oncotype DX assay (Genome Health) which identifies a panel of genes linked to a more aggressive phenotype [31]. The Decipher assay, a tissue-based 22-marker genomic classifier evaluating non-coding RNA sequences has been demonstrated to accurately predict the risk of biochemical progression after radical prostatectomy [32], The Mitomics assay, which identifies the presence of a functional mitochondrial DNA deletion associated with aggressive prostate cancer [33] is not yet FDA approved. These tests hold the promise of interrogating the microfocus of Gleason 6 found on biopsy to identify the higher grade cancer elsewhere in the prostate. That the biomarkers can achieve this confirms the inter-relationship of heterogeneous multifocal cancers.

These tests, performed on biopsy tissue, are a proxy for predicting future biological behaviour based on identifying genetic alterations in low-grade cancer cells. A patient with low-grade prostate cancer and a strongly

positive Oncotype DX or Prolaris test should have an MRI and be treated according to the result. A further area for research is to better understand how to integrate the results of genetic biomarker tests and MRI. For example, optimal management of the patient in whom results are discrepant (i.e. genetic test indicates high risk but MRI is negative) is currently unknown. False-positive and false-negative results undoubtedly occur with both diagnostic approaches, but how commonly is unknown. While they may meet the unmet need of better risk assignment, further validation of their performance is needed before they are widely adopted in the surveillance scenario.

Role of MRI

All groups have relied on systematic transrectal ultrasound (TRUS)-guided biopsies performed serially, at varying intervals. This technique has significant limitations. Most importantly, TRUS-guided biopsy tends to undersample the anterior prostate, apex and anterolateral horn. Thus, a confirmatory biopsy to target these areas is considered critically important. Since prostate cancer in most cases starts early and takes 10–20 years to reach clinical significance, the delay of 6–12 months in finding occult higher grade cancer is unlikely to alter curability. MRI has an emerging role in the management of AS patients. In these patients, there are two potential benefits: reassurance that no higher risk disease is present in those with no visualized disease and in the subset harbouring higher grade disease, earlier identification of this cancer. With respect to the former benefit, the key metric is the negative predictive value of a negative test. This has been reported to be 97 % for a group of about 300 surveillance candidates at MSKCC [34•]. This observation requires validation. Similarly, an MRI abnormality with a Prostate Imaging Reporting and Data System (PiRADS) score of 4 or 5/5 had a 90 % positive predictive value for high-grade cancer. This abnormality is characterized by a lesion seen on T2-weighted image, with both restricted diffusion and enhanced contrast. Such a lesion in a patient is very significant and should lead at least to a targeted biopsy or perhaps definitive intervention. An equivocal lesion (PiRADS 3/5) should trigger a targeted biopsy.

If the results of single-centre cohorts are validated, this performance of MRI as a diagnostic test would permit a level of confidence in a negative MRI that would allow it to replace the biopsy. This would decrease the number requiring biopsies (a major unmet need) and facilitate early identification of clinically significant disease earlier. A limitation of multiparametric MRI is that the skill set for accurate interpretation is demanding and not yet widely prevalent. This situation is improving rapidly, however.

Impact on Management

Understanding that Gleason pattern 3 has little or no metastatic phenotype has altered the approach to patients with this cancer. Gleason pattern 3, which can invade locally, does fulfil sufficient traditional pathological criteria to be called a cancer, despite its non-metastasizing phenotype (analogous to basal cell carcinoma of the skin or gliomas). However, it clearly does not behave in a lethal fashion, which the word 'cancer' implies to lay people. Changing the terminology away from the emotionally loaded term 'cancer' would significantly reassure the patient and derail the headlong rush into aggressive treatment. Terms like 'pseudo-cancer', 'pseudo-disease', 'part of the ageing process' and 'pre-cancer' may be utilized in counselling these men.

Young age is not a contraindication to conservative management. The benefits of avoiding treatment with respect to maintenance of erectile function and continence are greater in young men, and the risks of second malignancies as sequelae of radiation are also greater in men with a long life expectancy. Microfocal low-grade cancer is present in 40 % of men in their 40s http://www.uspreventiveservicestaskforce.org/uspstf12/prostate/prostateart.htm. Diagnosing this on a transrectal ultrasound (TRUS)-guided biopsy does not mean that disease progression is inevitable. A key point, however, demonstrated in many studies, is that men with high-volume Gleason pattern 3 have a considerably higher risk of harbouring higher grade cancer. The reported 'high volume' of Gleason 3 on biopsy at which point higher grade cancer is more likely to be present is variable. A threshold effect of more than 8 mm of total cancer on systematic biopsy has recently been described [35]. Another approach to the question of the significance of higher volume Gleason 6 has been to use the ERSPC database to identify those patients with clinically significant Gleason 6 cancer. The threshold for clinically significant Gleason 6 disease was a cancer volume of $>1.3\ cm^3$ [36]. This is an important refinement of the traditional definition of $>0.5\ cm^3$, defined by Stamey based on 149 cystoprostatectomy specimens from the pre-PSA era. Thus, the management of these patients is to rigorously exclude the presence of higher grade cancer (based on MRI, targeted/template biopsies and biomarkers). Such patients are unlikely to require treatment.

Given the consensus on the problem of overdiagnosis and overtreatment, the evidence for the indolent nature of low-risk disease, and the concern about occult higher risk disease in some patients, an approach of initial expectant management with selective delayed intervention for the subset who are reclassified as higher risk overtime is sensible. This is also consistent with the current zeitgeist of 'personalized medicine'.

Active surveillance not only offers the prospect of reduced morbidity and improved quality of life, but an improvement in survival. The logic is as follows. PSA screening has been

discarded by policy makers such as the USPSTF because of concerns about overtreatment and a high number needed to treat (NNT) for each death avoided. Selective treatment employing active surveillance would result in a decrease in the NNT for each death avoided. If widely adopted, active surveillance would eventually result in a re-appraisal of the benefits of PSA screening and a greater acceptance of its value by policy makers such as the USPSTF. The result will be 'rehabilitation' of PSA screening, earlier identification of those with aggressive disease, lives saved and an overall reduction in prostate cancer mortality (compared to no screening resulting from the perceived hazards of overtreatment).

Outcome of Surveillance

The commonest cause of death in men on AS is cardiovascular disease. Death from prostate cancer is uncommon. In the most mature surveillance cohort [37, 38••], with a median follow-up of 8 years, the cumulative hazard ratio (or relative risk) of non-prostate cancer death was 10 times that for prostate cancer. To date, the published literature on surveillance includes 13 prospective studies, encompassing about 5000 men [38••, 39–50]. Most of these studies have a duration of follow-up that is insufficient to identify an increased risk of prostate cancer mortality as a result of surveillance. For example, a pivotal Swedish study reported that the risk of prostate cancer mortality in patients managed by watchful waiting was low for many years, but tripled after 15 years of follow-up [51, 52] ('Watchful waiting' meant no opportunity for selective delayed intervention, whereas about 30 % of patients in the surveillance series have had radical treatment). In the Toronto experience, 70 patients have been followed for 14 years; about 1.5 % have had late disease progression, but there is no evidence of a sharp increase in mortality to date [38••]. Thus, a critical question in this field is what the long-term prostate cancer mortality will be beyond 15 years. It will be 5–7 years before the most mature cohorts have a median of 15 years of follow-up. Table 2 summarizes the results of the 13 prospective series. The key outcome measures include the proportion of patients treated, overall, and cause specific survival. Overall, about one third of patients are treated; most series have few or no prostate cancer deaths. The most mature series, from Toronto, has 70 patients followed for 14 years or more; in this group, 5 % have died of prostate cancer. The rate of other cause mortality is 10 times greater than that of the prostate cancer mortality. However, few of the other publications have significant numbers of patients followed more than 10 years.

Table 2 Outcomes of AS in large prospective series

Reference	*n*	Median follow-up (months)	% treated overall; % treatment free	Overall and disease-specific survival (%)	% BCR post deferred treatment
Klotz et al. (2014) [38••] University of Toronto	993	92	30; 72 at 5 years	79 and 97 at 10 years DSS 95 % at 15 years	25 % (6 % overall)
Bul et al. (2013) [39], Multicentre, Europe	2500	47	32; 43 at 10 years	77 and 100 at 10 years	20 %
Dall'Era et al. (2008) [40] UCSF	328	43	24; 67 at 5 years	100 and 100 at 5 years	NR
Kakehi et al. (2008) [41], Multicentre, Japan	118	36	51; 49 at 3 years	NR	NR
Tosian J et al. (2011) [42], Johns Hopkins, USA	407	NR	36; NR	NR	NR: 50 % 'incurable' based on RP pathology
Roemeling et al. (2007) [43], Rotterdam Netherlands	273	41	29; 71 at 5 years	89 and 100 at 5 years	NR [31 % of 13 RP positive margins]
Soloway et al. (2007) [44], Miami, USA	9 9	35	8; 85 at 5 years	NR	NR
Patel et al.(2004) [45], Memorial Sloan Kettering, USA	88	35	35; 58 at 5 years	NR	NR
Barayan GA (2014) [46] McGill, Canada	155	65	20 %	NR	NR
Rubio-Briones J (2014) [47] Spain	232	36	27 %	93 and 99.5 % at 5 years	
Godtman (2014) [48]	439		63 %	81 and 99.8	14
Thomsen (2013) [49] Denmark	167	40	35 %/60 % 5 years		
Selvadurai (2014) [50] UK	471	67	30	98 and 99.7	12

Further, some variation exists with respect to eligibility criteria and triggers for intervention, but there are consistent themes.

Eligibility for Surveillance

Who is a candidate? The 2005 re-classification of the Gleason scoring system resulted in Gleason 2–5 being taken out of the needle biopsy grading. Low-risk disease based on biopsy is widely defined as Gleason 6 and PSA <10 ng/ml. Technically, patients with T stage>T2a are excluded; in fact, most such patients are T1c. This group includes around 45 % of newly diagnosed patients in the USA and Canada, which is approximately 150,000 men per year. Low-risk disease has been stratified into very low and low based on the number of cores, extent of core involvement and PSA density. The Epstein criteria are only one or two cores positive (regardless of how many cores were taken), no core with more than 50 % involvement and PSA density <0.15. The Epstein criteria were based on those biopsy criteria which predicted for the Stamey definition of clinically insignificant disease (<0.5 cm^3 of Gleason 6 prostate cancer). As mentioned above, this definition is too stringent and would exclude many patients with low-risk disease who would otherwise be excellent candidates. Based on the contemporary definition of clinically insignificant disease as being a low-grade tumour volume>1.3 cm^3 [36] (referred to above) and since the number of cores taken at biopsy has increased (to above 80 in patients having template biopsies), these criteria warrant re-definition. Informed by the genetic characterization of Gleason pattern 3 and the clinical experience with Gleason 6, we believe that all Gleason 6 are at very low risk of metastasis. The significance of higher volume disease is as a predictor of occult higher grade cancer. In the absence of higher grade cancer, metastasis is exceedingly unlikely. Thus, these patients require close scrutiny to preclude as much as possible coexistent higher grade disease, but do not necessarily require treatment in the absence of higher grade cancer.

Most patients who are upgraded harbour occult higher grade cancer at the time of diagnosis. However, biological grade progression (Gleason 3 cells giving rise to Gleason 4 or 5 progeny) occurs, but this is uncommon. In the Toronto surveillance cohort, we observed that the likelihood of grade progression increased approximately 1 % per year from the time of the original biopsy [53]. This is a likely estimate of the frequency of grade progression. The implication is that long-term follow-up is required, although in most cases, the Gleason grade remains stable.

Low prostate volume and more specifically a high PSA density (PSA:prostate volume ratio) has been demonstrated in many studies to be a predictor for risk progression. A high PSA density in some surveillance candidates reflects PSA arising from a large occult cancer. Increased caution is warranted in these cases.

In particular, this includes young men (age <50 years) who have extensive Gleason 6 cancer on biopsy. In these patients, uncertainty exists about the risk of true tumour progression overtime, as well as the risk of harbouring occult high-grade disease. It is reasonable to offer these men treatment. Where exactly to draw the line in terms of age and cancer volume is a matter of clinical judgement.

Race may also play a role. African Americans on AS have a higher rate of risk re-classification and PSA failure when treated than Caucasian men [54]. Black men who are surveillance candidates also have a higher rate of large anterior cancers than Caucasians [55]. Japanese men younger than 60 have a lower rate of histological 'autopsy' cancer than Caucasian men. Thus, the finding of low-grade prostate cancer in young Asian men is perhaps less likely to represent overdiagnosis. However, Black and Asian patients diagnosed with low-grade prostate cancer include many men who have little or no probability of a prostate cancer related-death during their remaining lives, and active surveillance is still an appealing option for those who have been appropriately risk stratified.

Modelling

The utility of surveillance compared to surgery and radiation has been modelled by several groups. One propensity score analysis compared 452 men from the Toronto surveillance cohort to 6485 men having RP, 2264 treated with external beam and 1680 with brachytherapy. There was no difference in prostate cancer mortality and an improved overall survival in the surveillance group (due to an increase in other cause mortality in the radiation patients) [56]. A decision analysis of surveillance compared to initial treatment showed that surveillance had the highest QALE even if the relative risk of prostate cancer-specific death for initial treatment vs active surveillance was as low as 0.6 [57] (In fact, it is almost certainly greater than 0.95 at 15 years).

While surveillance has become more widely accepted over the last decade, the modification of the Gleason system in 2005 has, ironically, resulted in a decrease in the number of newly diagnosed Gleason 6 compared to 7 and therefore a smaller proportion of prostate cancer patients eligible for surveillance. There is an increasing recognition that patients with Gleason 3+4=7 where the component of pattern 4 is small (<10 %) have a very similar natural history to those with Gleason 3+3, perhaps reflecting the stage migration phenomenon [58].

Active Surveillance Technique

The clinical management of men on AS has evolved over the last 15 years. Currently, most experienced clinicians use the following approach or a variation of it: Following the initial diagnosis of Gleason 6 prostate cancer on ten or more core systematic biopsy, PSA is performed every 3 months for the first 2 years and then every 6 months. A confirmatory biopsy must be carried out within 6–12 months of the initial diagnostic biopsy on which cancer was identified. This confirmatory biopsy should target the areas of the prostate that have been shown to harbour significant cancer in patients who are initially diagnosed with Gleason 6. These are the areas that are typically undersampled on the initial diagnostic biopsy. This includes the anterior prostate and the prostatic apex and base. If the confirmatory biopsy is either negative or confirms microfocal Gleason 3+3 disease, subsequent biopsies are performed every 3–5 years until the patient reaches age 80 or has a life expectancy <5 years because of comorbidity. Multiparametric MRI should be performed on those patients whose PSA kinetics suggest more aggressive disease (usually defined as a PSA DT<3 years), whose biopsy shows substantial volume increase or who is upgraded to Gleason 3+4, and surveillance is still desired as a management option. Identification of an MRI target suspicious for high-grade disease should warrant a targeted biopsy, or if the lesion is large and unequivocal, intervention.

Overtime, about one third of patients will be re-classified as higher risk for progression and offered treatment. This will depend on the inclusion criteria used for eligibility for surveillance. An inclusive approach, offering surveillance to all patients with Gleason 6 and PSA<15, for example, will include more patients with occult high-grade disease than a narrower approach, restricting surveillance to those who meet Epstein criteria (≤2 positive cores, <50 % involvement of any one core and PSA density<0.15). However, the more stringent eligibility denies the benefits of AS to many men with indolent disease who do not fit the Epstein criteria and thus are discouraged from choosing AS.

Most cases that are upgraded on the confirmatory or initial subsequent biopsy are upgraded based on re-sampling (about 25 % of patients). More than 85 % are upgraded to Gleason 3+4 [59].

We have developed a risk calculator (Fig 1) which incorporates the important clinical parameters associated with grade progression in a surveillance cohort [53]. Note that, based on simple clinical factors, a patient's likelihood of upgrading varies from 10 to 70 %.

Limitations of PSA Kinetics

PSA kinetics are currently used as a guide to identify patients at higher risk, but not to drive the decision to treat. This represents a shift in practice. Until multiparametric MRI became available, men on AS with poor PSA kinetics (doubling time< 3 years) were offered treatment. In the PRIAS multi-institutional AS registry, 20 % of men being treated had intervention based on a PSA doubling time <3 years [39]. In a report of the five men dying of metastatic prostate cancer in the Toronto cohort, all had a PSA doubling time <2 years [60]. The limitation of PSA kinetics is lack of specificity. Vickers, in an overview of all of the studies of more than 200 patients examining the predictive value of PSA kinetics in localized prostate cancer, concluded that kinetics had no independent predictive value beyond the absolute value of PSA [61]. In a

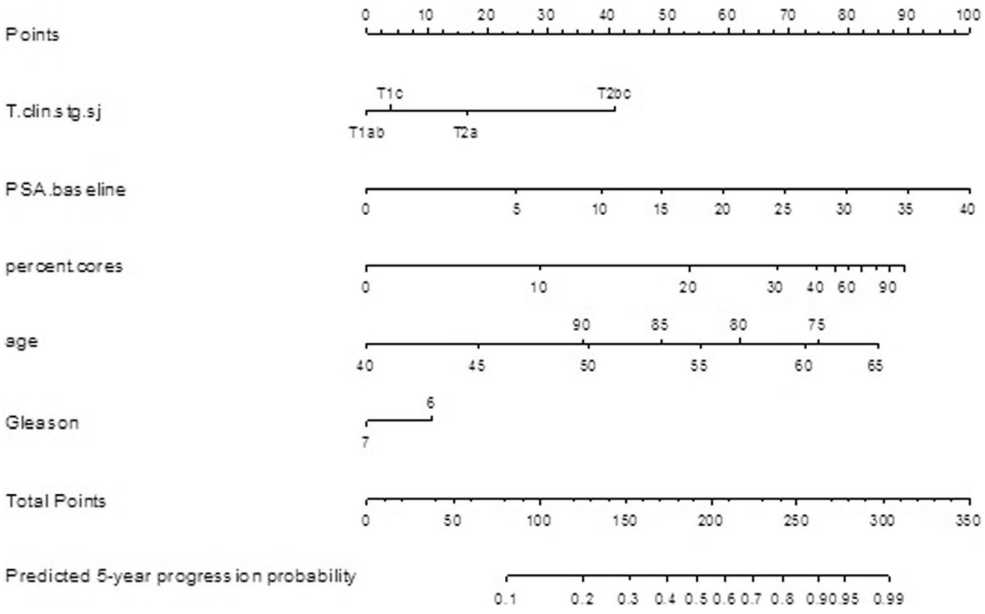

Fig. 1 Risk of pathological upgrading or radical therapy 5 years after diagnosis in men on surveillance in the Sunnybrook cohort

study of PSA kinetics in a large surveillance cohort, false-positive PSA triggers (doubling time<3 years or PSA velocity>2 ng/year) occurred in 50 % of stable untreated patients, none of whom went on to progress, require treatment or die of prostate cancer [62].

Conclusions

Active surveillance, with close monitoring and selective delayed intervention based on risk re-classification overtime, is an appealing approach for low-risk patients and an antidote to the widely recognized problem of overtreatment. Widespread adoption of surveillance would result in a reduction in the number needed to treat for each death avoided without the risk of increasing disease mortality. A dispassionate re-assessment of PSA screening based on these improved metrics should lead to a re-consideration of the value of prostate cancer screening by organizations such as the USPSTF. Further, ongoing improvements in diagnostic accuracy based on multiparametric MRI and genetic biomarkers should reduce the need for systematic biopsies, improve the early identification of occult higher risk disease and enhance the ability to detect patients destined to have grade progression overtime. A minimum standard currently is a confirmatory biopsy targeting the anterolateral horn and anterior prostate within 6–12 months. PSA should be performed every 6 months, and subsequent biopsies every 3–5 years until the patient are no longer a candidate for definitive therapy. MRI is indicated for men with a grade or volume increase or adverse PSA kinetics. Treatment should be offered for most patients with upgraded disease.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Laurence Klotz declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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