Review

Active Surveillance for Low-risk Prostate Cancer

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Abstract. *Surgery, and radiation therapy remain the standard treatments for newly diagnosed prostate cancer patients. Nonetheless, these aggressive treatments are associated with decreased quality of life with altered sexual and urinary functions. Using modern risk stratification, several centers have gained significant experience in identifying patients with a low risk of prostate cancer progression and have adopted an active surveillance program with delayed, selective, or curative therapy. Interestingly, only limited numbers of patients under active surveillance require additional treatment. Recent data suggest that delayed treatment does not appear to alter the clinical outcome among those highly selected patients. A better understanding of the molecular determinants of prostate cancer behavior would not only enable healthcare professionals to identify which cases need aggressive treatment but, perhaps more importantly, would also indicate potential targets for the development of novel therapeutic strategies.*

The annual incidence of prostate cancer (PCa) has more than doubled since the introduction of the prostate-specific antigen (PSA) test. This rise is consistent with the possibility that most PSA-screen-detected cases are overdetected, that is, even without treatment, they would not have become symptomatic. The rate of overdetection of PCa is suggested to be as high as 56% (1, 2). However, PCa is by no means a uniformly indolent condition, being responsible for 3% of all male deaths in the USA and Europe.

The challenge of managing early PCa is to distinguish patients with clinically relevant cancer from those whose disease is destined merely to be an incidental histological event (3). At present, it is not possible to accurately predict PCa behavior in an individual, so a standard approach is to offer curative treatment to all patients with localized disease, while acknowledging that this treatment may be unnecessary in most cases. This approach is far from ideal, not least because of the signi-ficant risks of urinary incontinence and impotence associated with such treatment. This policy of radical treatment for all will become harder to sustain as PSA testing has become more widespread, with associated overdetection.

Using modern risk stratification, certain centers have gained significant experience in better identifying patients with a low risk of PCa progression and have started to use active surveillance (AS) with delayed, selective, or curative therapy (4). Interestingly, only limited numbers of patients under AS require additional treatment. With short follow-up, it appears that delayed treatment in these highly selected cases does not alter outcome.

Active Surveillance

The aim of AS of early prostate cancer is to individualize therapy by selecting for curative therapy only those patients with significant cancers. Patients with favorable tumor characteristics in terms of T stage, Gleason score and serum PSA testing are closely monitored using serum PSA kinetics and repeat prostate biopsies. The choice between radical treatment and continued observation is based on evidence of disease progression, with progression defined in terms of the

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Table I. *Active surveillance vs. watchful waiting.*

	Active surveillance	Watchful waiting
Aim	To individualize treatment	To avoid treatment
Patient characteristics	Fit for radical treatment Age 50-80 years	Age>70 years or life expectancy <15 years
Tumor characteristics	T1-T2, GS≤7, Initial PSA<15 ng/ml	Any T stage, GS≤7, any PSA
Monitoring	Frequent PSA testing Repeat biopsies	PSA testing unimportant No repeat biopsies
Indications for treatment	Short PSADT Upgrading on biopsy	Symptomatic progression
Treatment timing	Early	Delayed
Treatment intent	Radical	Palliative

PSA doubling time (PSADT) and 'upgrading' at repeat biopsy. The aim is to identify cases for treatment long before any symptoms or overt clinical signs of tumor progression are evident (5).

The use of PSADT to guide management is based on the knowledge that preoperative serum PSA concentrations correlate significantly with the volume of PCa in radical prostatectomy (RP) specimens (6), together with the finding that temporal PSA trends in untreated patients conform to an exponential model, suggesting that PSADT is constant over time for a given patient (7). It seems intuitive that PSADT will approximate to the rate of tumor growth. In support of this, PSADT is well established as an important predictor of the risk of metastatic disease (8) and survival (9) in patients with PSA failure after radical treatment.

AS should be distinguished from 'watchful waiting' (WW). WW involves relatively lax observation with late, palliative treatment for those who develop symptoms of progressive disease, whereas AS involves close monitoring, with early, radical treatment in those with signs of progression (5, 10) (Table I).

Selection Criteria for Cancer with Low Risk of Progression

A critical factor for successful AS is the best possible selection of patients with PCa with low risk of progression, *i.e.* insignificant PCa in the RP specimen. Multiple selection or entry criteria based on preference or on experience and not always obtained on hard data have been published (11, 15-23) (Table II). The most common clinical data used to define low-risk prostate cancer include a Gleason score ≤6 (no pattern 4 or 5 disease), PSA level ≤10 ng/ml, and clinical stage T1 to T2a disease. Other characteristics to consider

Table II. *Entry criteria for active surveillance (authors in alphabetic order).*

Source	Entry criteria
Dall'Era *et al.* (17) (Most common clinical criteria)	• Gleason score 6 • No Gleason pattern 4 or 5 • PSA level <10 ng/ml and stable PSA kinetics • ≤50% Single core involvement • ≤33% Positive cores
D'Amico *et al.* (18)	• PSA level ≤10 ng/ml • No Gleason pattern 4 or 5 • Clinical stage T2a or lower
Epstein *et al.* (11)	• Clinical stage T1c • PSA density <0.15 ng/ml • No Gleason pattern 4 or 5 • <3 Positive cores • <50% Cancer per core
Patel *et al.* (20)	• Clinical stage T3 or lower • Gleason sum ≤7
PRIAS (Van den Bergh *et al.*) (23)	• Clinical stage T1c-T2b • No Gleason pattern 4 or 5 • PSA density <0.20 ng/ml • PSA level <10 ng/ml • Fewer than three positive cores
Soloway *et al.* (21)	• Clinical stage T2 or lower • PSA level <15 ng/ml • No Gleason pattern 4 or 5 • <50% Cancer per two positive cores
Van As *et al.* (22)	• Clinical stage T1-T2a • Gleason sum ≤7 (3+4) • PSA level <15 ng/ml • <50% Positive biopsy cores

PRIAS, Prostate Cancer Research International Active Surveillance

Table III. *Prostate cancer aggressiveness risk strata and related care options*[a].

Early-stage prostate cancer aggressiveness category	Measures of prostate cancer severity			Prostate cancer care options
	Gleason score	Clinical stage	Serum PSA	
Low risk	≤6	T1 or T2a	<10	Active surveillance, prostatectomy, brachytherapy, or external radiotherapy
Intermediate risk	≤6	T1 or T2a or b	10-20	Prostatectomy, external radiotherapy with adjuvant androgen suppressive therapy or brachytherapy
	7	T1 or T2a or b	<20	
High risk	≤7	T1 or T2a, b, or c	>20	External radiotherapy with adjuvant androgen suppressive therapy or prostatectomy
	8-10	T1 or T2a, b, or c	Any PSA	

[a]Based on National Comprehensive Cancer Network Treatment Guidelines and D'Amico *et al*. (33)

include PSA density (PSAD) <0.15, positive cores at biopsy <33%, the extent of cancer in any core <50%) and PSA kinetics (stable) before diagnosis (17).

Prospective studies comparing entry criteria for AS protocols with subsequent disease progression and treatment patterns are needed to clarify the best candidates for AS. It is worth mentioning here the Epstein criteria applied in a small series of consecutive studies.

In the original work by Epstein *et al*. conducted on 157 consecutive patients with T1c PCa and published in 1994, criteria such as clinical stage T1c, PSA density <0.15 ng/ml, no Gleason pattern 4 or 5, fewer than three positive cores and <50% cancer per core accurately predicted 73% of cases with insignificant PCa (tumor volume <0.2 cc, pathologic Gleason score <7 and organ-confined disease in the RP specimen) in 73% of cases (11). In a successive study on 163 patients, published by the same group in 1998, 30.7% were found to be insignificant (in this study insignificant prostate cancers were organ confined with tumor volumes less than 0.5 cc and Gleason score less than 7). The model to predict preoperatively insignificant tumor included less than 3 cores involved, none of the cores with greater than 50% tumor involvement and Gleason score less than 7. With this model, to the positive predictive value for insignificant cancer was 94.4% (12). An update study on 237 patients was published in 2004 by the same group. According to the Epstein criteria, organ-confined prostate carcinoma was detected in 91.6% of all patients, whereas the remaining 8.4% of patients were found to have non-organ-confined disease (13). In 2008 Jeldres *et al*. published a European validation study of the Epstein criteria based on a cohort of 366 patients (14). In this series, 24% of patients had unfavorable findings at RP, which consisted of either pathologic Gleason 7-10, disease- or non–organ-confined pathologic stage, or a combination of these characteristics.

It should be emphasized that insignificant prostate cancer is a term that describes the pathologic criteria of the surgical specimen, and no data on the Epstein criteria concerning the natural history of PCa exist. In contrast to insignificant PCa, the term 'indolent' PCa has been introduced to describe prospectively detected PCa with tools such as nomograms (24, 25). Indolent PCa occurs, by definition, early in the natural history. When treated actively, there is an excellent chance of a positive outcome (24).

Risk Assessment of Prostate Cancer with Predictive Models

While the amount of localized PCa has been increasing, the amount of locally advanced cancer has been decreasing during the last decade (26). Due to this stage migration and PCa screening, a considerable lead-time bias occurs because cancers are diagnosed well before they may become clinically evident. In this context, screening may detect many more cases of that may never become clinically evident. Draisma *et al*. detected a lead-time bias based on the European Randomized Study of Screening for Prostate Cancer of 9.9 years up to 13.3 years (27). This was also confirmed by other studies (2, 28). In the ideal case, only potentially curable patients with clinically significant PCa and a significant risk to succumb to PCa would undergo treatment. Predictive models based on a well-performed, extended pattern biopsy at the time of initial diagnosis and assessment should be used to integrate clinical variables and help estimate risk to guide timing and choice of treatment (Table III).

Predictive models. The use of predictive models has been progressively gaining popularity to help clinicians when counseling patients to predict indolent and insignificant cancers (29). Variables such as pretreatment PSA level, biopsy Gleason sum and clinical stage are among the criteria most frequently included in these models. Commonly used tools are the D'Amico risk classification (18), the Kattan nomogram (24) and the Partin tables (30). The accuracy in the prediction of the pathological findings in the RP specimen ranges from 73% to 79% *vs*. 73% for the Epstein criteria. These studies indicate that these statistical tools are similar to the original Epstein criteria for insignificant PCa in their ability to predict pathologically confirmed insignificant PCa, but they offer the advantage of quantifying risks according to variable input of clinical information (15, 32, 33).

A nomogram with which to predict low volume/low-grade PCa in patients with a single positive biopsy core in an extended biopsy scheme has been proposed by Nakanishi *et al*. (31). The nomogram predicted low-volume/low-grade cancer with good discrimination. Calibration of this nomogram showed a good predicted probability. The authors recommended this nomogram for use in selecting patients for AS.

Chun *et al*. developed a nomogram to predict insignificant PCa. Predictors consisted of PSA, clinical stage, biopsy Gleason sum, core cancer length and percentage of positive biopsy cores (percentage positive cores). Insignificant PCa was defined as organ-confined PCa with tumor volume <0.5 cc and without Gleason 4 or 5 patterns. Insignificant PCa was pathologically confirmed in 5.7% of patients. The predictive accuracy of the new nomogram was 90% *vs*. 81% for the older models. (15). One possible reason for this improvement may be the use of cancer-tissue length in the model.

Issues on the Role of Prostate Biopsies in Patient Selection

Some authors have shown that a non-negligible proportion of patients who meet the entry criteria for AS actually harbor aggressive or locally advanced disease if they are submitted to RP (34-38). Ploussard *et al*. provided a detailed analysis evaluating, for the first time, the misclassification rate in patients who could be suitable for an AS program according to different biopsy schemes (39). All of their patients were submitted to a 21-core first biopsy mapped by location. The authors found that patients who could have been selected for AS programs based on a 12-core biopsy scheme showed higher rates of unfavorable PCa characteristics at RP compared to patients who would have been included only in a 21-core biopsy scheme (overall unfavorable PCa: 28.6-35.9% *vs*. 14.0-17.6%, respectively). Interestingly, among patients without cancer evidence in the 12-core scheme but with cancer diagnosed only at the 21-core biopsy, roughly 16% showed unfavorable disease at RP, defined as Gleason score ≥8 or category pT3 or higher. These data showed that a certain proportion of patients initially submitted to AS actually harbors aggressive disease at the time of diagnosis. The data by Ploussard *et al*. (39) could help reduce the misclassification risk by introducing detailed and aggressive biopsy strategies in the initial management of patients submitted to AS.

Follow-up Strategies to Detect Prostate Cancer Progression

Even though different AS follow-up strategies have been adopted (Table IV) (20-22, 40-44), the criteria are somewhat similar. For instance, patients with AS will have to undergo a yearly repeat biopsy at Johns Hopkins Hospital, compared with a repeat-biopsy scheme in Toronto of 12 to 18 months (40, 41, 44). Besides a regular repeat biopsy, regular PSA level testing, digital rectal examination (DRE) and optional transrectal ultrasound studies are warranted (44). During the individual counseling and decision making for AS for low-risk PCa, the clinician has to emphasize that regular follow-up visits are absolutely mandatory and that not overseeing progression constitutes higher risk (45).

The detection of PCa progression in a patient selected for AS remains a continuing challenge. What will serve as the best parameter to correctly identify patients that progress to more aggressive cancer in order not to miss the window of curability is still a matter of debate. At present, the choice between radical treatment and continued observation is based on evidence of disease progression, with progression defined in terms of PSADT and 'upgrading' at repeat biopsy.

PSA testing and PSA kinetics. The PSA level is still of major importance during the decision process. Different studies have underlined the importance of PSA testing and PSA kinetics to predict PCa behavior and to identify the correct timing for more aggressive treatment (46-49).

According to D'Amico *et al*., a rapid pre-treatment PSA rise is associated with an increased risk of dying from PCa (46). The study by Carter *et al*. supports such findings: PSA velocity 15 year before diagnosis was significantly higher in patients who died of PCa (47). Furthermore, Freedland *et al*. showed that the postoperative PSADT is a strong predictor of PCa-specific mortality in patients with biochemical failure following RP (48). Khatami *et al*. also showed that a PSADT of <2 years in patients undergoing surgical treatment following AS was the strongest predictor of biochemical failure (49).

The pitfalls of PSA testing in terms of sensitivity, specificity and reproducibility are well understood (45). PSA level seems to be a valid marker for PCa and its progression; however, novel markers are acutely needed to improve AS monitoring.

Table IV. *Predicting progression during active surveillance (authors in alphabetic order).*

Source	PSA	DRE	TRUS	Rebiopsy
Carter *et al*. (40,41)	Every 6 months	Every 6 months	No mention	Yearly
Dall'Era *et al*. (42)	Every 3 months	Every 3 months	6-12-Month interval	Every 12-24 months
Hardie *et al*. (43)	Every 3-6 months for 2 years, then every 6 months if PSA is stable	Every 3-6 months for 2 years, then every 6 months	Not routine	Not routine
Klotz *et al*. (44)	Every 3 months for 2 years, then every 6 months if PSA level is stable	Every 3 months for 2 years, then every 6 months if PSA level is stable	Optional	At 12-18 months
Patel *et al*. (20)	Every 3 months for 1 year, then every 6 months	Every 3 months for 1 year, then every 6 months	At 6 months	At 6 months
Soloway *et al*. (21)	Every 3 months for 2 years	Every 3 months	No mention	At 6-12 months, afterwards when indicated
Van As *et al*. (22)	Year 1: monthly Year 2: every 3 months Afterwards: every 6 months	Every 3 months for 2 years, then every 6 months	No mention	At 18-24 months, then biannually

DRE, Digital rectal examination; TRUS, transrectal ultrasound; PSA, prostate-specific antigen.

Prostate cancer 'upgrading' at repeat biopsy. Prostate cancer 'upgrading' at repeat biopsy is a major criterion for active treatment (20-22, 40-44, 50-53). The study by van As *et al*. used PSA kinetics profiles, progression of Gleason grade, and increased percentage of cancer per core as indicators to stop AS in patients with low-risk PCa (22). Interestingly, in the cohort of Klotz *et al*., only 4% of patients were treated because of progression of Gleason grade alone (51). The greatest trigger for intervention in the Toronto cohort remained the PSADT, with 21% of the cohort having a PSADT <3 years (52).

Digital rectal examination. Stephenson *et al*. found that patients with stage progression detected by DRE on AS were more likely to have a PSADT <2 years (54). Again, this underlines the importance of PSA kinetics in the progression of presumed clinically insignificant PCa.

Imaging techniques. Current serial imaging techniques, such as ultrasound or magnetic resonance, may also have a potential role, but are unproven. It will be interesting to see whether contrast-enhanced ultrasound can improve the detection of progression.

Outcomes

Multiple studies have reported their experience with AS, but the value of most studies is limited by a relatively short follow-up time (Table V) (20-22, 40-44, 52, 53, 55-58). In a recent study by Van As *et al*. it was found that 20% of patients received delayed radical treatment after a median follow-up of 22 months. Within this time frame, no patient developed metastatic disease or died of PCa (22). Hardie *et al*. reported similar findings at a median follow-up of 42 months (43). Approximately 91% of the patients had a Gleason score ≤6 and 73% a PSA level <10 ng/ml. All patients revealed organ-confined disease in the RP specimen.

Johns Hopkins Hospital experience. In 2002 Carter *et al*. described evidence of PCa progression in 31% of 81 patients (median age 65 years, range 52 to 72 years) with stage T1c prostate cancer who were thought to have small volume prostate cancer, based on needle biopsy findings and PSA density, and followed for more than 1 year with semi-annual PSA and DRE, and annual prostate biopsies (median follow-up 23 months) (40). Of the 81 patients, 25 (31%) had progression of disease at follow-up. 13 patients underwent RP, and 12 of 13 patients (92%) had curable PCa (41). PSA density was significantly higher and the percentage of free PSA was significantly lower in patients with progression compared with patients without evidence of progression.

In 2007, Carter *et al*. updated their experience on AS (41). Of 407 patients, 239 (59%) remained on active surveillance at a median follow-up of 3.4 years (range 0.43 to 12.5 years), 103 (25%) underwent curative intervention at a median of 2.2 years after diagnosis (range 0.96 to 7.39 years) and 65

Table V. *Treatment criteria (authors in alphabetic order).*

Source	Treatment criteria	Median follow-up, months	Percentage of patients with treatment
Carter *et al.* (40, 41)	Gleason score ≥7 on rebiopsy, any pattern 4/5, >2 cores involved, >50% any single core involved	23	31
Dall'Era *et al.* (42)	Gleason score ≥7 on rebiopsy, rising PSA, increase in volume by biopsy parameters	24	21
Ercole *et al.* (55)	Increase in tumor volume, Gleason score progression, urinary symptoms, change of DRE, patient preference	48	7.8
Hardie *et al.* (43)	Rising PSA, clinical judgment	42	14
Klotz *et al.* (44)	PSADT <2 years, Gleason score ≥8 Update 2001: PSADT <3 years Gleason score ≥7 (4 + 3)	64	34
Patel *et al.* (20)	Gleason score increase, PSAV >0.75/year, increase DRE/TRUS detected lesion, increase biopsy volume	44	35
Roemeling *et al.* (32)	PSADT	40	29
Soloway *et al.* (21)	Gleason score increase, PSA and PSADT increase, stage progression, increase biopsy volume, patient preference	45.3 (mean)	<1
Van As *et al.* (22)	PSAV >1 ng/ml per year Gleason score ≥4+3 or >50% cancer per core	22	20

PSA, Prostate-specific antigen. PSADT, PSA doubling time. PSAV, PSA velocity. DRE, digital rectal examination. TRUS, transrectal ultrasound

(16%) were lost to follow-up (12), withdrew from the program (45), or died of causes other than PCa (8). Older age at diagnosis and an earlier date of diagnosis were significantly associated with curative intervention.

Toronto experience. In one of the largest studies by Klotz *et al.* (299 patients), the overall survival rate was 85%, and the disease-specific survival rate was 99.3% at 8 years (52). Again, the median PSADT was 7 years, while 42% had a PSADT >10 years. In agreement with the Johns Hopkins Hospital study, the Gleason grade remained the same in 92% of the cohort (44). Of 24 patients undergoing RP for a PSADT <2 years, 14 patients (58%) were pT3a to pT3c and 2 patients (8%) were N+. Considering it was a low-risk PCa cohort, these numbers seem rather high. However, at the beginning, patients with cT2b disease, PSA values of up to 15 ng/ml and a Gleason score of 7 were included, meaning that these patients were very likely to have more advanced disease. Interestingly, in a recent study, PSADT was increased to 3 years, hoping to improve the outcome of these patients (59).

Miami and UCSF experience. Soloway *et al.* reported on 99 patients undergoing AS with a mean follow-up of 45 months, mean age of 66 years, and a mean PSA level of 5.77 ng/ml (21). On the initial repeat biopsy, about 63% of patients did not have PCa, whereas 34% had PCa with a Gleason sum ≤6. Of these patients, eight underwent treatment (three patients underwent androgen deprivation therapy, and five were treated with curative intent). Of the five patients treated with curative intent, two underwent RP and three chose radiotherapy. These patients were free of biochemical recurrence with a follow-up time of up to 83 months. Kaplan-Meier analyses revealed a 5-year probability of

treatment-free survival on AS of 85%. No patient in this cohort died of PCa. Cox regression analysis identified PSADT and clinical stage as significant predictors to predict progression to treatment.

In a University of California at San Francisco (UCSF) study of 500 patients, 24% received secondary treatment with a median of 3 years following the initiation of AS. In this cohort, 38% of patients had a Gleason grade progression in their repeat biopsy, and this was the greatest driver of secondary treatment (17).

Active Surveillance, Patient Anxiety and Focal Therapy

Concerns about overdetection of prostate cancer and consequent overtreatment of clinically insignificant tumors in combination with the significant morbidity that traditional therapies carry have resulted in questioning the need for radical treatments of PCa for selected groups of patients with low-risk PCa. AS has been introduced as a conservative management option for PCa that closely monitors patients and treats them when progression is identified.

Patient anxiety can be a greater confounder than biochemical progression or other clinical parameters in active surveillance of patients heading into active treatment. There is no doubt that thorough patient education about the low-risk nature of the cancer is the best instrument to circumvent psychological problems, even though cultural, social and intellectual differences cannot be neglected.

Recently, because of technological advances, focal therapy has been introduced to optimize control of low-risk cancer while minimizing the adverse events of whole-gland therapy and the anxiety associated with delayed treatment (60).

The Future

AS may prove to be not just an attractive alternative to immediate radical treatment, but also a step towards a new paradigm for PCa management. AS provides an ideal opportunity for healthcare professionals to improve their understanding of the basis for the extraordinary variation in PCa behavior. If patients receive immediate radical treatment, only 15-25% of them will develop recurrence, which typically is detected years later. Long-term follow-up of large numbers is therefore needed to obtain outcome data to assess the use of candidate biomarkers, and it is impossible to distinguish insignificant tumors from those that are significant but were treated successfully. By contrast, outcome in terms of PSADT is available for all patients on AS within a matter of months, so those candidate biomarkers can be assessed rapidly in a modest number of patients. A better understanding of the determinants of PCa behavior would not only enable healthcare professional to identify which cases need treatment but, perhaps more importantly, would also indicate potential targets for the development of novel therapeutic strategies.

Molecular makers. Multiple susceptibility genes and many additional mechanisms involved in carcinogenesis and cancer progression have been discovered (61). However, no single biomarker capable of improving the common clinical parameters included in the currently used predictive models has yet been identified (62).

Epigenetic events, mainly DNA hypermethylation at various gene loci, are of major importance during prostate carcinogenesis and progression. DNA hypermethylation was introduced about 25 years ago by Vogelstein *et al*. (63), while Nelson *et al*. introduced *GSTP1* hypermethylation as a central part of prostate carcinogenesis (64). One study comparing the *GSTP1* hypermethylation status in serum samples of patients undergoing RP showed it to be the single most powerful predictor of biochemical recurrence in patients with presumed localized cancer (65).

A promising study from Demichelis *et al*. demonstrated an association of the *TMPRSS2:ERG* gene fusion with PCa-specific mortality (66). They suggested that PCa containing the *TMPRSS2:ERG* fusion gene may have a more aggressive phenotype, possibly mediated through increased *ERG* gene expression (66).

The study by Haese *et al*. investigated the use of PCA3 in a rebiopsy setting of patients with a negative prostate biopsy. In their work, the risk to detect PCa increased with increasing PCA3 scores (67). These findings were also supported by Nakanishi *et al*. in a North American study (68). Contrary to this, Deras *et al*. found that PCA3 testing is independent of tumor volume, thus the true value of the test in the setting of AS remains unclear at this point (69).

In a study by Tosoian *et al*. in patients with low-risk PCa who were carefully selected for active surveillance, PCA3 score was not significantly associated with progressive disease in the short term (70). While there was a trend toward higher PCA3 scores in patients with high grade disease on surveillance biopsy, significant overlap between the groups prevented the identification of a threshold PCA3 score for clinical use.

Assessment of therapeutic agents. AS could also provide an attractive setting for the assessment of therapeutic agents. Cancer prevention trials typically require tens of thousands of healthy subjects, at low risk of developing cancer, followed up for decades. Patients with early PCa on AS could take part in trials of prevention strategies, with the aim being the prevention of clinically significant disease. Prevention strategies could be rapidly tested in small numbers of patients, with early endpoints based on PSADT, functional imaging, and repeat biopsies. This novel approach to clinical trials could accelerate progress towards a situation

where the management of early PCa will be based on observation, with the selective use of therapies designed, not to eradicate the disease, but to alter its natural history.

Conclusion

AS is a new strategy that aims to individualize therapy by selecting only those patients with significant cancer for curative therapy. Patients with favorable tumor characteristics are closely monitored using serum PSA concentrations and repeat prostate biopsies. The choice between radical treatment and continued observation is based on evidence of disease progression, defined in terms of the PSADT and 'upgrading' at repeat biopsy.

As is well-known from clinical practice, the diagnosis of cancer dramatically changes the lives of every patient and their families. Additionally, the decision-making process of therapy choice has become complicated. Interestingly, only limited numbers of patients under AS require additional treatment (58, 71). It should be recognized that prognostic risk assessment is far from perfect, but there is plenty of time to provide counsel and to discuss all available treatment options.

AS provides an excellent opportunity for studies to identify markers of PCa behavior. Knowledge of PCa biomarkers would have an immediate effect on clinical decision-making and would also identify targets for the development of novel therapeutic strategies. In the longer term, AS may accelerate progress towards a new treatment paradigm for early PCa based on the selective use of therapies designed, not to eradicate the disease, but to alter its natural history.

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