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REVIEW ARTICLE

Role of histopathology and molecular markers in the active surveillance of prostate cancer

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Abstract

Surgery or radiation therapy remain the standard curative treatments for newly diagnosed prostate cancer patients. Nonetheless, these aggressive treatments are associated with decreased quality of life with altered sexual and urinary functions. The objective was a systematic review of active surveillance protocols to investigate the role of histopathology and molecular markers in the active surveillance of prostate cancer. Medline was searched using the following terms: prostate cancer, active surveillance and expectant management. *Selection criteria, follow-up strategies and outcomes*. Using modern risk stratification, several centres have gained significant experience in identifying patients with a low risk of prostate cancer progression and have adopted an active surveillance program with delayed 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. *The future and conclusions*. A better understanding of the molecular determinants of prostate cancer behaviour 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 aim of active surveillance (AS) of early prostate cancer is to individualise therapy by selecting for curative therapy only patients with significant cancers. Patients with favourable tumour characteristics in terms of clinical T stage, Gleason score and serum prostate specific antigen (PSA) testing are closely monitored using serum PSA kinetics and repeat prostate biopsies. The choice between continued observation and radical treatment is based on evidence of disease progression, with progression defined in terms of 'upgrading' at repeat biopsy and PSA doubling time (PSADT). The aim is to identify cases for treatment long before any symptoms or overt clinical signs of tumour progression are evident [1].

AS should be distinguished from 'watchful waiting'. The latter 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 [1–3].

Selection criteria

A critical factor for successful AS is the best possible selection of patients with prostate cancer with low risk of progression (Table I). Patients with an identifiable low risk of progression are most likely to be safely observed and treated only when necessary. Epstein et al. introduced prostate biopsy criteria to predict insignificant prostate cancer (PCa) in the radical prostatectomy (RP) specimens [4]. In addition to the original Epstein criteria, multiple selection or entry criteria, based on preference or on experience and not always obtained on hard data, have been published [1,4–9] (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

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Table I. Prostate cancer aggressiveness risk strata and related care options.

Early Stage Prostate Cancer Aggressiveness Category	Measures of prostate cancer severity			Prostate Cancer Care Options
	Biopsy Gleason Score	Clinical Stage	Serum PSA (ng/ml)	
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	

level ≤10 ng/ml, and clinical stage T1 to T2a disease. Other characteristics which have been used include PSA kinetics (stable) before diagnosis, PSA density (PSAD) <0.15 ng/ml/cm^3, percent positive cores at biopsy <33%, and the extent of cancer in any core <50% [1]. The percentage of core involvement and percentage positivity of the biopsies are both dependent on the length and number of cores respectively. Measurements of cancer length may be more helpful. Prospective studies comparing entry criteria for AS protocols with subsequent disease progression and treatment patterns are needed to clarify the best candidates for AS.

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

Source	Entry criteria
Dall'Era et al. [1] (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. [5]	PSA level ≤10 ng/ml No Gleason pattern 4 or 5 Clinical stage T2a or lower
Epstein et al. [4]	Clinical stage T1c PSA density <0.15 ng/ml/cm^3 No Gleason pattern 4 or 5 <3 positive cores <50% cancer per core
Patel et al. [6]	Clinical stage T3 or lower Gleason sum ≤7
PRIAS* (Van den Bergh et al.) [9]	Clinical stage T1c–T2b No Gleason pattern 4 or 5 PSA density <0.20 ng/ml/cm^3 PSA level <10 ng/ml Fewer than three positive cores
Soloway et al. [7]	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. [8]	Clinical stage T1–T2a Gleason sum ≤7 (3 + 4) PSA level <15 ng/ml <50% of biopsy cores positive

*PRIAS, Prostate Cancer Research International Active Surveillance.

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 harbour aggressive or locally advanced disease if they are submitted to RP [10]. 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 [10]. 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 unfavourable prostate cancer characteristics at RP compared to patients who would have been included only in a 21-core biopsy scheme (overall unfavourable prostate cancer: 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 unfavourable 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 harbour aggressive disease at the time of diagnosis. The data by Ploussard et al. [10] could help reduce the misclassification risk by introducing high density 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 III) [6–8,11–15], the criteria are somewhat similar. Besides a regular repeat biopsy, regular PSA level testing, digital rectal examination (DRE) and optional transrectal ultrasound studies are warranted [15].

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

Source	PSA	DRE	TRUS	Rebiopsy
Carter et al. [11,12]	Every 6 months	Every 6 months	No mention	Yearly
Dall'Era et al. [13]	Every 3 months	Every 3 months	6–12-month interval	Every 12–24 months
Hardie et al. [14]	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. [15]	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. [6]	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. [7]	Every 3 months for 2 years	Every 3 months	No mention	At 6–12 months, afterwards when indicated
Van As et al. [8]	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.

The detection of prostate cancer 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 'upgrading' at repeat biopsy and PSADT.

Prostate cancer 'upgrading' at repeat biopsy is a major criterion for active treatment [6–8,11–17]. 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 prostate cancer [8]. Interestingly, in the cohort of Klotz et al., only 4% of patients were treated because of progression of Gleason grade alone [16]. The greatest trigger for intervention in the Toronto cohort remained the PSADT, with 21% of the cohort having a PSADT <3 years [17].

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 IV) [6–8, 11–15,17–19]. However, recent data suggest that delayed treatment does not appear to alter the clinical outcome among those highly selected patients. 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 prostate cancer [8]. Hardie et al. reported similar findings at a median follow-up of 42 months [14]. 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.

The future

AS provides an ideal opportunity for healthcare professionals to improve their understanding of the basis for the extraordinary variation in prostate cancer behaviour. A better understanding of the molecular markers of prostate cancer behaviour 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 markers

Multiple susceptibility genes and many additional mechanisms involved in carcinogenesis and cancer progression have been discovered [20–23]. However, no single biomarker capable of improving the common clinical parameters included in the currently used predicting models has yet been identified in any prospective active surveillance series.

The Prostate CAncer gene 3 (PCA3) assay is a novel tool that might aid in the diagnosis of prostate cancer and that might indicate the significance of the disease [24,25]. The PCA3 urinary assay might be used to guide biopsy decisions in: (i) men with an elevated serum total prostate specific antigen (tPSA) level and one or more previous negative biopsies; (ii) men with a normal tPSA level and a family history of prostate cancer; (iii) men with an elevated tPSA level (2.5–10 ng/mL) and no previous biopsy; (iv) men with an elevated tPSA level and a concomitant urinary condition. In addition, in men diagnosed

Table IV. Treatment criteria (authors in alphabetic order).

Source	Treatment criteria	Median follow-up, months	Percentage of patients with treatment
Carter et al. [11,12]	Gleason score ≥7on rebiopsy, any pattern 4/5, >2 cores involved, >50% any single core involved	23	31
Dall'Era et al. [13]	Gleason score ≥7 on rebiopsy, rising PSA, increase in volume by biopsy parameters	24	21
Ercole et al. [18]	Increase in tumor volume, Gleason score progression, urinary symptoms, change of DRE, patient preference	48	7.8
Hardie et al. [14]	Rising PSA, clinical judgment	42	14
Klotz et al. [15]	PSADT <2 years Gleason score ≥8 Update 2001: PSADT <3 years Gleason score ≥7 (4 + 3)	64	34
Patel et al. [6]	Gleason score increase, PSAV >0.75 ng/ml per year, increase DRE/TRUS detected lesion, increase biopsy volume	44	35
Roemeling et al. [19]	PSADT	40	29
Soloway et al. [7]	Gleason score increase, PSA and PSADT increase, stage progression, increase biopsy volume, patient preference	45.3 (mean)	<1
Van As et al. [8]	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.

with prostate cancer, the PCA3 assay could aid in the decision of whether active therapy is needed or active surveillance is appropriate. In a study by Tosoian et al. in patients with low risk prostate cancer who were carefully selected for active surveillance PCA3 score was not significantly associated with progressive disease in the short term [26]. 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. Therefore, the true value of the test in the setting of AS remains unclear at this point.

Conclusions

AS is a new strategy that aims to individualise therapy by selecting only those patients with significant cancers for curative therapy. Patients with favourable tumour characteristics are closely monitored using serum PSA concentrations and repeat prostate biopsies [27]. 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 provides an excellent opportunity for studies to identify molecular markers of prostate cancer behaviour and of assessment therapeutic agents.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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