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Platinum Priority – Editorial

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Active Surveillance for Low-risk Prostate Cancer: Will it Become Obsolete?

Monique J. Roobol *

Department of Urology, Erasmus University Medical Centre, Rotterdam, The Netherlands

With the introduction of serum prostate-specific antigen (PSA) testing for detection of prostate cancer (PCa), the incidence of the disease has risen dramatically. As early as 1991 there was concern whether screening for PCa would also detect cancers that might never harm the patient [1]. Nevertheless, in the 1990s there was a general feeling of optimism since, contrary to before, the cancers that were detected were predominantly localized and thus considered curable. The vast majority of cases were actively treated using either surgery or radiation [2].

However, awareness of the PCa prevalence of 30–50% in autopsy studies and the generally slow natural history of the disease soon led to questions regarding the need for invasive therapy for many patients with newly diagnosed PCa. The first report on a new concept called active surveillance (AS) appeared in 2001 and described results from a study initiated in 1995 that included 206 patients with low-risk PCa followed with PSA testing and digital rectal examination; a PSA doubling time of <2 yr triggered prostate biopsy. The actuarial probability of freedom from disease progression was 67% (±12%) at 4 yr, suggesting that up to two-thirds of men could be spared radical treatment with this approach [3]. In the years after, many (mostly single-center) studies on AS were initiated with different inclusion criteria and follow-up strategies. In 2006 the global web-based PRIAS study (www.prias-project.org) was initiated, which currently includes more than 6000 men. In 2014 the Movember GAP-3 project was started to gather many of the worldwide AS registries together in one database, which currently includes data for more than 13 000 patients with low-risk PCa [4]. These national and global initiatives have considerably increased our knowledge on the course of low-risk PCa and different AS strategies and form the basis of current recommendations. In addition, they resulted in a trend towards broadening the initially very strict inclusion and follow-up criteria [5–7]. Nowadays the majority of men with low-risk PCa are initially treated with AS.

The essence is thus to distinguish PCa patients with disease that becomes aggressive during their lifetime and for which curative therapy is strongly warranted from those with indolent malignancy for which conservative management is equally efficacious. In this context, this issue of *European Urology* includes a study by Carter et al. [8] that provides a first indication that genetic testing might assist in the inclusion or perhaps better exclusion of men for AS. In a cohort of 1211 patients of whom 97.6% had Gleason grade (GG) 1 disease, the authors tested whether germline mutations (*BRCA1/2* and *ATM* in a three-gene panel) were associated with grade reclassification (GR) defined as an increase in GG group. After median follow-up of 4 yr, 289 men showed GR; 11 of 26 men with mutations and 278 men among the 1185 noncarriers (hazard ratio 1.96, 95% confidence interval 1.004–3.84; $p = 0.004$). The association between GR and mutation carrier status was strongest for *BRCA2* and among men with BRCA2 mutations who were reclassified to GG >3. The authors concluded that within this cohort of men with predominantly low-risk disease (virtually all based on random systematic biopsy) assessment of mutation status can help in informing decisions between AS and curative intervention.

A few critical notes are in order. First, it is unclear whether these findings influence the decision to opt for AS or the decision to perform a prostate biopsy or switch to active treatment while on AS.

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* Department of Urology, Erasmus University Medical Centre, Rochussenstraat 125, Rotterdam 3015 EJ, The Netherlands. Tel. +31 6 50001743; Fax: +31 10 7035315.
E-mail address: m.roobol@erasmusmc.nl.

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In this context, it must be noted that it is questionable whether the endpoint used indeed reflects disease progression. Knowing the considerable rate of undergrading with the systematic biopsy approach and looking at the "cumulative incidence of upgrading" figures showing that most of the so-called upgrading occurred at the time of the 1-yr repeat biopsy, it is more likely that these figures actually reflect reclassification of the disease. In this context it is important to note that the use of the magnetic resonance imaging (MRI) targeted biopsy (TBx) can result in so-called "risk inflation" whereby a PCa that is deemed suitable for AS may be more accurately sampled at TBx and found to include higher-risk features than when it was sampled in a routine systematic manner. Appropriate risk thresholds are not yet fully understood when an MRI ± TBx strategy is used, and again the risk of overtreatment should be considered [9].

The number of men with germline mutations in DNA repair genes is very low and it might be more relevant to perform mutational analyses on tumor tissue rather than normal blood DNA. This will also reveal somatic mutations. In addition, most of the disruptive DNA mutations in cancer cells will also be measurable at the mRNA level. This provides an opportunity to combine germline and somatic mutational analyses with gene expression profiles, such as the Oncotype DX, Prolaris, and Decipher tests. With all the technical possibilities now available, the potential of omics analyses of cancers seems limitless and ongoing omics analyses of cancers, combining changes in DNA, RNA, protein, and metabolites, will provide a comprehensive overview of tumor alterations with complementary biomarker efficacy. Although they are all technically feasible, verification of whether *BRCA1/2* and *ATM* mutational analyses and gene expression profiling provide significant additive prognostic value in contemporary, often nomogram-driven diagnostic procedures is required, including cost-effectiveness.

AS certainly has the potential to reduce the harms of unnecessary invasive therapy. It is encouraging to see that AS is considered an option not only for (very) low-risk disease but now also for selected cases of intermediate-risk disease and younger men. This shift is also reflected in the report by Carter et al. [8]. In their introduction, AS is only considered suitable for favorable-risk PCa, while the discussion of the manuscript states that AS is suitable for both favorable-risk and intermediate-risk PCa.

One thing is certain: overdetection needs to be avoided as much as possible, and the burden of becoming a PCa patient, despite the option of AS, is something that should not be underestimated. It is encouraging to see that upfront risk stratification, and MRI and TBx if indicated, can already reduce potential overdiagnosis by more than 60% [10].

Conflicts of interests: The author has nothing to disclose.

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