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Real-time Watchful Surveillance Looks Like Active Waiting

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Once upon a time, many years ago, when active surveillance (AS) had not yet been invented, and there were hardly any computers that could manage the heavy computational load for Markov modeling, a cohort of men diagnosed with prostate cancer initially decided not to be treated; this sounds like a fairy tale, but it was only 20 yr ago. The substantial cohort of more than 600 Finnish, Swedish, and Dutch men participated in the ERSPC prostate cancer screening trial and were observed until death. No-one followed a structured monitoring protocol with scheduled repeat biopsies, and switches to active therapy were not related to potential signs of progression. The overall 10-yr survival was 77%, and no man died of prostate cancer [1], which represents excellent results.

This was not the first group on expected management. T1a disease (<5% of transurethral resection of the prostate samples positive for prostate cancer) was still frequently seen because medical treatment for obstructive clinical benign prostatic hyperplasia was not that common. The guidelines at that time advised no further diagnostic or therapeutic interventions in cases with well-differentiated adenocarcinoma. Outcomes were good, with disease-specific survival of >95% at 15 yr [2].

Men diagnosed with low-risk prostate cancer may choose monitoring instead of invasive treatment to avoid unwanted side effects of (immediate) treatment. Alternatively, they may opt for maximal security and control by following protocols including rebiopsy, imaging, and even genetic profiling of their tumor. Or they may choose minimal monitoring by deciding not even to repeat prostate-specific antigen (PSA) measurements and to wait for certain symptoms to occur: the traditional watchful waiting (WW). Most men who are comfortable with the ease of an annual medical check-up like to follow their PSA periodically, and certainly when they are older than 75 yr or when serious comorbidity exists. They invent their own follow-up protocol with which they are satisfied: active waiting.

The modeled comparison of different AS protocols and WW in the article by Loeb et al [3] helps in advising men with low-risk tumors according to the traditional parameters of Gleason score, estimated tumor size (in line with the number of positive cores in systematic biopsies), and PSA levels. Indeed, we are unable to provide level 1 scientific evidence from clinical studies, and we will never be able to. The modeling tries to map uncertainties around the impact of events such as biopsies and treatment on quality of life (QOL) as much as possible by using utilities taken from the literature.

The model illustrates the theoretical remaining (quality-adjusted) life expectancy after diagnosis of localized prostate cancer when following either a WW approach or an AS protocol, assuming 100% compliance with the different diagnostic tests. But real life is different. Strict compliance to protocols appears to be difficult for patients and physicians [4,5], and protocol adjustment over time to preferences that minimize diagnostic interventions including biopsies and PSA measurements is evident. We do not know about imaging compliance, and this might be very dependent on nonmedical factors such as availability and reimbursement of costs.

Some of the authors' conclusions follow our intuition and are self-evident. Following a strict protocol (including invasive treatment when tumor reclassification towards higher risk occurs) provides better clinical outcomes than waiting for symptoms of metastatic disease. Men with localized prostatic tumors will know that, because they have been confronted with that information by the time

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they choose AS instead of immediate invasive treatment to avoid overtreatment. It is the predicted overall better QOL they are choosing [6], and this is exactly the most uncertain factor in the modeling.

The article suggests introduction of a new paradigm for personalized tailoring of diagnostic tests and treatment; this has been argued before for screening and later stages of the disease, for example [7]. The tailoring (ie, adapting the frequency of PSA testing or switching to active treatment) will then be based on an individually assessed probability-based criterion instead of a rule-based criterion. As we still are unaware of the value of imaging or genomics in risk assessment, current designs for this type of probability-based protocol can only be reliably assessed using large data sets with sufficient events, such as the data compiled in the GAP3 Movember database initiative with traditional parameters [8].

The actual differences in outcome between AS protocols and WW appear to be small, as illustrated in the traditional cohorts mentioned above and the data derived from the current modeling study. Taking into account the burden of repeat testing, AS may even look worse than doing nothing (waiting).

But this is 2017, and we have markers, imaging, and genomics. In many countries around the world, the acceptance and reliability of AS are very high and still increasing (in Scandinavian countries and the Netherlands, 95% of men with low-risk tumors are on AS [9]), which might partly be a result of offering monitoring technology and of increasing detection of more low-risk tumors. Especially for men in their fifth or sixth decade of life, choice of a WW strategy while on conservative management is nonexistent: when informed of the current diagnostic tests, they all opt for AS. The tradeoff between more and less intense methods of monitoring only counts for men aged $\geq$65 yr. For those aged $>$75 yr, making a choice is irrelevant, and one can stop offering or selecting any form of monitoring. Thus, AS for low-risk prostate cancers is better than doing nothing, especially for those younger than 65 yr. But doing nothing has already yielded excellent results, so it remains a challenge how exactly to balance the benefit of improved clinical outcome versus the harm of repeat testing.

Most important, however, remains the ability to avoid diagnosis of low-risk prostate cancers. The harm of unnecessarily becoming a cancer patient cannot be reversed by WW or AS.

Conflicts of interest: The authors have nothing to disclose.

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