



Editorial – referring to the article published on pp. 475–482 of this issue

Watching the Face of Janus – Active Surveillance as a Strategy to Reduce Overtreatment for Localised Prostate Cancer

Ola Bratt*

Department of Urology, University Hospital of Lund, SE-221 85 Lund, Sweden

Prostate cancer is a disease with the two faces of Janus: having one benevolent face of small, indolent tumours, abundant among middle-aged and elderly men, it also has the grim face of a great killer, being the second most common cancer-related cause of death within the European Union and in the United States [1,2]. Because symptomatic prostate cancer most often is incurable, efforts are made to diagnose the disease in a preclinical, asymptomatic stage. At present, screening with prostate-specific antigen (PSA) is the best method available to identify men with curable prostate cancer. Following repeated screening, almost all patients are diagnosed with clinically localised tumours, the vast majority of which are also pathologically organ confined and curable [3]. However, we know that many patients with prostate cancer detected by screening would not develop lethal, and some not even symptomatic, disease during their entire lifetime even if left untreated. In the United States where screening is common, the cumulative incidence of prostate cancer is 17% at the age of 85 yr, whereas prostate cancer is the cause of death for 2% who die before that age, a ratio of 8.5:1 [2]. In Sweden, where <10% of the male population is screened for prostate cancer, the corresponding figures are 24% and 4%, a ratio of 6:1 [4]. This constitutes a veritable dilemma for urologists and oncologists when counselling patients with localised prostate cancer. For which patient will Janus show his benevolent smile throughout life and for which patient will he turn

around and show the ruthless face of painful skeletal metastases and death?

Fortunately, it seems that the decision to treat or not to treat the patient with localised prostate cancer does not always have to be made immediately following diagnosis. In this issue of *European Urology*, Roemeling et al. report on the outcome for 293 patients with low-risk, localised prostate cancer diagnosed during the first screening round of the Dutch part of the European Randomized study of Screening for Prostate Cancer (ERSPC) [5]. Of these, 64 patients were managed with active surveillance, whereas the others received immediate treatment with either radical prostatectomy or radiotherapy. After a median follow-up of almost 7 yr, none of the 64 patients initially managed with active surveillance developed skeletal metastases or died from prostate cancer. Eight (18%) of the 64 patients died from other causes, 15 (23%) received deferred treatment with curative intent and 4 (6%) received endocrine therapy, leaving more than half of them alive with no treatment. In the entire group of 293 patients with low-risk prostate cancer the prostate cancer-specific survival rate was 99% and the overall survival rate was 85% at 8 yr.

Similar results are reported from Toronto in Canada [6], Baltimore in the United States [7], Sutton in the United Kingdom [8], and Gothenburg in Sweden [9]. Although all these reports conclude that deferred curative treatment is feasible following initial active surveillance and that the majority

of patients are still untreated after several years of follow-up, some critical issues must be elucidated before this alternative to immediate radical therapy can be recommended to patients with a long life expectancy.

First, how should low-risk, localised prostate cancer be defined? The definition made by Roemeling et al. includes patients having only one or two biopsy cores with cancer, a Gleason score of ≤ 6 , a PSA level of ≤ 15 ng/ml, a PSA density of ≤ 0.2 ng/ml/cc, and a clinical stage of T1c or T2 [5]. This definition is similar, but not identical, to those by the Toronto, Baltimore, Sutton, and Gothenburg groups. The critical issue is: How great is the risk that the patient's prostate cancer is already at the edge of "the window of opportunity" and should be treated without delay? Most urologists and oncologists agree that patients with a life expectancy of >10 yr should be recommended immediate treatment if there is a significant proportion of Gleason grade 4 or 5 in the tumour. The problem in this respect is that sampling of the prostate with transrectal biopsies commonly underestimates the Gleason score of the tumour compared to the prostatectomy specimen. Roemeling et al. based their categorisation of patients into the low-risk group on sextant biopsies [5], which clearly are inadequate for predicting the true Gleason score of the tumour [10]. If a patient has had one set of biopsies only, especially if fewer than 10 cores were taken and the patient is comparatively young and healthy, it seems prudent to recommend a new set of biopsies before the decision to embark on active surveillance is made.

Second, what is the risk that the tumour dedifferentiates over time? Roemeling et al. did not include scheduled biopsies in the follow-up of their patients [5], whereas the Baltimore group recommended annual biopsies and the Toronto group performed a new set of biopsies after 1.5–2 yr of surveillance [6,7]. The latter two groups report higher Gleason scores in 4–8% of patients rebiopsied during follow-up [6,7], but it is not possible to know whether this represents a true progression of tumour grade or merely that tumour areas with higher grade were missed by the initial set of biopsies. Regardless of the answer to that question, it seems wise to include new biopsies in the follow-up, at least of younger patients.

Third, what parameters can reliably predict the development of lethal prostate cancer? They must herald progression before the disease becomes incurable, which for prostate cancer equals when the primary tumour seeds metastases. Prostate cancer is most often a slowly progressing disease, but metastases occur at a comparatively small tumour volume (e.g., compared to renal cancer,

which has an excellent prognosis if the primary tumour is <7 cm, a tumour volume 30 times larger than when prostate cancers commonly are incurable). Most likely, the chance for cure is decreased substantially when tumour progression is obvious with digital rectal examination or transrectal ultrasound. In the study of Roemeling et al., increasing PSA was the most common reason for deferred treatment [5], which is in accordance with other reports [6–9]. One of the criteria set up by the Toronto group for changing from surveillance to active treatment is a calculated PSA doubling time <2 yr, although according to their later experience 3 yr may be more appropriate [6]. One problem with PSA as a marker of tumour progression is that poorly differentiated tumours produce less PSA than slowly growing, well-differentiated tumours. Another problem is that many patients with low-risk localised prostate cancer have benign prostatic hyperplasia, which in many cases contributes to most of the PSA measured in plasma. A small but comparatively rapidly progressing cancer in a large gland may not give rise to a short PSA doubling time until metastases are seeded. This problem may to some extent be overcome by correcting the PSA value for the size of the benign hyperplasia as suggested by the Toronto group [6].

Fourth, at what intervals should the patients be reassessed? Most groups reporting on active surveillance have visits scheduled every third month for the first 1–2 yr and every sixth month thereafter. For the majority of patients tumour progression is slow and not much happens from one year to another, but will biannual visits detect progression for all patients with potentially lethal disease? Our knowledge on the biology of the progression from localised prostate cancer to metastatic disease is still too scarce.

Fifth, what is the appropriate information to be discussed with the patient before the treatment strategy for localised prostate cancer is decided? The study by Roemeling et al. contributes significantly to our knowledge, but we need more long-term data assessing the risks and benefits of active surveillance to present to our patients. In some countries, the patient has to sign a written informed consent prior to major surgery. In many aspects, postponing potentially curative therapy for cancer is as important a decision as accepting it, and written informed consent could be appropriate.

Sixth, How does active surveillance for localised prostate cancer affect quality of life? The majority of patients avoid the side-effects of curative treatment, but what is the psychological impact of the knowledge of having an untreated cancer and of the

uncertainty of whether active treatment will be recommended or not at the next scheduled visit? What feelings of guilt may be the result if deferred treatment turns out to be initiated too late, at a time when the disease has already spread? There is definitely a need for prospective assessment of the quality of life for patients initially managed with active surveillance.

In summary, active surveillance is beyond doubt effective as a strategy to reduce overtreatment, but we still know too little about the risk of missing the window of curability and what criteria to rely on for changing from surveillance to curative therapy in time to minimize that risk. The smiling face of Janus may not always be trustworthy—it can unexpectedly turn away and be replaced by its opposite.

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