Re: Active Surveillance Program for Prostate Cancer: An Update of the Johns Hopkins Experience Tosoian JJ, Trock BJ, Landis P, et al

| Clin Oncol 2011;29:2185-90

Experts' summary:

Results from the large (n = 796) prospective active surveillance (AS) cohort followed at Johns Hopkins Hospital (Baltimore, Maryland, USA) are reported with a median 2.7-yr follow-up. This trial enrolled patients using the updated Epstein criteria: cT1c, prostate-specific antigen density <0.15, fewer than three positive cores, Gleason score <7, <50% length of cancer per core. Follow-up included yearly biopsy. About 10% of men withdrew from the program. The incidence of curative intervention was 10 per 100 personyears. The 5- and 10-yr intervention-free rates were 59% and 41%, respectively, corresponding to a median survival free of intervention of 6.5 yr. Overall, 33.2% of men underwent deferred intervention at a median 2.2 yr after diagnosis, 73.7% of whom were treated on the basis of reclassification biopsy (12– 14 cores). No cancer-related death were observed.

Experts' comments:

Findings from the Johns Hopkins program are in line with previous published data and validate AS as a safe alternative to immediate curative treatment in carefully selected men [1,2]. Selection criteria were slightly different between these programs with similar outcomes[em]all different, all good. The main limitation of this study is the median follow-up of 2.7 yr, which cannot be a satisfactory deadline when studying prognostics of low-risk prostate cancer patients for whom a 15-yr follow-up would be more suitable. Results were also contaminated by a subgroup of men who were probably candidates for watchful waiting and not AS.

The use of the updated Epstein as entry criteria for AS is highly interesting. To date, they are the most widely used preoperative criteria for predicting an insignificant prostate cancer, and more recent attempts to predict insignificance after positive biopsies and before surgery are based on this

Re: Delay of Surgery in Men with Low-Risk Prostate Cancer

O'Brien D, Loeb S, Carvalhal GF, et al

J Urol 2011;185:2143-7

Expert's summary:

In this retrospective study, the authors aimed to explore the potentially negative impact of delaying radical prostatectomy (RP) for ≥ 6 mo in men with low-risk prostate cancer (PC) according to the D'Amico criteria (at diagnosis: Gleason score ≤ 6 , clinical stage \leq T2a, prostate-specific antigen [PSA] \leq 10 ng/ml). The study outcomes were RP-specimen pathology and biochemical recurrence rates (PSA > 0.2 ng/ml). For this analysis, 1052 men who received RP within 6 mo (*immediate-RP*)

definition. Thus, findings from the Johns Hopkins study might be able to definitively link AS and potentially insignificant prostate cancer.

Recent studies of immediate repeat biopsies in men under AS have highlighted the risk of encountering upgraded and/or upstaged disease on the second pathologic assessment [3]. The use of immediate repeat biopsies varies among AS programs. The Johns Hopkins program did not integrate it at inclusion. However, the authors highlighted the impact of extended biopsy and they now include transition-zone sampling in the follow-up biopsy protocol.

As in the Klotz et al [1] cohort, Tosoian et al surprisingly did not report the final pathologic evaluation from men who underwent a deferred radical prostatectomy (at least 96 patients). It is surely not the best end point to address conclusion in men eligible for AS; however, it can strengthen the oncologic safety of surveillance management.

Conflicts of interest: The authors have nothing to disclose.

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group; mean: 2.4 mo after diagnosis) were compared with 59 men who received RP after 6 mo (*delayed-RP* group; mean: 15.6 mo after diagnosis).

It was found that the immediate-RP group had a RPspecimen Gleason score upgrading to \geq 7 significantly less often than the delayed-RP group: respectively 27% versus 47%, not corrected for baseline differences. Also, the immediate-RP group showed significantly more favourable biochemical recurrence rates than patients in the delayed-RP group, respectively 5% versus 12%, which remained significantly different after correcting for PSA and clinical stage.

Expert's comments:

The dilemma of the most appropriate treatment choice for men diagnosed with low-risk PC remains. The generally assumed drawback of the option of active surveillance is the risk of tumour progression with resulting worse disease-specific outcomes and/or lower quality of life after delayed treatment. So far, conflicting results have been published from retrospective studies on the effect of a delay between diagnosis and surgery in men with low-risk PC. The ideal, but difficult to achieve, study design would be to randomize patients between immediate surgery and surgery after a fixed period of time.

A number of comments should be made on the current article to nuance the message that an initial short-term delay of surgery in men with low-risk PC is unquestionably unsafe. First, the reasons for delaying RP in the study subjects are unknown. These may include surgery scheduling issues and time needed for a patient to acquire data on different treatment options, but also may be due to the specific choice of an active surveillance strategy. The large difference in time between diagnosis and treatment between the groups (2.4 vs 15.6 mo), however, makes the first two options less likely.

Second, in the case of active surveillance, potential reasons for switching to surgery during follow-up are unknown. These may include patient anxiety and repeated diagnostics, such as a second biopsy. The risk reclassification based on a repeat biopsy showing a higher Gleason score would be a very important reason to switch to surgery, but this parameter was not uniformly recorded in this patient group.

Third, the natural history of these favourable tumours is very long [1]. In case of a screening-based diagnosis, this natural history is even extended by a preceding lead time of >10 yr [2]. It may be questioned what the true effect of treatment delays of 3.6 mo (threshold of 6 - 2.4) or even of 13.2 mo (15.6 - 2.4) might be regarding disease outcomes. Disease characteristics upgrading after RP is therefore also more likely due to initial undersampling than true biologic tumour progression.

Fourth, it is likely that there is also a group of men unaccounted for who started on active surveillance and were still so at the moment of this study analysis.

The reasons mentioned above make it unlikely that true biologic tumour progression due to treatment delay is the only reason for the very large differences in RP-specimen Gleason score (27% vs 47%) and in biochemical recurrence rates (5% vs 12%). As mentioned in the article, the results may have been confounded by a selection bias. Based on the currently available data on this subject, the message for men diagnosed with low-risk PC should be that when they choose to initially withhold radical treatment, and thereafter, during follow-up, they fall into the self-selected category of patients in whom indications arise to switch to surgery, there is a possibility of worse pathologic outcomes and biochemical recurrence-free survival. There is, however, a substantially higher chance that they will remain on active surveillance for many years, with a conserved quality of life.

Conflicts of interest: The author has nothing to disclose.

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Re: Adjuvant Androgen Deprivation for High-Risk Prostate Cancer After Radical Prostatectomy: SWOG S9921 Study

Dorff TB, Flaig TW, Tangen CM, et al

J Clin Oncol 2011;29:2040-5

Experts' summary:

The Southwest Oncology Group (SWOG) reports the largest experience of androgen deprivation therapy (ADT) adjuvant to radical prostatectomy (RP) for patients with high-risk prostate cancer (HRPCa). The SWOG 9921 randomly assigned HRPCa patients after RP to receive ADT for 24 mo or ADT in combination with mitoxantrone. The trial included patients in complete remission (prostate-specific antigen [PSA] < 0.2 ng/ml) with one of the following: Gleason score >7, preoperative PSA > 15 ng/ml, stage pT3b-T4, N1, or the combination of Gleason score of 7 with either PSA >10 ng/ml or a positive margin.

Accrual was stopped early after the occurrence of three cases of acute myeloid leukemia in the mitoxantrone arm. This publication reports, at median follow-up of 4.4 yr, the survival of 481 patients of the PSA-only control arm. The 5-yr overall survival and biochemical recurrence-free survival rates were 96% and 92.5%, respectively. For patients presenting (1) Gleason score >7 or pT3b and (2) Gleason score 7 with R+ or PSA > 10 ng/ml, the 5-yr overall survival and biochemical recurrence-free survival rates were 96.8% and 92.2% and 95.9% and 99.1%, respectively.

Experts' comments:

External beam radiotherapy combined with ADT is the standard of care for the curative treatment of HRPCa [1]. But, except for patients with positive lymph nodes, the role of the ADT in association with surgery remains unclear. No randomized prospective study has been published with luteinizing hormone-releasing hormone agonists in the PSA era, which is