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## Re: Radical Prostatectomy or Watchful Waiting in Prostate Cancer—29-Year Follow-up

Bill-Axelsson A, Holmberg L, Garmo H, et al

*N Engl J Med* 2018;379:2319–29

### Experts' summary:

This prospective randomized study investigated the impact of radical prostatectomy (RP) versus watchful waiting (WW) on overall survival for men with clinically detected localized prostate cancer and initial prostate-specific antigen <50 ng/ml ( $n = 659$ , recruiting from November 1989 to February 1999) [1]. After median follow-up of 23.6 yr, the authors found lower mortality among patients undergoing prostatectomy (RP 71.9% vs WW 83.8%;  $p < 0.001$ ) and a lower rate of metastatic disease (RP 26.5% vs WW 43.1%;  $p < 0.001$ ).

### Experts' comments:

Prostate carcinoma is the second most common tumor among men. A 10-yr survival rate of >90% suggests a low oncologic threat, but prostate cancer still has the fifth highest mortality rate among all tumors worldwide [2]. In this context, SPCG-4 is of rare and high value, especially since—not least for ethical reasons—such a trial could not be repeated today knowing the aggressiveness of the high-risk tumors included.

In 2002, after follow-up of 6.2 yr, the first results of this study showed no significant difference in terms of overall survival between RP and WW [3]. At that time, the perception by a large part of the medical community was that treatment with RP may cause more harm than good. However, even at that time a lower risk of distant metastases was observed for men undergoing RP. In 2005, the lower disease-specific mortality became significant for the RP group [4]. Today, the advantage for RP is highly significant (see above), although the procedure was not performed for patients with N+ disease, a group that would have benefited most from RP [1]. In this respect, it is

important to note that the PIVOT study also shows an advantage for RP over WW among patients with intermediate- and high-risk cancers, albeit not significant because of insufficient statistical power for relevant subgroup analysis [5].

The course of SPCG-4 shows that therapy studies for prostate cancer require sufficient long-term follow-up. It also highlights the oncologic efficacy of RP in patients with intermediate- and high-risk disease.

**Conflicts of interest:** The authors have nothing to disclose.

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## Re: Prostate Cancer-specific Mortality Across Gleason Scores in Black vs Nonblack Men

Mahal BA, Berman RA, Taplin ME, Huang FW

*JAMA* 2018;320:2479–81

### Experts' summary:

Mahal et al. [1] used the Surveillance, Epidemiology and End Results (SEER) prostate active surveillance (AS)/watchful waiting database from 2010 to 2015 to identify

192 224 men (31 841 black and 160 383 nonblack) with localized prostate cancer (PC). On multivariable competing-risks analysis there was no difference in PC-specific mortality (PCSM) between black and nonblack patients in the overall cohort ( $p = 0.17$ ); however, black patients with Gleason 6 disease had a higher risk of PC death compared to nonblack patients (adjusted hazard ratio 1.95, 95% confidence interval 1.42–2.67). This racial effect was not observed for Gleason 7–10 disease ( $p = 0.94$ ). The authors concluded that low-grade PC may be distinct in black men, although differences in patterns of care may have contributed to these findings.

#### Experts' comments:

Gleason 6 PC lacks metastatic potential. Among 14 000 radical prostatectomies with Gleason 6 disease, no lymph node metastases were identified [2]; therefore, patients with only Gleason 6 PC are unlikely to experience PCSM. Thus, the patients identified by Mahal and colleagues diagnosed with Gleason 6 disease who experienced PCSM were undergraded at diagnosis or developed subsequent grade progression.

Undergrading, the underestimation of true histologic grade due to the sampling inherent to prostate biopsy, is an acknowledged issue in PC risk assessment. It has been estimated that biopsy undergrading occurs for one-third of patients [3]. Rates may be higher among black men owing to a higher baseline risk of high-grade PC and their predisposition to anterior tumors, which are difficult to sample on transrectal ultrasound-guided prostate biopsy. Ancillary testing, including confirmatory biopsy for men opting for AS and multiparametric magnetic resonance imaging (mpMRI), may decrease rates of unrecognized high-grade PC by identifying disease in regions that are more difficult to sample on biopsy. Despite their higher likelihood of harboring disease that would be detectable on mpMRI, black men in the USA are significantly less likely to undergo mpMRI than white men are [4].

It is estimated that true biologic grade progression of Gleason 6 PC occurs in 1.2–2.4% of patients per year [5], warranting long-term follow-up with treatment for those

with grade progression. Less comprehensive follow-up care in the black population may also, therefore, explain some of the difference in long-term mortality.

Finally, black men are less likely than nonblack men to receive guideline-concordant treatment of PC. Notably, Mahal and colleagues found no difference in PCSM for men with higher-grade PC, suggesting that differences in treatment allocation may not explain their observations.

**Conflicts of interest:** The authors have nothing to disclose.

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