Optimizing Prostate Cancer Screening: Is Less Better?

Roobol MJ, Grenabo A, Schröder FH, Hugosson J. Interval cancers in prostate cancer screening: comparing 2- and 4-year screening intervals in the European Randomized Study of Screening for Prostate Cancer, Gothenburg and Rotterdam. J Natl Cancer Inst 2007;99:1296–303.

Study Overview

Objective. To compare the incidence rates of prostate cancers clinically diagnosed between screening intervals in an every 4-year versus every 2-year screening program.

Design. Randomized controlled trial.

Setting and participants. Participants were recruited from 2 centers participating in the European Randomized Study of Screening for Prostate Cancer (Gothenburg, Sweden and Rotterdam, the Netherlands). Participants were men aged 55 to 75 years.

Intervention. Participants randomized to the screening arm in Gothenburg underwent serum prostate-specific antigen (PSA) testing at 2-year intervals, and participants randomized to the screening arm in Rotterdam underwent serum PSA testing at 4-year intervals. Patients with a PSA level of ≥ 3.0 ng/mL were referred for lateralized sextant prostate biopsies. All cancers were classified by TNM classification and were graded using the Gleason grading system.

Main outcome measures. The primary outcome measures were interval prostate cancers, defined as any cancer diagnosed outside the screening protocol (ie, every 2 or 4 years) and within a screening interval; and aggressive interval cancers, defined as an interval cancer that was stage M1 or N1, had plasma PSA concentration > 20 ng/mL, or had a Gleason score > 7.

Main results. 21,210 and 9973 men were randomized at Rotterdam and Gothenburg, respectively. For the purposes of this analysis, only men aged 55 to 65 years at the time of initial screening were included, resulting in a sample of 13,301 men at Rotterdam and 4202 at Gothenburg. The overall mean follow-up was approximately 7 years. 1582 prostate cancers were detected through screening, and 88 were detected clinically (the interval cancers). The overall detection rate of interval prostate cancers was 0.43% at Rotterdam (4-year interval) versus 0.74% at Gothenburg (2-year interval). In the control group (no serum PSA screening), the overall rate of detection of prostate cancers was 2.38% in Rotterdam and 6.76% in Gothenburg. The rate of interval cancers divided by the rate of prostate cancers diagnosed within the control group was 0.18 at Rotterdam and 0.11 at Gothenburg. The 10-year cumulative incidence for all prostate cancers was 8.4% in Rotterdam versus 13.1% in Gothenburg ($P < 0.001$). The cumulative incidence of interval cancers between the Rotterdam and the Gothenburg site was 0.43% and 0.74%, respectively ($P = 0.51$). There was no difference in the cumulative incidence of aggressive interval cancers between the centers (0.11% vs. 0.12%; $P = 0.72$).

Conclusion. The total cancer detection rate was higher for the 2-year screening interval compared with the 4-year screening interval; however, the rate of interval cancers and aggressive interval cancers was similar.

Commentary

Despite widespread use, screening for prostate cancer with serum PSA remains controversial [1,2]. Many clinically insignificant prostate cancers are detected, resulting in substantial treatment-related morbidities and no mortality benefit. The appropriate time interval for screening for prostate cancer is unknown. Determining the "optimal" screening interval would facilitate public health cancer control policies and allow for a better understanding of the cost-effectiveness of prostate cancer screening in general. In order to determine the optimal screening interval, it is necessary to compare the rates of prostate cancers that might be missed by screening as well as those cancers clinically detected between different potential screening intervals. Comparing these rates provides an indication of the sensitivity of a screening test. Roobol et al conducted a large randomized controlled trial to compare the rates of interval cancers between a 2-year and 4-year screening interval. Their results suggest that decreasing the screening interval from 4 to 2 years does not decrease the number of detected interval prostate cancers.

There are several caveats that limit the interpretation of this study. First, there was a significant difference in the overall number of cancers detected between the 2 centers (1118 in Rotterdam, 552 in Gothenburg). At the Gothenburg center (2-year screening interval), the rate of cancers detected was more than double within the control arm compared with

Rotterdam (6.76% vs. 2.38%). When taking the overall higher cancer rate into account, the difference in interval cancers detected disappears. It is unclear why the overall rates of cancer detection would be so different between the centers. One possible explanation may be related to the difference in study procedures. At Gothenburg, patients provided informed consent prior to randomization, whereas patients in Rotterdam were asked for consent once they were randomized to the intervention. Nevertheless, it is unclear how these biases might have impacted the study. Another possibility may be related to the level of opportunistic screening between the 2 countries.

Applications for Clinical Practice

Unfortunately, this study is difficult to interpret, as the overall rate of prostate cancers (even in controls) was higher at the 2-year screening center (Gothenburg). After adjusting for this overall increased rate, there were no differences in the number of interval cancers detected. Screening more frequently for prostate cancer does not appear to reduce the overall number of clinically detected (interval) prostate cancers; however, additional studies are needed.

—Review by Harvey J. Murff, MD, MPH

References

1. U.S. Preventive Services Task Force. Screening for prostate cancer: recommendation and rationale. Ann Intern Med 2002; 137:915–6.
2. Prostate-specific antigen (PSA) best practice policy. American Urological Association. Oncology (Williston Park) 2000;14: 267–72, 277–8.