

Radical prostatectomy or watchful waiting in early prostate cancer?

β See related article page 44

Holmberg L, Bill-Axelsson A, Helgesen F, Salo JO, Folmerz P, Haggman M, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med* 2002;347:781-9.

Background: The clinical importance and disease burden of prostate cancer — the second leading cause of cancer-related death among men in Canada — are unquestioned, yet significant controversy remains concerning the role of screening and the optimal management of early stage disease. To date, the potential benefits of aggressive local therapy over watchful waiting have not been studied in the context of a randomized controlled trial. Systematic overviews of observational studies have confirmed the dearth of reliable data upon which specific recommendations can be made.

Question: Does radical prostatectomy in early prostate cancer reduce cancer-specific mortality? Also, does it affect metastasis-free survival, local progression and overall mortality?

Methods: In this randomized controlled trial the Scandinavian Prostatic Cancer Group randomly assigned 695 men with early prostate cancer to watchful waiting or radical prostatectomy. To be eligible, men had to be less than 75 years old, have a general medical condition that would permit radical prostatectomy and follow-up of at least 10 years, have a tumour in stage T2 (confined to the prostate) or lower that was well or moderately well differentiated, have no metastases or urinary tract obstruction and have a prostate-specific antigen (PSA) level of less than 50 ng/mL ($\mu\text{g/L}$).

Follow-up included regular clinical, laboratory and radiologic examinations to detect evidence of local progression or distant metastases. The end points were disease-specific mortality, rate of distant metastases and overall mortality. Outcome decisions for all deaths were

adjudicated by an independent end-points committee. Analysis was done according to the intention-to-treat principle and was based on complete follow-up of all eligible participants.

Results: After enrolment 3 men were found to be ineligible and were excluded. A total of 348 men were assigned to watchful waiting and 347 to radical prostatectomy. During follow-up, 30 men originally assigned to watchful waiting underwent radical prostatectomy with curative intent, and 25 men assigned to surgery decided against it. The baseline characteristics of the watchful waiting and surgery groups were similar: mean age 64.7 (standard deviation 5.1) years and mean PSA levels 12.3 and 13.5 $\mu\text{g/L}$ respectively.

During a median follow-up of 6.2 years, 62 men in the watchful waiting group and 53 in the surgery group died. Cancer-specific mortality was lower in the surgery group (4.6% [16/347] v. 8.9% [31/348]), yielding a relative hazard of 0.50 (95% confidence interval [CI] 0.27–0.91). At 8 years' follow-up the rate of local progression (19.3% v. 61.1%, relative hazard 0.31, 95% CI 0.22–0.44) and the development of metastatic disease (13.4% v. 27.3%, relative hazard 0.63, 95% CI 0.41–0.96) favoured the surgery group. Overall mortality, however, did not differ significantly between the watchful waiting and surgery groups (28.3% v. 22.0%, relative hazard 0.83, 95% CI 0.57–1.2).

Commentary: Despite the short follow-up period for a prostate cancer trial, this study for the first time shows clear evidence that surgical treatment of localized prostate cancer can reduce disease-specific mortality. (These data may be more difficult to reproduce in a PSA-screened population over a similar time-frame, as the lead-time bias of a screened population may be in excess of 5 years.) Although no significant overall survival benefit from surgery was shown in this

study, the risk of death from prostate cancer persists well beyond 10 years from diagnosis, and longer follow-up is needed to determine whether the cumulative benefit of surgery will increase over time.

These results must be interpreted in the context of the possible complications of prostatectomy. In a companion article to this study, Steineck and associates¹ reported on the quality of life in a subset of study participants. Although baseline data were not collected prospectively, men in the surgery group had higher rates of erectile dysfunction and urinary incontinence but a lower rate of urinary obstruction than men in the watchful waiting group. On average, however, there was little difference in well-being and subjective quality of life between the 2 groups.

Implications for practice: Based on the results of this study, practitioners treating men with early prostate cancer can inform them that, over 10 years of follow-up, radical prostatectomy reduces the rate of local recurrence, progression to metastatic disease and disease-specific mortality, but it offers no advantage over watchful waiting in overall mortality. Using these new data, together with knowledge of quality-of-life outcomes from the companion study, practitioners will be better equipped to elicit their patients' preferences and help them arrive at a better-informed treatment decision.

D. Robert Siemens

Assistant Professor
Department of Urology
Queen's University
Kingston, Ont.

In the Literature is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont.

Reference

1. Steineck G, Helgesen F, Adolfsson J, Dickman PW, Johansson JE, Norlén J, et al. Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med* 2002;347:790-6.