

## THERAPEUTICS

# Radical prostatectomy reduced death and progression more than watchful waiting in early prostate cancer

Bill-Axelsson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2005;352:1977-84.

**Clinical impact ratings:** GIM/FP/GP ★★★★★★ Nephrology ★★★★★☆ Oncology ★★★★★☆

## QUESTION

In men with early prostate cancer, how do radical prostatectomy (RP) and watchful waiting (WW) compare for long-term mortality outcomes?

## METHODS

**Design:** Randomized controlled trial (Scandinavian Prostate Cancer Group Study Number 4).

**Allocation:** {Concealed}†.\*

**Blinding:** Blinded {outcome assessors, data safety and monitoring committee, and data analysts}†.\*

**Follow-up period:** Mean 8.5 to 8.8 years (median 8.2 y).

**Setting:** 14 centers in Sweden, Finland, and Iceland.

**Patients:** 695 men < 75 years of age (mean age 65 y) with newly diagnosed, untreated, localized prostate cancer; tumor stage T0d (later changed to T1b), T1, or T2; life expectancy > 10 years; prostate-specific antigen (PSA) level < 50 ng/mL; and no abnormalities on bone scan.

**Intervention:** RP ( $n = 347$ ) or WW ( $n = 348$ ).

**Outcomes:** Death from prostate cancer, distant metastasis, local progression, and death from any cause.

**Patient follow-up:** 100% (intention-to-treat analysis).

## MAIN RESULTS

Fewer patients in the RP group died from prostate cancer than did patients in the WW group (Table). The absolute risk reduction between groups increased from 2% at 5 years to 5.3% at 10 years. Patients who received RP also had lower rates of distant metastasis, local progression, and death from any cause (Table). The benefit of RP in reducing death

from prostate cancer was greatest in men < 65 years of age. PSA level at diagnosis or Gleason score did not affect the results.

## CONCLUSION

In men with early prostate cancer, radical prostatectomy reduced death from prostate cancer, distant metastasis, local progression, and death from any cause more than watchful waiting over 10 years of follow-up.

*Source of funding:* Swedish Cancer Society.

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\*See Glossary.

†Information provided by author.

### Radical prostatectomy vs watchful waiting for localized prostate cancer at median 8.2 years†

| Outcomes                   | Radical prostatectomy | Watchful waiting | RRR (95% CI)     | NNT (CI)       |
|----------------------------|-----------------------|------------------|------------------|----------------|
| Death from prostate cancer | 8.6%                  | 14%              | 40% (8.2 to 61)  | 18 (10 to 101) |
| Distant metastasis         | 14%                   | 23%              | 37% (13 to 54)   | 13 (8 to 40)   |
| Local progression          | 18%                   | 43%              | 57% (45 to 67)   | 5 (4 to 6)     |
| Death from any cause       | 24%                   | 30%              | 21% (-0.3 to 39) | 16 (8 to ∞)    |

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

## COMMENTARY

There are 2 main questions to ask of the study by Bill-Axelsson and colleagues: What does it show, and should it influence practice? The study claims that RP is better than WW for early-stage prostate cancer, a conclusion that is largely based on improved survival in patients < 65 years of age treated with RP. Based on Figure 1b in the paper, it would seem that RP is no better than WW in patients > 65 years of age.

The second question is more important. The study was designed nearly 20 years ago, and in the meantime, ad hoc screening and stage migration have changed the clinical picture of early prostate cancer. The trialists did well to persuade so many men to accept such a difficult choice for randomization. Until 2003, patients in the WW group who developed local progression were not offered any treatment. A planned disparity existed between the 2 groups, one that would bias any conclusions in favor of RP. It would be difficult now to defend such a policy: WW has been replaced by active surveillance. This is not mere semantics; patients are followed closely and at any hint of disease progression, appropriate systemic therapy is started.

The study did not include radiotherapy, either external beam (EBRT) or brachytherapy. Both forms are effective in early prostate cancer (1), but no modern randomized trials have compared radiotherapy with either WW or RP. The ProtecT study in the United Kingdom, which is currently accruing patients, is revisiting the com-

parison of active monitoring with RP or EBRT. Only 10% of patients with early prostate cancer will die of prostate cancer—event rates are low, and trials have to be large to show significant differences between treatments. Quality-of-life issues are also important and deserve a thorough discussion. All patients allocated to active intervention will have both acute and chronic symptoms related to the intervention. Patients who are actively monitored may have a higher risk for symptoms related to disease recurrence or progression, plus any anxieties associated with having untreated cancer. Trade-offs between harms and benefits are complex, particularly when 90% of patients may be at risk for harm without benefit. Patients' attitudes and preferences are vital to appropriate decision making, but we know hardly anything about them.

Does this study prove that RP is better than WW for all patients with early prostate cancer? No. Should the results of this study be used to influence practice? Possibly, but because it reflects the choices of a bygone era, any extrapolation to contemporary practice must be tempered by caution.

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## Reference

1. Nilsson S, Norlen BJ, Widmark A. A systematic overview of radiation therapy effects in prostate cancer. *Acta Oncol*. 2004;43:16-81.