Is radical prostatectomy of benefit in men with localised prostate cancer?

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In men with intermediate- to high-risk prostate cancer, radical prostatectomy has been shown to lower the risk of local or systemic progression, and cancer-specific and overall mortality, compared with watchful waiting.

IN the preceding two decades there has been widespread use of radical prostatectomy (RP) in the treatment of men diagnosed with prostate cancer, as a result of both accumulating surgical expertise and an ongoing shift towards early diagnosis. Despite this, data on the efficacy of RP in controlling prostate cancer have been derived from numerous nonrandomised and generally single-institutional investigations.[1] In some studies, long-term cancer-specific survival rates for patients with clinically localised prostate cancer appear to be similar regardless of initial therapy, thus fuelling speculation on the need for RP.[2]

This active trial (see opposite) reported by the Scandinavian Prostate Cancer Group is based on 695 patients randomly assigned to undergo surgery or watchful waiting between 1989 and 1999, and provides the only high-level evidence of the oncological effectiveness of RP in the treatment of prostate cancer. Earlier reports of this trial had demonstrated improved progression-free and disease-specific survival,[3] with no detriment to quality-of-life[4] among surgically treated patients. With a median follow-up of 8.2 years, the authors extend their previously reported findings. Among men treated with RP, compared with those managed by watchful waiting, the authors observed a further reduction over time in the rates of local progression (10-year cumulative incidence 19.2% vs 44.3%), systemic progression (15.2% vs 25.4%) and death from prostate cancer (9.6% vs 14.9%). In addition, statistically significant benefits of RP in terms of overall mortality (27.0% vs 32.0% at 10 years, P=0.04) and the utilisation of hormonal therapy (110 vs 177 patients at follow-up, P<0.01) are also demonstrated for the first time.

It is crucial, however, to interpret these results in the context of the patient population treated. The patients seen in clinical practice today represent a lower-risk population than this study cohort, where approximately three-quarters of tumours were palpable and serum levels of PSA (prostate-specific antigen) were higher than 10 ng/ml in almost half the patients. Notably, even in this group of patients, the benefits of treatment only emerge gradually, over at least a five- to ten-year timeframe, in keeping with the long natural history of localised prostate cancer.[1,5] Furthermore, on exploratory subgroup analysis, the survival advantage conferred by RP appears greatest among men under the age of 65 years. Taken together, the above data suggest that, for the spectrum of disease studied herein, RP is of benefit to men aged 65 years or less with a life expectancy of at least 10 years.

It is sobering to note that the absolute reduction in mortality is only moderate, and is likely to be even smaller among lower-risk patients. Recently-proposed protocols for active surveillance,[6] which recommend selective delayed curative intervention (based on parameters such as PSA doubling-time), instead of the palliative hormonal therapy on progression, as utilised in the watchful-waiting arm of this trial, might further attenuate the observed

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differences. Additionally, comparative assessments of RP against other therapeutic alternatives, such as external beam or interstitial radiation, are not yet available. As such, therapeutic decision-making by the patient with localised prostate cancer and their treating physicians is likely to remain complex, despite the publication of these results.

References

1. H Zincke et al. (1994) Radical prostatectomy for clinically localized prostate cancer: long-term results of 1,143 patients from a single institution. J Clin Oncol 12:2254–2263
2. JE Johansson et al. (1997) Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. JAMA 277:467–471
3. L Holmberg et al. (2002) A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med 347:781–789
4. G Steineck et al. (2002) Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 347:790–796
5. JE Johansson et al. (2004) Natural history of early, localized prostate cancer. JAMA 291:2713–2719
6. L Klotz (2005) Active surveillance with selective delayed intervention using PSA doubling time for good risk prostate cancer. Eur Urol 47:16–21

Synopsis

A Bill-Axelson, L Holmberg, M Ruutu et al. (2005) **Radical prostatectomy versus watchful waiting in early prostate cancer.** *N Engl J Med 352:1977–1984*

Background. Preliminary results of a randomised trial comparing radical prostatectomy (RP) with watchful waiting (also known as observation) in early prostate cancer showed that after a mean follow-up of 6.2 years, RP was associated with significant reductions in disease-specific mortality and distant metastases, but had no effect on overall mortality.

Objective. The present study is an updated analysis of the prostate cancer trial, with an additional 3 years of follow-up, to determine whether the decrease in disease-specific death with RP is caused by the reduced incidence of metastasis, and to further investigate the effect of RP on overall survival.

Design and intervention. Men with untreated localised prostate cancer were enrolled in this Scandinavian study between 1989 and 1999. Those aged ≥75 years, or those who had a poorly differentiated tumour, prostate-specific antigen (PSA) level >50 ng/ml, bone scan abnormalities, or a life expectancy of ≤10 years were ineligible. Patients were randomised to RP or surveillance. Hormonal therapy was recommended for local progression or disseminated disease; transurethral resection was recommended for urinary obstruction. Follow-up comprised clinical examinations and blood tests at 6-month intervals during the first 2 years and annually thereafter, plus regular bone scans and chest radiographs. The cause of each death was determined by blinded assessment carried out by an independent panel, and analyses were conducted on an intention-to-treat basis.

Outcome measures. The endpoints were disease-specific death, distant metastasis, local progression, and death from any cause.

Results. Of 695 participants (mean age 64.7 years), 347 were randomised to RP, and 348 were randomised to surveillance. Baseline characteristics for the two groups were similar. Over a median follow-up of 8.2 years, 30 men (8.6%) in the RP group died from prostate cancer, compared with 50 (14.4%) in the surveillance group (P=0.01). There were significantly fewer deaths from any cause in the RP group compared with the surveillance group (83 vs 106, P=0.04). The absolute risk reductions in favour of RP after 5 and 10 years of follow-up increased from 2.0% to 5.3% for disease-specific mortality, giving a relative risk of 0.56 (95% CI 0.36 to 0.88, P=0.01); from 1.7% to 10.2% for distant metastasis, giving a relative risk of 0.60 (95% CI 0.42 to 0.86, P=0.004); from 19.1% to 25.1% for local progression, giving a relative risk of 0.33 (95% CI 0.25 to 0.44, P<0.001); and from 2.0% to 5.0% for deaths from any cause, giving a relative risk of 0.74 (95% CI 0.56 to 0.99, P=0.04). More men managed by watchful waiting underwent hormonal therapy (177 vs 110, P<0.01), palliative radiation (38 vs 29, P=0.30), and laminectomy (4 vs 11, P=0.04). The effect of RP on disease-specific mortality differed according to age, with men <65 years old deriving the most benefit. Disease-specific mortality did not change with PSA level at diagnosis or Gleason score (the sum of grades assigned to the two largest cancerous areas of tissue samples; grades range from 1, least aggressive, to 5, most aggressive).

Conclusions. RP for early prostate cancer reduces disease-specific and overall mortality, and the incidence of metastasis and local progression.

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