Watchful Waiting and Radical Prostatectomy Offer Equivalent Survival in Localized Prostate Cancer

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Study Overview

Objective. To determine how effective prostatectomy vs. observation (watchful waiting) is for the treatment of localized prostate cancer.

Design. Randomized controlled trial using intention-to-treat analysis. Men were enrolled between November 1994 and January 2002 and followed through January 2010. Study visits occurred every 6 months for 8 to 15 years following randomization (or until the patient died), with bone scans to evaluate for metastatic disease at 5, 10, and 15 years. The radical prostatectomy technique was determined by each patient's surgeon; patients undergoing observation were offered palliative therapy or chemotherapy for symptomatic or metastatic disease.

Setting and participants. 731 men at 44 Veterans Affairs hospitals and 8 National Cancer Institute sites. Only 15% of men eligible for inclusion agreed to participate and were randomized; initially, the study team planned to enroll 2000 patients but was unable to reach this goal. Eligible men were ≤ 75 years of age with histologically confirmed, localized prostate cancer of any grade, diagnosed within the year prior to randomization. Men were also required to have a PSA < 50 ng/mL, a negative bone scan for metastatic disease, and an estimated life expectancy of ≥ 10 years at the time of randomization.

Main outcome measures. Primary: all-cause mortality; secondary: prostate-cancer mortality.

Main results. The average age of subjects was 67 years of age in both arms. 30% in the radical prostatectomy arm and 33% in the observation arm were black, and 64% and 60% were white. The great majority of subjects were fully active at baseline (86% and 84%), and a majority had the lowest Charlson comorbidity index score (a rating of risk for death, defined by the number and severity of medical problems; lowest score of 0 for 57% and 56% for this sample). Mean PSA was 10.1 ng/mL (SD 7.4) and 10.2 (7.9) respectively, with 24% in both arms having a PSA of 10.1 to 19.9 and 10% in both arms having a PSA of 20 to 49.9. 21% and 22% of men had high-risk prostate cancer at randomization (defined as a PSA > 20 ng/mL or a Gleason score of 8–10 or clinical stage T2c). Of patients assigned to radical prostatectomy, 79% received

an attempt at this treatment, with 85% of patients having some definitive therapy (either surgery, attempted surgery, or radiation of some type). Among men assigned to observation, 10% had attempted radical prostatectomy, and 20% had some definitive therapy.

After a mean duration of 10 years of follow-up, death occurred in 171 of 364 men (47.0%) in the radical prostatectomy arm and 183 of 367 men (49.9%) in the observation arm (hazard ratio 0.88, 95% confidence interval [CI] 0.71–1.08; $P = 0.22$). By 12 years after randomization, 41% and 44% of men had died. Age, Gleason score, self-reported performance status, race, and Charlson comorbidity index had no association with the effect of radical prostatectomy on all-cause mortality. In men with a PSA > 10, radical prostatectomy led to a lower rate of all-cause mortality than observation (hazard ratio 0.67, 95% CI, 0.48–0.94; absolute risk reduction of 13.2%). Men who had radical prostatectomy for an intermediate-risk prostate cancer had a significant 12.6% absolute risk reduction in all-cause mortality compared with those who received observation; those who had radical prostatectomy for high-risk cancer had a nonsignificant absolute risk reduction of 6.7%. Men who received observation for low-risk disease had a nonsignificant 5.4% absolute risk reduction in mortality compared with those who received radical prostatectomy.

In the radical prostatectomy arm, 21 men (5.8%) died of prostate cancer, compared with 31 men (8.4%) receiving watchful waiting (hazard ratio 0.63, 95% CI, 0.36–1.09; $P = 0.09$). Men with a PSA > 10 had a lower rate of prostate cancer mortality with radical prostatectomy (5.6%) compared with 12.8% for observation; similar results were evident for men with high-risk disease.

Bony metastases occurred in 17 men (4.7%) assigned to radical prostatectomy and 39 men (10.6%) assigned to observation (hazard ratio 0.40, 95% CI, 0.22–0.70; $P < 0.001$). Bone metastases were not increased for men with PSA levels ≤ 10. Radical prostatectomy was associated with a 21% adverse event rate within 30 days after surgery (10 with some additional surgical repair, 3 with sepsis, 3 with myocardial infarction, 2 with deep vein thrombosis, 2 with pulmonary embolism, 1 with renal failure, 1 death). After 2 years, 17% had urinary incontinence and 81% had erectile dysfunction in the radical prostatectomy group, compared with 6% and 44% in the observation group.

Conclusion. Radical prostatectomy was not associated with a lower rate of all-cause or prostate cancer morality. Men with a PSA > 10 ng/mL had lower all-cause mortality, prostate cancer morality, and less bony metastases after radical prostatectomy compared with observation.

Commentary

Men have a lifetime incidence of 15% to 20% for prostate cancer but only a 3% incidence of death from prostate cancer [1]. This disparity has driven concern that prostate cancer is being overtreated in the age of PSA screening, especially for those men with disease that is deemed to be low risk (PSA ≤ 10 ng/mL and a Gleason score of 6 or less and clinical stage T1c or T2a). Men with low-risk disease still receive some type of definitive treatment (radiation or radical prostatectomy) more than 90% of the time [2]. This study set out to assess the effectiveness of radical prostatectomy on all-cause mortality among men diagnosed with localized prostate between 1994 and 2002. The study found no difference in all-cause or prostate cancer mortality among those receiving radical prostatectomy compared with observation. Men with PSA > 10 ng/mL did appear to benefit from radical prostatectomy, with lower rates of both all-cause and prostate cancer mortality; men with intermediate- and high-risk disease showed some inconsistent benefits from radical prostatectomy.

This study had several strengths, including subjects that were representative of US cases of prostate cancer, long follow-up, and a relatively large sample size. Unfortunately, a few limitations were evident. Because the study team recruited less than half of their originally intended sample (731 of 2000), the study was only powered (at 90%) to find a 25% difference in all-cause mortality between the 2 arms, a fairly sizable difference. And, the results were biased to finding no effect from radical prostatectomy because 21% in the radical prostatectomy arm did not receive an attempt at surgery while 10% in the observation arm had attempted radical prostatectomy. These limitations are to be expected for a trial of aggressive versus passive treatment of cancer; however, the results must be examined within this context.

These results contrast those from a recent Scandinavian study of radical prostatectomy versus observation conducted in 14 centers in Finland, Iceland, and Sweden [3]. In this study of 695 men, crossover between treatment groups was similar to that seen in the Wilt et

al study. Yet as would be expected of a trial in Europe, where PSA screening has been substantially lower than in the United States, fewer men in the Scandanavian study had low-risk disease (12% with nonpalpable tumors compared with 51% for the Wilt study). Radical prostatectomy was associated with a lower rate of all-cause mortality. The absolute risk reduction in mortality after 15 years was 6.6% for those assigned to radical prostatectomy (relative risk 0.75, 95% CI 0.61–0.92; $P = 0.007$). Prostate cancer mortality also was lower in the radical prostatectomy group. The benefit was evident even for men with low-risk disease, but only men < 65 years of age at enrollment had a reduction in mortality.

Dueling results have also been seen in recent randomized controlled trials of PSA screening. In the PLCO trial of over 76,000 American men followed for a mean of 11.5 years, prostate cancer screening was not associated with lower prostate cancer mortality [4]. However, the ESPRC trial of over 162,000 European men found an absolute risk reduction of 0.71 deaths from prostate cancer per 1000 men among those receiving prostate cancer screening (a number needed to screen of 1410 to prevent 1 death) [5]. Ultimately, based on these studies, the US Preventive Services Task Force came out with a recommendation against routine prostate cancer screening [6]; however, the somewhat contrasting results has presented some residual confusion about exactly what to recommend for patients. Finding no difference between observation and radical prostatectomy would lend further credence to a strategy that minimized screening, as well as encouraging a less aggressive strategy after diagnosis. However, such clarity remains elusive.

What does seem clear, based on this study, is that a PSA level of 10 may well emerge as a new cutoff for pursuing aggressive therapy. The robust findings of limited benefit of surgery for men with a PSA ≤ 10 ng/mL suggests that perhaps this cut-off point will prove helpful for deciding whether to pursue both evaluation and aggressive therapy. Providing patients with this information, coupled with the evidence for high rates of adverse events in the postoperative period and frequent long-term challenges of urinary incontinence and near-universal erectile dysfunction, may help them make better informed decisions that properly balance the risks and benefits of treatment.

Applications for Clinical Practice

Physicians should counsel patients about the contrasting results for radical prostatectomy vs. observation for localized prostate cancer (one study showing no benefit, the other showing a 6.6% absolute reduction in all-cause mortality after radical prostatectomy). Providing this information, and the evidence on harms of treatment, may help patients make informed choices on screening and treatment based on their personal values.

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References

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