# *A systematic review of randomized trials in localized prostate cancer*

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***Introduction:*** *Most treatment studies of localized prostate cancer are observational in nature. The recent publication of a large randomized trial of radical prostatectomy (RP) versus watchful waiting (WW) has focused increased attention on the treatment of localized prostate cancer. We reviewed all published randomized trials that compared different primary treatment modalities for localized prostate cancer.*

***Materials and methods:*** *We performed a comprehensive Medline search from 1966 to March 2003 to identify all English-language randomized trials of RP, external-beam radiotherapy (EBRT), brachytherapy, watchful waiting, and primary androgen-deprivation therapy in localized prostate cancer.*

***Results:*** *Nine publications dealing with four separate randomized trials were identified. Two studies examined RP and WW; one study examined RP and EBRT; one study examined RP and EBRT, with both groups receiving neoadjuvant and adjuvant androgen-deprivation therapy. WW, in both studies, refers to no treatment until palliative therapy is required. Two of the four trials, conducted in Veterans Administration medical centers, had small sample sizes and were plagued by several methodological limitations. Neither trial was able to convincingly demonstrate an advantage of RP over WW or RP over EBRT. One trial of RP versus EBRT included patients with both localized and locally advanced disease. The fourth trial demonstrated statistically significant reduction in disease-specific mortality, local progression, and development of metastases in patients with primarily clinically detected, well- or moderately well differentiated prostate cancer who underwent RP as compared to WW.*

***Conclusions:*** *There is high-quality evidence from one randomized trial in favor of surgery over watchful waiting with palliative intent for non-high grade localized prostate cancer. However, most tumors in this study were clinically diagnosed rather than screen-detected. Further randomized trials examining the treatment of screen-detected, localized prostate cancer are needed; several are currently underway.*

**Key Words:** prostate cancer, treatment, randomized controlled trials, treatment outcome, radical prostatectomy, radiotherapy

## Background

Prostate cancer remains the most common internal malignancy and second most common cause of cancer mortality in men.[1] The vast majority of men will have localized disease at the time of diagnosis. Deciding upon treatment for localized prostate cancer remains challenging for patients and their clinicians. There are a myriad of treatment options, including radical prostatectomy (RP), external-beam radiotherapy (EBRT), interstitial brachytherapy, primary androgen deprivation therapy, multimodality therapies (e.g. EBRT and either interstitial brachytherapy or androgen deprivation therapy), and watchful waiting (WW).[2,3] Each active treatment option has

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associated short-term morbidity and long-term complications such as incontinence and erectile dysfunction. For the majority of these options, there are no randomized trials demonstrating any advantage in clinically important endpoints such as disease-specific mortality. Conversely, existing evidence from case-series and cohort studies generally suggest similar biochemical control and overall survival, regardless of which treatment is selected.[4-7] However, non-randomized study designs are subject to several important biases,[8] the most important of which is volunteer/selection bias. Men who receive, for example, RP in non-randomized studies may be fundamentally different from men who undergo WW. These characteristics cannot always be measured and/or fully adjusted for in treatment comparisons. Randomized trials are the most powerful tool available to minimize this bias, and other important biases, and are thus considered the most informative of study designs.[9,10]

The recent publication of a randomized trial of RP versus WW in the New England Journal of Medicine[11] has intensified the debate surrounding optimal treatment of localized prostate cancer. Although several authors have lamented the lack of previously published clinical trials in this field, at least two other randomized trials in localized prostate cancer exist. In this article, we critically review the design, findings, and limitations of the published randomized trials that compared primary treatment modalities of localized prostate cancer.

## Methods

We performed a computerized search using the MEDLINE database from 1966 to March 2003. Combinations of the following medical subject headings and text words were employed: prostatic neoplasms, brachytherapy, radiotherapy, surgery, watchful waiting, clinical trial, controlled clinical trial, meta-analysis, randomized trial. Citations were restricted to the English language. Reference lists from identified studies, published review articles, book chapters, and our own files were also examined. One author (SMHA) read all citation titles and/or abstracts and identified all potentially relevant articles. Articles were included if included patients were randomized to treatment and at least two primary therapeutic modalities (e.g. RP, EBRT, brachytherapy, or WW) were compared. Studies examining neoadjuvant or adjuvant hormonal therapy were excluded. Because of the small number of identified studies, we did not exclude articles on the basis of methodological quality.

## Results

Nine articles, reporting on outcomes from four separate randomized trials, met our inclusion criteria Table 1.[11-19]

### *VACURG trial*

The first randomized trial in localized prostate cancer was published by the Veterans Administration Cooperative Urological Research Group (VACURG).[12,13] The VACURG conducted three distinct studies in localized prostate cancer.[17,20] Study one randomized patients to RP plus 5 mg diethylstilbestrol (DES) daily or RP plus placebo. At a median follow-up of 13 years, there was no statistically significant difference in survival between the two groups; 7.7% of deaths were due to prostate cancer. However, an excess of cardiovascular deaths was noted in the group receiving DES.[12] The study will not be considered further here.

Studies two and three employed identical designs and have been presented in combined fashion.[12,13] A total of 142 patients were enrolled from 19 Veterans Administration hospitals between 1967 and 1975. Patients had VACURG stage I (TNM T1a/T1b) or stage II (T2) disease. The distribution of patients by stage and Gleason score is provided in Table 1. Staging included a digital rectal examination, measurement of acid phosphatase levels, and a skeletal survey. Bone scan and staging laparotomy were not employed. Patients were randomized to RP versus WW. The method of randomization was not described. The primary endpoints were time to progression (defined as first metastasis, rise of acid phosphatase to twice normal, or death due to prostate cancer) and overall survival. Patients were analyzed based on treatment received. Thirty-one patients (22%) were omitted from analyses because of treatment refusal, incorrect staging, or other protocol violations.

Of the 111 patients who were included in the analysis, 43 patients died during follow-up; five deaths were attributed to prostate cancer. There was no difference in time to death in unadjusted and adjusted analyses (for age and grade). Sixteen patients showed disease progression; nine among the WW group and seven among the RP group; these results were not statistically significant. Conversely, more patients (six versus three) in the RP group developed metastases, although the difference was not

TABLE 1. **Selected study characteristics**

| **Study** | **VACURG** | **UORG** | **Akakura et al** | **Scandinavian PCG** |
|---|---|---|---|---|
| Reference | 13,16 | 15 | 18 | 11 |
| Treatment modalities | RP, WW | RP, EBRT | RP, EBRT | RP, WW |
| Sample size | 142 | 106 | 95 | 695 |
| Enrolment years | 1967-1975 | 1975-1978 | 1989-1993 | 1989-1999 |
| Location | 19 VA hospitals in the United States | 13 VA hospitals in the United States | 6 hospitals in Japan | 14 hospitals in Scandinavia |
| Patient age (range) | 67 y (stage I; 50-84)<br>61 y (stage II; 44-78) | N/A | 68 y | 64.7 y |
| TNM stage | 76 T1 (stage I)<br>66 T2 (stage II) | T1-2 | 30 T2b<br>65 T3 | 83 T1b<br>81 T1c<br>529 T2 |
| Grade | 21 Gleason 2-4<br>26 Gleason 5<br>49 Gleason 6<br>11 Gleason 7-10<br>4 unknown | mean Gleason 5.1 (EBRT)<br>mean Gleason 5.5 (RP) | 19 well<br>47 moderately<br>28 poorly differentiated | 91 Gleason 2-4<br>331 Gleason 5-6<br>159 Gleason 7<br>35 Gleason 8-10<br>79 unknown |
| Prostate-specific antigen level | N/A | N/A | mean 19.9 ng/ml RP (range 1.7-140)<br>mean 21.6 ng/ml EBRT (range 1.5-150) | 106 <4 ng/mL<br>120 4-6.9 ng/mL<br>135 7-10 ng/mL<br>195 10.1-20 ng/mL<br>129 >20 ng/mL<br>10 unknown |
| Duration of follow-up, median | 6.8 y (stage I)<br>7.7 y (stage II) | up to 5 years | 58.5 months | 6.2 y |
| Neoadjuvant/adjuvant hormonal therapy | none | none | 8 weeks prior to RP/EBRT, continued after RP/EBRT | none |
| Quality of Life analyses | no | no | beginning in 1996 | median 4 y after treatment |
| Comments | 31 (22% of all patients) protocol violations | 16 (9 RP, 7 EBRT) did not receive assigned treatment | results not reported by clinical stage | no loss to follow-up |

RP = radical prostatectomy; EBRT = external-beam radiotherapy; WW = watchful waiting; VA = Veterans Administration; N/A = not available or not reported; NS = not significant.

statistically significant Table 2.

Subsequent publications described follow-up of the VACURG cohort at a median of 15[16] and 23[17] years. At 15 years, survival status for 95 of the 111 evaluable patients was established. Characteristics were not provided for the patients whose survival status could not be determined. The principal end-point was all-cause survival, which was similar in the RP and WW groups.[16] At 23 years, the median unadjusted survival of the RP and WW groups were 10.6 years and 8 years, respectively. Both unadjusted and age-adjusted comparisons showed no significant difference between RP and WW. However, among stage I patients, there was a trend in favor of survival with RP (relative risk 1.53, 95% CI 0.87-2.67).[17]

### *UORG trial*

Paulson et al from the Uro-Oncology Research Group performed the only completed randomized trial of surgery versus EBRT.[14,15] A total of 106 patients were enrolled between 1975 and 1978 at 13 Veterans Administration medical centers. The distribution of patient age at the time of treatment was not provided. Patients had American Urological Association clinical stage A2 or stage B disease. The distribution of stage and Gleason scores was similar in the two groups; actual Gleason scores were not reported. Patients were randomized in blocks of four to either RP or EBRT. The method of randomization was not described. RP was performed through either the suprapubic or perineal route. Patients assigned to EBRT received a dose 45 Gy-50 Gy in the prostate field

TABLE 2. **Study outcomes**

| **Study** | **VACURG** | **UORG** | **Akakura et al** | **Scandinavian PCG** |
|---|---|---|---|---|
| Reference | 13,16 | 15 | 18 | 11 |
| Biochemical progression | N/A | N/A | N/A | N/A |
| Disease progression | 7/61 (11.5%) RP<br>9/50 (18%) WW<br>(p = NS) | 4/41 RP<br>17/56 EBRT<br>(p = 0.037) | 90.5% 5 y RP PFS<br>81.2% 5 y EBRT PFS<br>(p = 0.044) | 9.4% 5 y RP<br>35.5% 5 y WW<br>19.3% 8 y RP<br>61.1% 8 y WW<br>(p <0.001) |
| Development of metastases | 6/61 (9.8%) RP<br>3/50 (6%) WW<br>(p = NS) | 2/41 RP<br>14/56 EBRT | N/A | 8.6% 5 y RP<br>11.0% 5 y WW<br>13.4% 8 y RP<br>27.3% 8 y WW<br>(p = 0.03) |
| Disease-specific mortality | N/A | N/A | 96.6% 5 y RP DSS<br>84.6% 5 y EBRT DSS<br>(p = 0.024) | 2.6% 5 y RP<br>4.6% 5 y WW<br>7.1% 8 y RP<br>13.6% 8 y WW<br>(p = 0.02) |
| Overall survival | stage I 60% WW<br>80% RP<br>stage II 84% WW<br>76% RP<br>5-year survival<br>(p = NS) | N/A | 85.6% 5 y RP<br>75.9% 5 y EBRT<br>(p = NS) | 91.3% 5 y RP<br>89.7% 5 y WW<br>88.0% 8 y RP<br>71.7% 8 y WW<br>(p = 0.31) |

RP = radical prostatectomy; EBRT = external-beam radiotherapy; WW = watchful waiting; N/A = not available or not reported; NS = not significant; PFS=progression-free survival; DSS=disease-specific survival.

with a 20 Gy boost. The primary endpoint was disease progression, which was defined as either an elevation in acid phosphatase on two consecutive occasions or development of bony or parenchymal disease. Local recurrence was not considered evidence of disease progression. Of the 47 patients originally randomized to RP, nine did not receive surgery, including four who demanded and received EBRT. Of the 59 patients randomized to EBRT, seven did not receive radiotherapy, including three who demanded and received RP. Patients were analyzed by the actual treatment received (41 RP, 56 EBRT). Acid phosphatase level, chest x-ray, and bone scan was performed at a minimum of 6-month intervals during follow-up.

Of the 41 patients who received RP, four had evidence of disease progression within 5 years of follow-up (two had positive bone scans, two had acid phosphatase elevations). Of the 56 patients who received EBRT, 17 had disease progression within 5 years of follow-up (11 had positive bone scans, three had elevations of acid phosphatase, three had non-bony metastases). The difference between RP and EBRT was statistically significant (p=0.037) Table 2. This difference in progression rate persisted after an additional 20 months of follow-up (p=0.022).[15]

### *Akakura et al*

Akakura et al performed a randomized trial of patients with localized and locally advanced prostate cancer.[18] A total of 100 patients were enrolled between 1989 and 1993 in six Japanese hospitals. Patients had stage T2b or T3 disease of any histological grade at entry. Patients with enlarged pelvic lymph nodes on imaging (either computed tomography or magnetic resonance imaging) were excluded. No patients had preoperative bone scans. The majority of patients had prostate-specific antigen (PSA) levels above 20 ng/mL. Patients were randomized to RP with pelvic lymph node dissection or EBRT. Stratified randomization by stage, grade, and institution was performed. The method of randomization was not described. Patients receiving EBRT received 40 Gy-50 Gy to the whole pelvis with a 20 Gy prostatic boost. All patients received androgen-deprivation therapy (primarily DES diphosphate 300 mg daily) 8 weeks prior to radical therapy and continued thereafter. The primary endpoint was not specified. Progression was defined as local regrowth of tumor and/or appearance of distant metastases. Disease-specific and overall survival were reported. Frequency of follow-up investigations (e.g. PSA level, bone scan) was not specified. There was no independent end-point committee. Death due to prostate cancer was defined as death after disease progression.

Of the 95 patients who were randomized, progression was observed in four of 46 who underwent RP and 12 of 49 who underwent EBRT; three and seven patients developed systemic metastases, respectively. Progression-free survival was 90.5% at 5 years for the RP group and 84.6% for the EBRT group (p = 0.044). Disease-specific survival at 5 years was 96.6% and 84.6%, respectively (p = 0.024). Overall survival at 5 years was 85.6% and 75.9%, respectively; the difference was not statistically significant Table 2. Outcomes were not stratified by disease stage.

Quality of life (QOL) was reported by 46 of 77 living patients approximately 4 years after study enrolment closed. Patients undergoing RP had worse functional status and social activity than EBRT patients.[18]

### *Scandinavian PCG study*

The largest and most recent randomized trial in localized prostate cancer was published last year by Holmberg et al on behalf of the Scandinavian Prostate Cancer Group.[11] A total of 675 patients were enrolled between 1988 and 1998 in 14 Scandinavian hospitals. Patients had stage T1b, T1c, or T2 disease that was judged to be well- or moderately well differentiated at entry. All patients had negative preoperative bone scans and a PSA level <50 ng/mL. Patients were randomized to RP (using the bilateral nerve-sparing approach where feasible) or WW. Stratified randomization by degree of differentiation and centre was performed using an external telephone service. Recommended treatment for local progression was transurethral resection of the prostate in the WW arm and androgen-deprivation therapy in the RP arm. The intention-to-treat principle was employed in statistical analyses. The primary outcome measure was disease-specific mortality. Secondary outcomes included local progression (defined as a histologically confirmed local tumor in the RP group and either palpable transcapsular tumor growth or obstructive symptoms in the WW group), time to metastasis and overall mortality. A blinded independent end-point committee determined cause of death. To reduce the risk of ascertainment bias, deaths ascribed to prostate cancer had to be autopsy-diagnosed or associated with evidence of progressive metastatic disease. During a median of 6.2 years of follow-up, 115 men died (53 in the RP arm and 62 in the WW arm). Forty-seven of 115 men died of prostate cancer (16 in the RP arm and 31 in the WW arm). Disease-specific mortality was

7.1% and 13.6% at 8 years in the RP and WW arms, respectively. The relative hazard for RP was 0.50 (95% CI 0.27-0.91, p = 0.02), indicating a lower risk of disease-specific mortality with surgery. Rates of disease progression, both local and metastatic, were similarly statistically significantly in favor of RP Table 2. Overall mortality was not different between the two groups, although there was a trend in favor of RP (relative hazard 0.83 (95% CI 0.57-1.2), p = 0.31).

A companion article reported QOL outcomes for both groups at a mean follow-up of 4 years.[19] Erectile dysfunction and urinary leakage were more common in the RP group, whereas urinary obstruction was more common in the WW group. Subjective mood, well-being, and general QOL were similar in the two groups.

## Discussion

The major therapeutic options for localized prostate cancer were described several decades ago. Despite this, and despite prostate cancer being the most common malignancy in men, only four randomized treatment trials have been performed to date in localized prostate cancer. We will discuss methodological considerations of each trial in turn and then summarize our findings, focus on areas of uncertainty, and highlight future research in this field.

### *VACURG trial*

Both the VACURG and UORG trials were published in an era prior to standardized reporting of clinical trials.[21] The omission of certain pieces of information from the published reports of these studies makes it difficult to assess their overall validity.[22,23] Reporting difficulties aside, three key limitations to the VACURG trial exist. First, the sample size is very small, particularly to detect important differences in overall survival. Second, a large number of patients were dropped from the analyses because of protocol violations. This not only reduces the sample size further but may introduce significant biases into the study by neutralizing the effects of randomization among the remaining trial participants. Third, and perhaps most important, diagnostic testing for both staging purposes and to detect progression were relatively crude compared to the current era. No patients underwent bone scans or staging lymphadenectomy. PSA testing was not available. As a result, a significant proportion of patients with clinical T2 disease likely had T3 or nodal disease.[24] This would bias against any observable benefit with surgery. Similarly, PSA is a much more sensitive marker of disease progression than prostate acid phosphatase. The availability of PSA testing would likely have significantly altered the endpoint of time to disease progression, although it would have had no effect on overall survival. The publication of 15-year and 23-year follow-up data does not address any of these limitations. Moreover, the survival status of 14% of patients could not be determined, adding a further degree of uncertainty. Thus, the VACURG study does not allow any definitive conclusions to be drawn about the utility of surgery.

### *UORG trial*

The UORG Trial represents the only published head-to-head comparison of surgery and radiotherapy. Unfortunately, it is subject to many of the same criticisms as the VACURG trial. Of interest, it was also subject to several critical letters by members of the radiation oncology community.[25,26] The sample size was equally small, and numerous patients were omitted from the analyses or included in the arm of the treatment they actually received, rather than the arm they were assigned to. At the very least, results of a parallel intention-to-treat analysis would have been useful.[22] Staging was significantly better in this study, with all patients undergoing bone scan and staging pelvic lymphadenectomy at baseline. The choice of primary endpoint is particularly troublesome for two reasons. First, time to treatment failure is considerably more useful to clinicians and patients if it correlates with other relevant endpoints, such as disease-specific or overall mortality. Unfortunately, no such endpoints were reported. Second, treatment failure was defined differently for RP and EBRT patients and included the relatively insensitive acid phosphatase elevation as one criterion of treatment failure. Independent adjudication of the endpoints, particularly interpretation of the bone scan, would have enhanced study validity. The small sample size and questionable primary outcome measure do not allow definite conclusions to be drawn about the superiority of surgery or radiation, particularly in light of the fact that the VACURG trial had demonstrated no advantage of RP over WW.

### *Japanese trial*

Although the results of this study are provocative, several design and methodologic issues deserve comment. The overall sample size was small. More importantly, a minority of patients had stage T2b disease; the majority had locally advanced disease. Results were not presented by subgroup, and the small sample size would make it virtually impossible to demonstrate

superiority of surgery or radiation in stage T2b disease. The dose of radiation used was considerably less than the dose currently recommended for high risk disease, and this may have had an impact on the progression rate in the radiation arm. The method of randomization was not specified and most patients did not undergo what would be considered acceptable current staging procedures. The utility of neoadjuvant hormonal therapy remains controversial,[27,28] and DES may be associated with significant cardiovascular toxicity.[20] The definition of disease progression favored the surgery group by including local regrowth as a criterion. Systematic surveillance of patients and blinded reporting of imaging studies were not performed, leading to potential bias. Problems with definition of disease progression and non-standardized surveillance of patients may also have biased the outcome of disease-specific survival, which was also not independently adjudicated. Overall survival was not significantly different between the two groups, further highlighting potential concerns of bias among other outcome measures. The small sample size with localized disease and problems with both study design and outcome measures do not support any firm conclusions about the superiority of either surgery or radiotherapy.

### *Scandinavian PCG trial*

This large, well-designed randomized trial is the first and only randomized study to date to demonstrate a survival advantage of radical therapy over conservative management. Patient characteristics were clearly described, as were the method of randomization, follow-up procedures, and statistical analyses. The primary outcome measure, disease-specific mortality, is a relatively robust and clinically important endpoint; several clinically relevant secondary outcome measures were also included.

Two concerns need to be raised about the study participants and results. First, as pointed out in an accompanying editorial,[29] the enrolled patients may not be representative of current North American practice; 75% of patients were diagnosed clinically in the study, whereas 75% of patients in practice today undergo a diagnostic biopsy on the basis of an elevated PSA level. Therefore, North American patients have earlier stage disease and may require several extra years of follow-up before survival benefits similar to those observed by Holmberg et al[11] become apparent. A second concern relates to the primary endpoint. Determining cause of death is a challenging exercise, even by an independent review committee. Six excess non-prostate cancer deaths were noted in the RP arm; if these six are added to the 16 prostate cancer deaths, the benefit of RP becomes attenuated. Overall survival was not different between the groups, although the confidence interval around the relative hazard estimate confirms that the sample size was too small to exclude a clinically important benefit. These concerns must be tempered by the statistically significant and clinically important benefits in disease-specific mortality, local progression, and the development of metastases. Over time, the difference between RP and WW in each of these endpoints appears to be growing, supporting the widely-held biological hypothesis that local disease control improves survival. Further follow-up of the study participants may address this issue more definitively.

### *Areas of uncertainty*

The publication of the four randomized trials reviewed above leaves several important treatment issues unresolved for clinicians and patients. First, the role of radiotherapy (both EBRT and brachytherapy) remains uncertain at this time. Second, the treatment of high-grade (Gleason 8-10 and perhaps primary Gleason pattern 4) disease is unclear. This group of patients was excluded from the Scandinavian trial. There are data suggesting patients with high-grade disease benefit from adjuvant hormonal therapy,[30,31] but whether the primary modality should be RP, EBRT, or neither is not certain. Third, which particular age groups and subgroups of men (low/intermediate/high risk, based on PSA, grade, and stage) benefit from RP. It is noteworthy that the patients in the Scandinavian trial were largely accrued without PSA screening. It is likely that in a screened population, the increased lead time will result in both an increased rate of cure and a longer interval before this increased rate of cure becomes apparent.

It is striking that the QOL effects in the two groups in the Holmberg article were similar.[19] This likely reflects the fact that the effects of surgery on QOL are minor, and the effects of disease progression over time can be considerable. On the other hand, surgery may be associated with deleterious effects in specific domains, as suggested by Akakura et al.[18] Incorporation of QOL analyses in future trials will provide important data on the impact of treatment on QOL.

### *Ongoing trials*

Two important trials in localized prostate cancer are at various stages of recruitment. The Prostate Intervention Versus Observation Trial (PIVOT) is a randomized trial of RP versus WW.[32] The study was designed with sufficient power to detect a 15% reduction in overall mortality and a 35% reduction in disease-specific mortality. PIVOT has finished recruiting subjects; 731

of the initially scheduled 2000 subjects have been enrolled and will be followed for up to 15 years (http://www.va.gov/PIVOT/page5.html). The second trial is the Surgical Prostatectomy versus Interstitial Radiation Intervention Trial (SPIRIT), which will enroll 2000 men with T1c or T2a prostate cancer, Gleason score ≤6, and a PSA <10 ng/mL. Patients will be randomized to RP or interstitial brachytherapy and followed for 6 years. Recruitment began in late 2002. Both trials will include QOL measurement. The results of PIVOT and SPIRIT will add significantly to our knowledge base of prostate cancer treatment.

## Conclusion

On the basis of the randomized trials published to date, surgery has been shown to decrease disease-specific mortality and local and systemic disease progression, compared to expectant management, in men with low or moderate grade prostate cancer who are in otherwise good health. The role of external-beam radiotherapy remains uncertain at this time. Two important trials examining surgery and brachytherapy are underway and will shed important light in this area; however, results are years away. □

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