Follow-up of Prostatectomy versus Observation for Early Prostate Cancer

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Objective. To determine differences in all-cause and prostate cancer–specific mortality between subgroups of patients who underwent watchful waiting versus radical prostactectomy (RP) for early-stage prostate cancer.

Design. Randomized prospective multicenter trial (PIVOT study).

Setting and participants. Study participants were Department of Veterans Affairs (VA) patients younger than age 75 with biopsy-proven local prostate cancer (T1–T2, M0 by TNM staging and centrally confirmed by pathology laboratory in Baylor) between November 1994 and January 2002. They were patients at NCI medical center–associated VA facilities. Patients had to be eligible for RP and not limited by concomitant medical comorbidities. Patients were excluded if they had undergone therapy for prostate cancer other than transurethral resection of prostate cancer (TURP) for diagnostic purposes including radiation, androgen deprivation theory (ADT), chemotherapy, or definitive surgery. They were also excluded if they had a PSA > 50 ng/mL or a bone scan suggestive of metastatic disease.

Main outcome measures. The primary outcome of the study was all-cause mortality. The secondary outcome was prostate cancer–specific mortality. These were measured from date of diagnosis to August 2014 or until the patient died. A third-party end-points committee blinded to patient arm in the trial determined the cause of death from medical record assessment.

Main results. 731 men with a mean age of 67 were randomly assigned to RP or watchful waiting. The median PSA of patients was 7.8 ng/mL with 75% of patients having a Gleason score ≤ 7 and 74% of patients having low- or intermediate-risk prostate cancer. As of August 2014, 468 of 731 men had died; cause of death was unavailable in 7 patients (2 patients in the surgery arm and 5 in the observation arm). Median duration of follow-up to death or end of follow-up was 12.7 years. All-cause mortality was not significantly different between RP and observation arms (hazard ratio 0.84, 95% confidence interval [CI] 0.7–1.01, $P = 0.06$). The incidence of death at 19.5 years was 61.3% in patients assigned to surgery versus 66.8% in the watchful waiting arm (relative risk 0.92, 95% CI 0.82–1.02). Deaths from prostate cancer or treatment occurred in 69 patients in the study; 65 from prostate cancer and 4 from treatment. Prostate cancer–associated mortality was not significantly lower in the RP arm than in the watchful waiting arm (hazard ratio 0.63, 95% CI 0.39–1.02, $P = 0.06$). Mortality was not significantly reduced in any examined subgroup (age > or < 65, white or black ethnicity, PSA > 10 ng/mL or

< 10 ng/mL, low/high/intermediate grade, Gleason score). Fewer men who underwent surgery (40.9%) had progression compared to those who underwent observation (68.4%). Most of these patients experienced local progression: 34.1% in the surgery arm and 61.9% in the observation arm. Distant progression was seen in 10.7% of patients treated with RP and 14.2% in the untreated arm. Treatment for progression (local, asymptomatic or by PSA rise) occurred in 59.7% of men assigned to observation and in 33.5% of men assigned to surgery. ADT was more frequently utilized as a treatment modality in men who were initially observed (44.4%) than in men who had up-front surgery (21.7%).

With regard to patient-related outcomes (PROs), more men assigned to RP reported bothersome symptoms such as physical discomfort and limitations in performing activities of daily living (ADLs) at 2 years than in men who did not undergo the intervention. This difference did not persist at later time points beyond 2 years. The use of incontinence pads was markedly higher in surgically treated men than in untreated men. 40% of patients in the treatment arm had to use at least 1 incontinence pad per day within 6 months of RP; this number remained unchanged at 10 years. Rates of erectile dysfunction were reported as lower at 2 (80% versus 45%), 5 (80% versus 55%) and 10 (85% versus 70%) years in men who were watched versus those who underwent surgery. Rates of optimal sexual function were reported as lower in resected men at 1 (35% versus 65%), 5 (38% versus 55%) and 10 (50% versus 70%) years than in men who were watched.

Conclusion. Patients with localized prostate cancer who were randomized to observation rather than RP did not experience greater all-cause mortality or prostate cancer–specific mortality than their surgical counterparts. Furthermore, they experienced less erectile dysfunction, less sexual function impairment, and less incontinence than patients who underwent surgery. Patients who underwent surgery had higher rates of ADL dysfunction and physical discomfort although these differences did not persist beyond 2 years.

Commentary

Nearly 162,000 men will be diagnosed with prostate cancer in 2017, and it is anticipated 27,000 will succumb to their disease [1]. This ratio of incident cases to annual mortality represents one of the lowest ratios amongst all cancer sites and suggests most prostate cancers are indolent. Localized prostate cancer is usually defined by low (Gleason score ≤ 6, PSA < 10 ng/mL and ≤ T2 stage) or intermediate (Gleason score ≤ 7, PSA 10–20 ng/mL, and ≤ T2b stage) risk characteristics. 70% of patients present with low-risk disease, which carries a mortality risk of close to 6% at 15 years [2]. Despite this, nearly 90% of these patients are treated with RP, external beam radiation, or brachytherapy. Some published studies suggest up to 60% of low-risk prostate cancer patients may be overtreated [3,4]. The decision to treat low-risk patients is controversial, as morbidities (eg, sexual dysfunction, erectile dysfunction, incontinence) from a radical prostatectomy or focal radiation therapy are significant while the potential gain may be minimal.

Two other trials in addition to current PIVOT follow-up study have sought to answer the question of whether observation (through either watchful waiting or active surveillance) or treatment (surgery or radiation) is the optimal approach in the management of patients with localized prostate cancer. The SPCG-4 trial [5], which began enrollment in the pre-PSA screening era, included Scandinavian patients with biopsy-proven prostate cancer who were < 75, and had life expectancy > 10 years, ≤ T2 lesions, and PSA < 50 ng/mL. Patients began enrollment in 1989 and were watched for more than 20 years. They were seen in clinic every 6 months for the first 2 years and annually thereafter. The primary outcomes of the trial were death from any cause, death from prostate cancer, or risk of bony and visceral metastases. 447 of 695 included men (200 men in the RP group and 247 men in the watchful waiting group) had died by 2012. The cumulative incidence of death from prostate cancer at the 18-year follow-up point was 17.7% in the surgery arm versus 28.7% in the observation arm. The incidence of distant metastases at the 18-year follow-up point was 26.1% in the radical prostatectomy arm and 38.3% in the watchful waiting group. 67.4% of men assigned to watchful waiting utilized ADT while 42.4% of men treated with prostatectomy utilized ADT palliatively post progression [5].

The ProtecT trial was a United Kingdom study that enrolled 1643 men with prostate cancer aged 50–69 years between 1999 and 2009. The trial randomized men to 3 arms: watchful waiting, RP, or radiation therapy. Patients were eligible for the study if they were < 70 and had ≤ T2 stage disease. 97% of patients had a

Gleason score ≤ 7. The primary outcome was prostate cancer–associated mortality at 10 years. Secondary outcomes included death from any cause, rates of distant metastases, and clinical progression. At the end of follow-up, prostate cancer–specific survival was 98.8% in all groups with no significant differences between groups. There was no evidence that differences between prostate cancer–associated mortality varied between groups when stratified by Gleason score, age, PSA, or clinical stage. Additionally, all-cause mortality rates were equivalently distributed across groups [6].

One of the primary reasons why PIVOT and ProtecT may have had different outcomes than the SPCG-4 trial may relate to the aggressiveness of tumors in patients in the various studies. Median PSA levels in the PIVOT and ProtecT trials, respectively, were 7.8 ng/mL and 4.2 ng/mL, compared with 13.2 ng/mL in the SPCG-4 trial. 70% and 77% of patients in PIVOT and ProtecT, respectively, had Gleason score ≤ 6 compared with 57% in the SPCG-4 trial. It is possible that SPCG-4 demonstrated the benefit of RP compared to observation because more patients had higher-risk tumors. Other studies have assessed the economic cost of treatment versus observation in low-risk prostate cancer patients using outcomes such as quality-adjusted life events (QALEs). In a 2013 decision analysis, observation was more effective and less costly than up-front treatment with radiation therapy or RP. Specifically, amongst modes of observation, watchful waiting rather than active surveillance (with every-6-months PSA screening) was more effective and less expensive [7].

Some of the strengths of the PIVOT trial include its prospective randomized design, multicenter patient cohorts, central blinded pathology review, and prolonged follow-up time of nearly 20 years. The trial also had several important limitations. First, the trial included a smaller sample size of patients than the investigators originally intended (2000 patients) and was subsequently underpowered to detect the predetermined outcome of mortality difference between the arms. Second, nearly 20% of patients were not adherent with their treatment arm assignments, which could have potentially confounded the results. Finally, the trial included a patient population that was sicker than the average patient diagnosed in the community with prostate cancer. Trial patients were more likely to succumb to diseases other than prostate cancer and thus may not have been alive long enough to demonstrate a difference between the trial arms (20-year mortality rate was close to 50% in trial patients compared with 30% in the general population post prostatectomy).

Applications for Clinical Practice

The NCCN guidelines suggest that patients with low-risk or intermediate-risk prostate cancer with life expectancies < 10 years should proceed with observation alone. In patients with low-risk disease and life expectancies > 10 years, active surveillance, radiation therapy, or RP are all recommended options. In intermediate-risk patients with life expectancies of > 10 years, treatment with surgery or radiation is warranted. Based on the findings from the PIVOT trial and other trials mentioned above, observation seems to be the most reasonable approach in patients with low-risk prostate cancer. The risks of treatment with RP or radiation outweigh the potential benefits from therapy, particularly in the absence of long-term mortality benefit.

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