The Prostate Cancer Intervention Versus Observation Trial (PIVOT) is a randomized trial designed to determine whether radical prostatectomy or expectant management provides superior length and quality of life for men with clinically localized prostate cancer. Conducted at Department of Veterans Affairs and National Cancer Institute medical centers, PIVOT will enroll over 1,000 individuals less than 75 years of age. The primary study end point is all-cause mortality. Secondary outcomes include prostate cancer- and treatment-specific morbidity and mortality, health status, predictors of disease-specific outcomes, and cost-effectiveness. Within the first 3 years of enrollment, over 400 men have been randomized. Early analysis of participants' baseline characteristics indicate that enrollees are representative of men diagnosed with clinically localized prostate cancer throughout the United States. Therefore, results of PIVOT will be generalizable. These results are necessary in order to determine the preferred therapy for clinically localized prostate cancer. [ONCOLOGY 11(8):1133-1143, 1997]

Introduction

Despite dramatic efforts to increase early detection and intervention for prostate cancer, it is not known whether radical prostatectomy or expectant management provides superior length and quality of life for men with clinically localized disease. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) is a multicenter randomized trial designed to answer the fundamental question, Does early intervention with radical prostatectomy reduce all-cause and prostate cancer-specific mortality and morbidity, when compared with expectant management?

At present, PIVOT is still enrolling patients, with results expected in 2008. This article discusses the rationale for conducting PIVOT, describes the trial's study design, and reports early baseline results from the first group of screened and enrolled men.

Trial Rationale

Many experts have emphasized the importance of conducting randomized trials to determine whether early intervention with radical prostatectomy reduces morbidity and mortality in men with clinically localized prostate cancer, as compared with expectant management.[1-10] In 1997, over 400,000 new cases of prostate cancer and 40,000 deaths due to this disease were expected among American men.[11] The number of patients diagnosed with localized prostate cancer has increased dramatically in recent years due, in large part, to enhanced early detection techniques. Despite widespread utilization of prostate-specific antigen (PSA) testing for early detection and a marked rise in the rate of radical prostatectomy, however, deaths due to prostate cancer have increased. This has led to scrutiny of the effectiveness of early detection and treatment.

Theoretically, prostate cancer confined within the prostate gland should be curable with the removal of the entire gland by surgery (radical prostatectomy) or curative radiotherapy. Screening tests can now detect disease that is localized to the prostate more often than would be the case among men presenting with symptoms. Therefore, it is tempting to speculate that screening for prostate cancer will result in curative treatment of cancers destined to cause future morbidity and mortality. However, this hypothesis has not been tested and may or may not be correct.

Barry and colleagues conducted a policy analysis to determine the cost and effectiveness of early...
detection and treatment of prostate cancer in Medicare-aged men.[12] They concluded that a strategy of early detection (with PSA testing) and treatment (with radical prostatectomy) was cost-effective, but only if unproven assumptions that were highly favorable with respect to treatment necessity, efficacy, and morbidity were used.

Lack of Randomized Data
Both the US Preventive Services Task Force and the Canadian Task Force on the Periodic Health Examination have recommended against routine screening for prostate cancer, in part, because the effectiveness of treatments in reducing morbidity or mortality, compared to expectant management, is unproven.[9] The only randomized controlled trial comparing radical prostatectomy with expectant management reported no difference in cumulative survival rates over 15 years.[10] However, this study was conducted in the 1970s and suffered from several design flaws. The Clinical Guideline Panel for the Treatment of Early Stage Prostate Cancer of the American Urological Association (AUA) recently published the results of a comprehensive survey and analysis of outcomes data for methods of treating clinically localized prostate cancer.[8] The panel concluded that the outcomes data were inadequate for valid comparisons of treatments. In particular, panel members cited major limitations that hindered their attempts to analyze the data; these included the scarcity of randomized controlled trials, insufficient data, and data that may not be representative because many treatment results, especially negative or equivocal ones, are not published. The data were obtained from case series, which are confounded by the lack of control groups, the use of older diagnostic and therapeutic techniques, and variability in patient populations, tumor grade, and stage. Reports from nonrandomized studies cannot provide the unbiased information necessary to determine treatment effectiveness.

The panel recommended that treatment alternatives should be presented as options and should include expectant management, radical prostatectomy, and radiation therapy. The term "options" was utilized because the panel concluded that "the health and economic outcomes of the interventions are not sufficiently well known to permit meaningful decisions, preferences among the outcomes are not known, patient preferences are divided among alternative interventions and/or patients are indifferent about the alternative interventions".[8] They emphasized the need for large randomized, prospective, controlled studies utilizing modern diagnostic and therapeutic approaches to investigate surveillance compared to active treatment of localized prostate cancer. PIVOT is the only randomized trial currently being conducted in the United States comparing radical prostatectomy with expectant management. PIVOT will compare overall and prostate cancer-specific mortality, morbidity, quality of life, and treatment costs in the two treatment groups.

Radical prostatectomy was chosen as the early intervention to be tested because it is the most common therapeutic strategy recommended for patients with clinically localized prostate carcinoma. Almost 100,000 radical prostatectomies will be performed in 1996. Rates of this procedure have increased by almost 100% from 1984 and can be expected to rise further with earlier and more frequent prostate cancer detection.[13] In addition, radical prostatectomy appears to be the early intervention strategy most likely to provide complete tumor eradication. Radiation therapy was not included as an initial treatment option because of sample size, cost, feasibility, and data suggesting that radiation is not superior to prostatectomy in providing prostate cancer-free survival.[8,14,15] Early Intervention vs Expectant Management
Both early intervention and expectant management involve potential risks and benefits. Radical prostatectomy and radiation therapy offer the possibility of complete tumor eradication and cure. They may reduce patient anxiety, the likelihood of cancer metastasis, and the need for subsequent interventions for disease progression. However, prostate cancer may be unique in that the majority of individuals die "with" not "because of" cancer. Furthermore, in individuals with poorly differentiated prostate cancer, early intervention is least likely to completely eliminate cancer.[16,17] Therefore, although early intervention is often considered curative, it may not be necessary in many patients and may not be effective in the remainder.

However, refinements in early detection and treatment may now provide an opportunity for necessary and effective early intervention. Prostate cancer detection has improved due to the widespread use of PSA testing. Cancers detected through PSA-based screening programs are more likely to be confined to the prostate gland than are those detected by digital rectal examination (DRE).[18] In addition, these tumors exhibit pathologic and clinical characteristics similar to tumors detected by DRE. Nonetheless, because of the lead and length biases associated with cancers detected by PSA testing, it is not known whether early intervention will reduce mortality and morbidity.[19-21] (see note) Finally, despite technical advances, early intervention with either radical prostatectomy or radiation therapy can result in iatrogenic morbidity and mortality, adversely
affecting quality as well as quantity of life.[2,22-24]

In contrast, with the expectant management strategy, palliative therapy is given only if men develop symptomatic or metastatic disease. Thus, in many men, treatment will not be necessary if expectant management is utilized. If men develop systems due to local disease progression, relief can be provided by minor interventions associated with minimal morbidity. Expectant management may also include hormonal therapy at the time of diagnosis or upon evidence of disease progression (eg) from PSA testing or physical examination. While not of proven benefit, such an approach is widely utilized. The rate of metastasis may also be similar regardless of whether expectant management may result in improved quality of life, as compared with early intervention.[20,24,25]

However, expectant management does not attempt to eradicate the tumor and may miss an opportunity to prevent metastatic disease and prostate cancer-related death. Morbidity associated with progression of prostate cancer is substantial and includes urinary tract obstruction, bone pain, and other sequelae of metastatic disease. Although palliative therapies generally relieve symptoms, they may only delay disease progression and are not curative. Palliative therapy can also result in iatrogenic morbidity and may not have been required if either radical prostatectomy or radiation therapy had been utilized.

Thus, currently available evidence is consistent with either early intervention or expectant management being the preferred treatment option. However, there may be a clinically important difference between the two options with respect to both quality and length of life. Determining whether or not such a difference exists would have great implications for a large segment of society. Because randomized trials are the most scientifically rigorous, clinically reliable method for evaluating the relative efficacy of two treatment approaches, such trials are ethical and necessary.

**Design of PIVOT**

**Study Population**

PIVOT is being conducted at over 50 Department of Veterans Affairs (VA) and National Cancer Institute (NCI) medical centers across the country (Figure 1). Rather than test the specific effect of a particular drug or individual procedure, PIVOT is designed to compare two general therapeutic strategies: radical prostatectomy and expectant management. Thus, the types of and indications for interventions, as well as determinants of patient eligibility, allow clinicians maximum flexibility while adhering to the primary study purpose.

Men are eligible for enrollment if they are up to 75 years of age and have biopsy-proven clinically localized prostate cancer (T1-T2, NX, M0) of any histologic grade. Men who are at high surgical risk or who have significant coexisting medical conditions resulting in a life expectancy less than 10 years are excluded. Individuals are also excluded if they have received therapy for prostate cancer (except minimally invasive therapies to relieve prostatic obstructive symptoms) or have evidence of nonlocalized prostate cancer, as determined by physical examination, bone scan, imaging studies, or a markedly elevated PSA level (50 ng/mL or greater).

**Screening and Enrollment**

All patients with newly diagnosed prostate cancer at VA Medical Centers are recorded on the PIVOT screening log and evaluated for study inclusion. Tumor registry data include: patient age, race, PSA level, whether prostate cancer is clinically localized, histologic tumor grade, initial therapy (radical prostatectomy, radiation, expectant management, and so forth), and vital status. This registry provides information regarding comparability of PIVOT enrollees to all men diagnosed with prostate cancer at these medical centers.

Men with prostate cancer who meet the eligibility criteria watch an information and randomization videotape that has been specifically developed for PIVOT. The videotape supplements the investigators' discussion with patients. It provides in-depth, standardized information about prostate cancer and treatment options, including the known risks, uncertain benefits, and the rationale for conducting the study. After they give informed consent, eligible men are randomized to: (1) radical prostatectomy, with additional intervention for subsequent disease persistence or recurrence; or (2) surveillance, with palliative therapy generally reserved for symptomatic or metastatic disease progression (expectant management or watchful waiting).

Baseline information on enrollees includes: age; race; family history of prostate cancer; marital, educational, and performance status; comorbidity; PSA level; clinical stage; histologic grade (Gleason score); and reason for prostate tissue sampling (eg, abnormal DRE, elevated PSA, prostatic symptom). A central, standardized histologic review of prostate biopsy and radical prostatectomy specimens is performed.
Patients randomized to radical prostatectomy undergo surgery within 6 weeks of randomization unless the investigator elects to utilize preoperative "downstaging hormonal therapy." Consistent with clinical practice, the exact type of procedure (ie, retropubic, perineal, nerve-sparing, preoperative hormonal downstaging, prior lymph node dissection) is left to the investigator’s discretion. Pathologic stage, type of surgical procedure, use of adjuvant therapy, and complications occurring within 30 days of surgery are noted.

Follow-up
Follow-up visits are scheduled 6 weeks following randomization, every 3 months for the first year, and then every 6 months for the duration of the trial (maximum, 15 years; minimum, 8 years). Data collected at follow-up visits include: urologic symptoms, disease- and treatment-related morbidity, and disease-specific and overall quality of life. Evidence of disease persistence, recurrence, or progression is obtained via questionnaire, physical examination, PSA level, and bone scan. The types of and indications for follow-up intervention in the radical prostatectomy group allow physician discretion consistent with current scientific evidence and clinical practice. Therapeutic options in the expectant management group also permit physician discretion. Emphasis is placed on using palliative therapies with low morbidity; in general, these palliative therapies are reserved for symptomatic or metastatic progression. Consistent with the variability observed in clinical practice, initiation of hormone therapy is at the discretion of the investigator. Predefined criteria characterize symptomatic or metastatic progression. The type, indication, clinical effectiveness, and side effects of therapy are recorded in both treatment groups. A breach of study protocol includes cancellation of surgery. Patients randomized to expectant management are considered to have violated protocol if they receive radical prostatectomy or "definitive radiation therapy."

Blood samples are sent to the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center for PSA testing and establishment of a serologic bank. Measurements of PSA among participants in the expectant management group are blinded in order to minimize interventions of unproven benefit for asymptomatic disease progression. Results of PSA determinations are unblinded if the PSA becomes greater than 20 ng/mL or if symptoms develop that, in the judgment of the investigator, require PSA testing to assist in further evaluation.

End Points
The primary study end point is all-cause mortality. Secondary outcomes include: prostate cancer- and treatment-specific mortality and morbidity, overall and disease-specific health status, disease recurrence, progression-free survival, determinants of disease-specific outcomes, and cost-effectiveness of care. A large sample size and long duration of follow-up have been utilized to detect small differences in mortality between treatment strategies. Deaths are evaluated, based on a review of relevant clinical information, by an independent Endpoints Committee who are blinded to initial treatment status.

Trial Safety and Monitoring
The overall safety and monitoring of men enrolled in PIVOT are under the direction of the Data Monitoring Board. This board is comprised of an independent group of experts in the fields of prostate cancer, epidemiology, and/or biostatistics. The group has overall responsibility for monitoring the progress of the trial and analyzing interim data for efficacy and safety. The Cooperative Studies Evaluation Committee of the Department of Veterans Affairs initially reviewed and approved the protocol. A Human Rights Committee appointed by the Cooperative Studies Program of the Department of Veterans Affairs is comprised of physicians, lay people, and ethicists (included to evaluate the ethical aspects of the trial).

Sample Size and Trial Duration
The original PIVOT protocol was designed to enroll 2,000 men over 3 years. Based on survival results from recently published studies with patient and tumor characteristics similar to the first 235 enrollees in PIVOT, the protocol was revised to enable PIVOT to enroll 1,050 participants over a 7-year period from approximately 50 VA and NCI medical centers. Participants will be followed for an average of 12 years (range, 8 to 15 years). Using a two-sided test of significance, PIVOT will provide 90% power to detect a 20% relative reduction in all-cause mortality (10% absolute risk reduction) by either treatment strategy. In calculating the revised PIVOT sample size, the following assumptions were utilized: (1) median survival of 10 years [6,8,10,27] and (2) an intention-to-treat analysis (ie, a patient is counted in the group to which he was randomized regardless of adherence to therapy).

From a clinical perspective, the number of patients needed to be treated with radical prostatectomy to save one life at 10 years is a useful measure of treatment effect size. PIVOT has the statistical
power to determine whether more than 11 patients would need to be treated with radical prostatectomy to save one life at 10 years (number needed to treat @ 10 years = 11 when the absolute risk reduction = 10%). This revision in the protocol was reviewed and approved in 1996 by the trial’s Data Monitoring Board, Human Rights Committee, and Cooperative Studies Evaluation Committee.

Early Results and Current Status

Reasons for Patient Exclusion
In the first 18 months of recruitment, 3,346 men with newly diagnosed prostate cancer were reported on the registry (Table 1). The mean age of these patients was 69 years, 25% were African-American, and approximately 80% had prostate cancer that was considered to be clinically localized. Hispanic men were slightly younger than either African-American or Caucasian men. There were no racial differences in the percentage of clinically localized cancers or the histologic tumor grade. When compared with Caucasian and Hispanic men, African-American men had a higher mean PSA value, were less likely to choose radical prostatectomy, and were more likely to choose expectant management or early hormone therapy. There were five factors with exclusion rates higher than 5%. These included: limited life expectancy (10.1%), age greater than 75 years (6.2%), nonlocalized prostate cancer (5.9%), PSA levels, 50 ng/mL (5.7%), and bone scan evidence of metastatic disease (5.1%).

Baseline Characteristics
In less than 3 years of recruitment, PIVOT has enrolled more than 400 men. Baseline characteristics of the first 238 enrollees, as well as 1,314 eligible men who declined enrollment, are listed in Table 2. Reasons that potentially eligible individuals were not randomized included: patient unwilling to leave decision for treatment to chance (74%), patient declines for other reason (37%), patient fears participating will interfere with receiving proper treatment (25%), patient not willing to participate in research of any kind (16%), physician prefers that patient not participate (15%), others (eg, family) prefer that patient does not participate (12%). No significant differences were noted between enrollees and men who were eligible but declined randomization (Table 2). The mean age was 67 years, and one-quarter were African-American. The mean PSA value was 9 ng/mL, and almost 90% had well- or moderately differentiated tumors. Self-rated health status was good to excellent in almost 90% of men. Treatment selection of the 1,314 men who were eligible but declined randomization included: radical prostatectomy (35%), observation (35%), radiation (17%), and hormone therapy (8%). The primary reasons for tissue biopsy in PIVOT enrollees were PSA elevation (72%) and DRE abnormalities (15%). Clinical stage included: T1c (49%), T2a (26%), T2b (13%), and T2c (8%). Men in PIVOT are healthy; comorbidity rates were less than 10%, except for smoking (26%), diabetes (18%), and myocardial infarction (11%). Two-thirds have at least a high school education, and 60% are married. Medical care was rated as good to excellent by 95%.

These early results of baseline demographic and tumor characteristics indicate that PIVOT enrollees are representative of men throughout the country with early-stage prostate cancer.

Discussion
Since the preferred therapeutic strategy for men with clinically localized prostate cancer, regardless of histologic grade, is unknown, a randomized trial, such as PIVOT, is necessary to obtain definitive answers. The objective of PIVOT is to determine the effectiveness of two treatment strategies recommended for such men: radical prostatectomy and expectant management. The study emphasizes a comparison of early intervention with radical prostatectomy and aggressive follow-up vs expectant management with palliative therapy generally reserved for symptomatic or metastatic disease.

In view of the existing scientific evidence and varying practice patterns among physicians, broad inclusion criteria and flexible follow-up therapies are utilized. This design allows for new interventions of proven efficacy or established clinical practice to be incorporated into the protocol during the course of this long study. Opponents of randomized trials for the evaluation of the early treatment of prostate cancer contend that such studies are unethical, infeasible, and unlikely to provide reliable answers for practitioners caring for patients with prostate cancer. Despite the previously mentioned scientific debate, these detractors suggest that advances in detection and early intervention have been coupled with a greater understanding of the natural history of prostate cancer. Therefore, selective use of early
intervention by skilled practitioners in appropriate men is already occurring and does not require evaluation by a randomized trial. In addition, critics state that patients will not submit such an important treatment decision to random assignment. They further argue the fraction of eligible subjects who do eventually participate in a randomized trial will not be representative of the population at large. Thus, such a trial cannot be reliably accomplished in the United States, and treatment decisions are better left to patient preferences and the best available judgment of clinicians.

These concerns do not provide convincing arguments against the need to conduct a randomized trial of radical prostatectomy vs expectant management in the United States. The feasibility of conducting a randomized trial comparing radical prostatectomy with expectant management in the United States is verified by the successful enrollment of PIVOT participants during the first 2 years of recruitment.

Consistent with many clinical trials, a substantial portion of individuals eligible for PIVOT are declining randomization. However, many patients are willing to participate in randomized trials in an attempt to resolve issues of great medical uncertainty and importance. Careful comparisons of eligible patients declining study participation with those actually randomized demonstrate the generalizability of PIVOT. The early baseline results show that enrollees are comparable to men being diagnosed with clinically localized prostate cancer nationwide (almost one-quarter were African-American, a group of men at increased risk for developing prostate cancer). Because a large number of VA and NCI medical centers from across the nation are participating in PIVOT, the clinical applicability of the trial will be enhanced. Therefore, results of the trial will be generalizable to many men with clinically localized prostate cancer.

Unfortunately, the results from PIVOT will not be available for at least 10 years. Until these results are available, medical decisions should incorporate patient preferences and practitioners' best clinical judgment. However, the AUA Treatment Guidelines panel, the US and Canadian Preventive Services Task Forces, the American College of Physicians, and the Health Care Evaluation Unit of the University of Bristol, UK[28] have all suggested that two major reasons why uncertainty and confusion persist in this area are the failure to conduct randomized trials and attempts by practitioners to make clinical judgments based on imprecise information. (see note) Clinicians should encourage eligible men to participate in PIVOT, as well as other randomized trials of prostate cancer treatment. Only randomized trials can provide reasonable assurance that the treatment groups are balanced in terms of known and unknown confounders, and that the comparisons of outcomes are unbiased.

**Summary**

The results from PIVOT will be useful regardless of which strategy proves to be superior. If treatment with radical prostatectomy is shown to be more effective, aggressive screening and treatment programs should be instituted and directed toward patients most likely to derive benefit. If expectant management provides equivalent long-term survival, observation with intervention reserved for palliative purposes would generally be preferable because it avoids the morbidity, mortality, and cost of early intervention.

Physicians and cancer support groups should encourage enrollment in PIVOT so that the preferred treatment approach for men with clinically localized prostate cancer can be determined. The clinical uncertainties surrounding the treatment of early-stage prostate cancer and the importance of such treatment make PIVOT not only ethical but necessary.

**References:**


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