APPENDIX

H

Current Research Efforts To Resolve the Effectiveness of Prostate Cancer Screening and Treatment

Most evidence-based criteria for evaluating screening maneuvers demand evidence from controlled studies on which to base recommendations. Randomized controlled trials (RCTs) are the best studies on which to base such recommendations. In the absence of RCTs, researchers and policymakers often examine less desirable cohort studies with concurrent nonrandomized controls and case-control studies. Unfortunately, in the area of early detection and treatment of prostate cancer, little controlled data are available, regardless of study design. A single case-control study has shown no evidence of benefit from digital rectal examination (DRE), in terms of lower exposure odds to DRE within the prior 10-year period among men with metastatic prostate cancer compared to controls (129). The point estimate of the DRE exposure odds ratio among men with metastatic cancer compared with controls in this study was 0.9, with a 95-percent confidence interval of 0.5 to 1.7. Similarly, a single small, underpowered randomized trial of radical prostatectomy versus expectant management showed no evidence of benefit from more aggressive treatment (54, 147), as discussed in detail earlier in this report.

TRIALS OF TREATMENT FOR CLINICALLY LOCALIZED PROSTATE CANCER

However, researchers are now planning or have already initiated clinical trials to address this lack of data. In terms of determining the optimal treatment for localized prostate cancer, the Scandinavian Prostate Cancer Group began a randomized trial of radical prostatectomy versus deferred treatment in 1989. Men less than age 75 with well or moderately differentiated (but not Stage T1a) cancer are eligible for the trial. Men randomized to surgery undergo a pelvic lymph node dissection, and proceed to radical prostatectomy if the nodes are uninvolved. However, an "intention to treat" analysis is planned to avoid biasing the results in favor of surgical treatment. The investigators plan to randomize 520 men and follow them for a minimum of 10 years to have adequate power to "rule out" a true improvement in 10-year cancer-specific survival from 85 to 95 percent, which represents a two-thirds reduction in cancer-specific mortality. This trial is more than halfway to its accrual target.

In the United Kingdom, the Medical Research Council has just opened a trial comparing the strategies of no immediate treatment, external beam radiotherapy, and radical prostatectomy for men with T1b/T1c/T2 N0 M0 prostate cancer (Trial PRO6). As part of the design, patients can be randomized among all three or any two of the treatment strategies, at the discretion of the physician and patient. Primary endpoints will be the development of documented metastases and survival time. The PRO6 protocol calls for the randomization of 400 men into each treatment arm over three years to achieve 90 percent power to detect a 10 percent difference in survival between any two arms.

Another large trial has been initiated in the United States. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) is to be conducted as a collaboration between the Veterans Administration Cooperative Studies Program and the National Cancer Institute. The investigators plan to enroll about 2,000 men up to age 75 with clinically localized prostate cancer of all grades. Men who provide consent would be randomized to a strategy of immediate radical prostatectomy with additional aggressive treatment for evidence of residual or recurrent disease, or a strategy of expectant management with treatment for symptomatic local progression or metastases. PIVOT started late in 1994, and will accrue patients over three years with an additional 12 years of followup. PIVOT is powered to detect a 15 percent decrease in overall mortality with radical prostatectomy, or roughly a one-third reduction in cancer-specific mortality.

TRIALS OF EARLY DETECTION OF PROSTATE CANCER

Randomized trials of early detection of prostate cancer are also being planned and initiated. The National Cancer Institute's Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial is a ten-center study designed to measure the net benefit of screening for a number of common malignancies. For the prostate cancer component, 74,000 men ages 60 to 74 will be randomized to four annual screens with PSA and DRE, versus "usual care." The study was initiated in 1993, and may need to continue as long as 16 years to have adequate power to detect a 20 percent reduction in prostate cancer mortality, allowing for some "dilution" in the intervention group (due to incomplete compliance with followup of suspicious screening studies) and "contamination" in the control group (due to DREs and prostate-specific antigen tests that may be done as part of usual care).

Finally, a European screening study is currently being planned, and a number of preparatory pilot studies have been conducted in Belgium and the Netherlands. The main study is currently envisioned as involving about 50,000 men in a number of European countries. Details of the design are still being finalized.

Despite many reasonable individual concerns about the designs of the PLCO and PIVOT studies, support for these trials was recently expressed by a group of U.S. prostate cancer experts at a meeting cosponsored by the American Urological Association and the American Cancer Society (253). As Kaufman (186) has recently reminded the medical community, well-designed clinical trials, even in the controversial area of cancer treatment, are "good medicine."