Editorials

Surgery and the Reduction of Mortality from Prostate Cancer

MORE than ever, it is important to establish definitively whether aggressive management of localized prostate cancer reduces the rate of death due to prostate cancer, because this tumor is now the second leading cause of cancer-related death among men in the United States.[1] The treatment of early prostate cancer, which has been the subject of great controversy for years, was well summarized by a question raised by Whitmore: "Is cure necessary in those in whom it may be possible, and is cure possible in those in whom it is necessary?"[2] In this issue of the *Journal,* a landmark study conducted by Holmberg et al. of the Scandinavian Prostatic Cancer Group[3] provides the first concrete evidence we need to answer Whitmore's question. The Scandinavian group conducted a randomized trial in which radical prostatectomy was compared with watchful waiting for localized prostate cancer. After eight years of follow-up, surgery had reduced cancer-specific mortality and the frequency of development of distant metastases by about 50 percent. For the first time, and after a surprisingly short follow-up period, we have clear evidence that surgical treatment of localized disease reduces the risk of death from prostate cancer.

Holmberg et al. found no difference between the two groups of patients in overall mortality, and the absolute reduction in cancer-specific mortality at eight years was only about 7 percent. However, an excess risk of death from prostate cancer persists for 20 to 25 years after diagnosis, and in a study from Sweden, 63 percent of conservatively treated men who lived longer than 10 years after receiving the diagnosis eventually died of prostate cancer.[4] In the trial by Holmberg et al., there was a 14 percent absolute reduction in the rate of development of distant metastases in the surgery group as compared with the watchful-waiting group after eight years of follow-up. Given that the median survival of men with distant metastases is only two to three years, I anticipate that with longer follow-up, the difference in mortality found by Holmberg et al. will increase.

During the past 20 years, the number of radical prostatectomies performed in the United States has risen dramatically, peaking at 104,000 in 1992 to 1993.[5] The estimated number of deaths from prostate cancer has declined from 40,400 in 1995 to 30,200 in 2002. It is difficult to know whether these two phenomena are related, but between 1983 and 1991, the proportion of men 60 to 79 years of age with prostate cancer who were treated surgically increased rapidly.[5,6] Men in this age group also had the greatest decline in mortality due to prostate cancer, which was lower in 1997 than it had been in any year since 1950.[7]

Quality of life in men who enrolled in the Scandinavian trial was evaluated approximately four years after randomization, reported in this issue of the *Journal* by Steineck et al.[8] Although base-line data were not collected prospectively, men in the surgery group had higher rates of erectile dysfunction and urinary leakage but a lower rate of urinary obstruction than men in the watchful-waiting group. Before 1980, radical prostatectomy was associated with severe complications: excessive life-threatening bleeding was common, and after the operation, all men were impotent and 10 to 25 percent had severe incontinence. However, anatomical discoveries made during the past 20 years have led to considerable refinements in surgical technique. Among men who are ideal candidates for radical prostatectomy (who are less than 65 years of age, with localized disease and no coexisting conditions), experienced academic urologists report potency rates of 62 to 86 percent and continence rates of 92 to 95 percent.[9] Other centers and surveys of individual surgeons, however, report potency rates of 10 to 30 percent and continence rates as low as 50 percent.[10]

In the Scandinavian trial, nerve-sparing surgery was not routinely performed. Furthermore, many patients in this trial were older than 65 years of age and thus more likely to have incontinence and impotence; 28 percent received hormonal therapy during follow-up. These factors — lack of standardized nerve-sparing surgery, older age, and the use of antiandrogen therapy — may explain why the frequency of complications of radical prostatectomy in this trial was higher than one might have expected if the procedure had been performed uniformly at a high-volume center.[11] Steineck et al. also found that patients in the watchful-waiting group had more erectile dysfunction and urinary leakage than would be expected in a control population, suggesting that local tumor progression, which occurred in 60 percent of the patients in the watchful-waiting group, or the treatment of progressive disease can also have side effects. As the authors of the study point out, a man evaluating treatment strategies for localized prostate cancer must recognize that all options can jeopardize his quality of life.

It is important to note that in this study, the diagnosis of prostate cancer was made clinically; 75 percent of the patients had palpable disease, and only 10 percent of the cases were diagnosed because of an elevated prostate-specific antigen level. These men are therefore not representative of most patients seen to-

day in the United States, where 75 percent of men who receive a diagnosis of prostate cancer have nonpalpable disease and undergo a biopsy because of an elevated prostate-specific antigen level. Consequently, the lead time in diagnosis (probably five years or more) must be taken into account before the findings from this study can be applied to contemporary patients.[12] Fortunately, several relatively advanced studies evaluating the efficacy of screening are under way in the United States and Europe, and they may have the statistical power to show definitive results by 2005 to 2008.[13] Furthermore, the Department of Veterans Affairs has just closed enrollment for a trial in which 731 patients were randomly assigned to radical prostatectomy or watchful waiting. In this trial, 50 percent of the participants have nonpalpable disease.[14]

How should the results of the Scandinavian study influence the advice we give to patients? Specifically, should no one be followed with watchful waiting? Should all patients undergo radical prostatectomy? The answer to both these questions is a categorical "no." There have always been, and always will be, many men who are best served by watchful waiting. They are the patients who are too old or too ill to survive longer than 10 years. If their cancer progresses to the point where it causes symptoms, there are many ways to palliate the disease. Furthermore, in the era of prostate-specific antigen screening, 10 to 20 percent of men with nonpalpable disease have small tumors and may also be candidates for watchful waiting. Criteria have been established to help identify such men.[15] For patients with larger tumors, definitive treatment with surgery, external-beam radiotherapy, or interstitial radiotherapy should be considered. In a young man with localized prostate cancer who is otherwise healthy, total surgical removal is an excellent option, and if it is performed by an experienced surgeon, the patient's subsequent quality of life should be more satisfactory. In an older patient or one with clinically significant coexisting conditions, however, radiation therapy is the best option and has the fewest side effects.

In between these two groups, there are many men who are candidates for either surgery or radiation therapy. During the past decade, substantial advances have been made in the technique of radiation therapy, making it possible to deliver high doses of radiation specifically to the prostate. As a result of these advances, patients with localized prostate cancer now clearly have two good options for treatment: surgery and radiotherapy. The Scandinavian Prostatic Cancer Group trial showed that surgery can reduce the rate of death from prostate cancer, but no similar trial of radiation therapy has been conducted. However, both randomized and cohort studies are being developed to compare radical prostatectomy with external-beam or interstitial radiotherapy. Until those trials have been completed, physicians must fully inform men with prostate cancer about their options and help them select the best specialist for the treatment they choose.

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REFERENCES

1. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. CA Cancer J Clin 2002;52:23-47. [Errata, CA Cancer J Clin 2002;52:119, 181-2.]
2. Whitmore WF Jr. Natural history of low-stage prostatic cancer and the impact of early detection. Urol Clin North Am 1990;17:689-97.
3. Holmberg L, Bill-Axelson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med 2002;347:781-9.
4. Aus G, Hugosson J, Norlen L. Long-term survival and mortality in prostate cancer treated with noncurative intent. J Urol 1995;154:460-5.
5. Wingo PA, Guest JL, McGinnis L, et al. Patterns of inpatient surgeries for the top four cancers in the United States, National Hospital Discharge Survey, 1988-95. Cancer Causes Control 2000;11:497-512.
6. Merrill RM. Changes in the use of radical prostatectomy for treating prostate cancer in the USA. Lancet 1996;348:963-4.
7. Tarone RE, Chu KC, Brawley OW. Implications of stage-specific survival rates in assessing recent declines in prostate cancer mortality rates. Epidemiology 2000;11:167-70.
8. Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002;347:790-6.
9. Walsh PC, Marschke P, Ricker D, Burnett Al. Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. Urology 2000;55:58-61.
10. Talcott JA, Reiker P, Propert KJ, et al. Patient-reported impotence and incontinence after nerve-sparing radical retropubic prostatectomy. J Natl Cancer Inst 1997;89:1117-23.
11. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002;346:1138-44.
12. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostate cancer. JAMA 1995;273:289-94.
13. de Koning HJ, Auvinen A, Berenguer Sanchez A, et al. Large-scale randomized prostate cancer screening trials: program performances in the European Randomized Screening for Prostate Cancer trial and the Prostate, Lung, Colorectal and Ovary Cancer trial. Int J Cancer 2002;97:237-44.
14. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial (PIVOT). Oncology (Huntingt) 1997;11:1133-9.
15. Carter HB, Walsh PC, Landis P, Epstein JI. Expectant management of non-palpable prostate cancer with curative intent: preliminary results. J Urol 2002;167:1231-4.

WORLD TRADE CENTER COUGH — A LINGERING LEGACY AND A CAUTIONARY TALE

ONE year has passed since the terrorist attacks in New York and at the Pentagon. As we struggle to address important issues related to the health consequences of warfare and terrorism, a simple question has arisen: Did working on the rescue and recovery operation at the World Trade Center have an effect on health? In this issue of the *Journal,* Prezant and