

CLINICAL DECISIONS

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Management of Prostate Cancer

This interactive feature addresses the diagnosis or management of a clinical case. A case vignette is followed by specific clinical options, none of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. In the online version of this feature, available at www.nejm.org, readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A 63-year-old man who has been under your care for the past 3 years undergoes an annual check-up. He believes he is in excellent health, and he has no medical problems to report. In 2006, his physical examination and routine laboratory tests were normal, and the prostate-specific antigen (PSA) level was 1.5 ng per milliliter. There had been no new findings in 2007, except that the PSA level had risen to 3.1 ng per milliliter. This year's annual check-up reveals a PSA level of 3.8 ng per milliliter, and a digital rectal examination is normal.

Concerned about the rising PSA level, you refer the patient to a urologist, who performs ultrasonography and biopsy of the prostate. The prostate volume is 22 cm³, and of 12 biopsy cores, 2 (10% of one and 20% of another) show involvement with adenocarcinoma, with a Gleason score of 6.

The patient, a widower with normal sexual function, plans to continue to run his advertising business. He does not smoke, drinks only occasionally, and jogs 2 miles three times a week. He

has inquired specifically about expectant management.

Which one of the following treatment options from the urologist, any of which could be considered correct, would you find most appropriate for this patient? Base your choice on the published literature, your past experience, recent guidelines, and other sources of information, as appropriate.

1. Expectant management.
2. Radiotherapy.
3. Radical prostatectomy.

To aid in your decision-making, each of these approaches to treatment is defended by an expert in the management of prostate cancer in the following short essays. Given your knowledge of the condition and the points made by the experts, which treatment approach would you choose? Make your choice on our Web site (www.nejm.org).

TREATMENT OPTION 1

Expectant Management

Fritz H. Schröder, M.D.

The case vignette recounts a common situation in which expectant management, radiotherapy, and radical prostatectomy are likely to come up for discussion. Expectant management is applicable only to men who are eligible for potentially curative management. The purpose of follow-up is to recommend potentially curative management to men whose cancer progresses and to avoid the side effects and cost of treatment, at least temporarily, in men whose cancer does not progress.¹

This patient is clearly eligible for radical sur-

gery or radiotherapy. Expectant management, also known as active surveillance, was brought up for discussion by the patient himself. A key question in this case is whether the cancer is potentially indolent, in which case treatment can be deferred or possibly avoided completely. A nomogram based on two large series of patients who underwent radical prostatectomy helps to identify potentially indolent prostate cancer.² It has been validated and updated by Steyerberg et al.³ for prostate cancer that is detected on screening. Considering the fact that PSA tests were repeated over a period of 3 years in our patient and that a PSA level of 3.8 ng per milliliter is considered to be an indication for biopsy, this patient's pros-

tate cancer can be considered to have been detected on screening, and thus the nomogram of Steyerberg et al. (available at www.uroweb.org) can be used.

Use of the nomogram requires knowledge of the PSA level, the prostate volume, the Gleason score, and the millimeters of prostate-cancer tissue and normal tissue in the core biopsy specimens. All this information is available for our patient. Assuming a length of each biopsy core of about 16 mm, the tumor has a length of about 5 mm. Since the indicator of the risk of prostate cancer is based on sextant-pattern biopsy, the length of 5 mm can be divided by 2, assuming that the sextant biopsies would have detected less prostate cancer than a standard 10- or 12-core biopsy, in which the length of the prostate-tissue specimen could exceed 100 mm. According to the nomogram, our patient's risk of having potentially indolent prostate cancer is 72%. With a probability threshold of 70% for identifying an indolent cancer, the chance that a potentially aggressive tumor is misclassified is only 6%. Thus, we can legitimately consider expectant management for our patient.

If the patient chooses this option, a strict follow-up regimen is required, including the measurement of PSA level and digital rectal examination every 3 months for 2 years. Biopsy should be repeated after 3 months or 1 year, or both. If the disease remains stable, frequency of the follow-up procedures can be relaxed to every 6 months or every 12 months. During the follow-up period, active treatment would be recommended if there were a PSA doubling time of less than 3 years, an abnormal rectal examination, or progression to a higher Gleason score on biopsy. With the recommended follow-up procedures, encouraging results have been obtained within observation periods of up to 10 years.⁴

There is, however, a serious limitation to this option. A PSA doubling time of 1.8 years translates into a PSA velocity of 0.77 ng per milliliter per year. If this rate of increase in the PSA level is confirmed in our patient, I would have to recommend active treatment. To evaluate more accurately the PSA velocity, follow-up visits (at least two) at 3-month intervals would be needed to relieve concerns that the rise in PSA level was due to normal biologic fluctuation. The relation between progression of nonpalpable biopsy-detected, untreated prostate cancer (T1c disease) and

PSA kinetics is unknown; however, data on PSA levels before and after potentially curative management suggest strong associations between PSA doubling times and mortality from prostate cancer. A PSA doubling time of more than 15 months is associated with death from any cause within a median of 15 years, whereas the median time to death from prostate cancer was not yet reached at 16 years.⁵

With proper information on risks and potential benefits, the patient could be supported in his choice of active surveillance. The benefit would be the avoidance of the adverse effects of treatment. But if PSA levels increase at the same rate within two or three more observation periods of 3 months each, my advice would change. Although the prostate is relatively small and has already been biopsied 12 times, repeat biopsy in advance of the 1-year follow-up visit might be advisable to exclude histologic progression or misclassification during the first biopsy.

No potential conflict of interest relevant to this article was reported.

From the Department of Urology, Erasmus University Medical Center, Rotterdam, the Netherlands.

TREATMENT OPTION 2

Radiotherapy

Mack Roach III, M.D.

A permanent prostate seed implant involves the placement of radioactive seeds directly into the prostate under guidance of transrectal ultrasonography and is an ideal option for this low-risk patient. This type of treatment is a form of brachytherapy. Only in the past 20 years has computer technology evolved to a point at which we can take optimal advantage of brachytherapy.

The major goals of this treatment are to control cancer, preserve sexual function, and maintain urinary continence while minimizing the risk of serious rectal or bladder complications. Permanent prostate seed implantation appears to have a more pronounced effect on prostate tissues than external-beam radiotherapy.⁶ When assessed by means of endorectal magnetic resonance imaging and spectroscopy, the median time to the resolution of spectroscopic abnormalities was 32.2 months with external-beam radiotherapy and 24.8 months with permanent

prostate seed implantation. Moreover, the degree of atrophy and the magnitude of the decline in PSA levels were more pronounced after a permanent seed implantation than after external-beam radiotherapy.

Permanent prostate seed implantation and radical prostatectomy appear to confer similar rates of control of prostate cancer.⁷ Low-risk men 62 years of age or younger had a 7-year rate of cancer control of 93% when assessed on the basis of a PSA threshold for treatment failure of 0.4 ng per milliliter or higher.⁷ Permanent prostate seed implantation also results in better rates of continence and sexual potency than is expected with radical prostatectomy.⁸

In a recent, large, multi-institutional series involving a validated quality-of-life instrument to assess urinary incontinence 1 year after treatment, 85% of men reported having “no problem or [a] very small problem” with urinary incontinence after permanent prostate seed implantation as compared with 76% after surgery.⁸ With regard to sexual function 1 year after treatment, 53% of men reported having “no problem or [a] very small problem” after permanent prostate seed implantation as compared with 29% after surgery. If erectile dysfunction does occur, it is typically responsive to phosphodiesterase type 5 inhibitors such as sildenafil.

Five years after undergoing a well-performed implantation, most men have a PSA level of less than 0.1 ng per milliliter, and less than 1% have serious rectal or bladder complications.⁷ The risk of a late complication such as a radiation-induced second cancer appears to be low, as long as 20 years after treatment.⁹ In a recent study, one of the largest studies of permanent prostate seed implantation, men who underwent the irradiation did not appear to have a significantly increased risk of developing a secondary cancer at any of the 20 most common sites, as compared with men who were not irradiated.¹⁰ This risk should be weighed against a very low (but not negligible) 30-day operative mortality rate associated with radical prostatectomy.^{9,11} Permanent prostate seed implantation is a more convenient approach than radical prostatectomy or external-beam radiotherapy, since it does not require hospitalization, is associated with easier recovery, and has shorter overall treatment time — many men return to work the next day.

The key to a successful outcome after perma-

nent prostate seed implantation is to deliver a high dose of radiation to the entire prostate while sparing adjacent normal tissues. These goals are generally best accomplished by ensuring that the procedure is performed by an expert team including a radiation oncologist, a urologist, and a medical physicist.

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From the Department of Radiation Oncology, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco.

TREATMENT OPTION 3

Radical Prostatectomy

Peter Scardino, M.D.

This patient has a multifocal prostate cancer (present in 2 of 12 needle-biopsy cores) of intermediate grade (Gleason score of 6). His PSA level, although relatively low (3.8 ng per milliliter), has risen rapidly (1.15 ng per milliliter per year on average) over the past 2 years. He has a small prostate for his age (volume, 22 cm³), and his PSA density (the serum PSA level divided by the prostate volume) is high (0.173 ng per milliliter per cubic centimeter). The PSA velocity and density suggest a larger volume and more aggressive cancer than is indicated by the biopsy, which often underestimates the extent of cancer.

Expectant management of prostate cancer is attractive because it avoids the immediate side effects of treatment. Successful implementation requires the accurate identification of cancers posing little immediate risk to the patient's life or health and intervention early enough to cure the cancer once it progresses. However, the feasibility of long-term expectant management remains unproved.¹² There is no validated test to signal the impending spread of the cancer soon enough for successful delayed intervention, which is likely to be less effective and carry greater risks than immediate therapy.

In population-based studies, as compared with expectant management, active treatment with surgery or radiotherapy within 6 months after diagnosis reduced the risks of death from any

cause and from prostate cancer.¹³ In the only prospective randomized trial of active therapy as compared with watchful waiting, radical prostatectomy reduced the risks of metastasis and death from cancer or any cause over 10 years, regardless of the features of the cancer at the time of diagnosis.¹⁴

Radiotherapy is associated with 5-year rates of cancer control similar to those with radical prostatectomy and could be used to treat this patient's cancer. However, effective radiation, whether external beam or brachytherapy, requires very high doses and is associated with troublesome sexual and urinary side effects (from brachytherapy) or bowel side effects (from both external-beam radiotherapy and brachytherapy).⁸ In a recent comparative study of the quality of life after treatment of localized cancer, both forms of radiotherapy were associated with one or more bothersome complication — rectal urgency, frequency of elimination, pain, fecal incontinence, or hematochezia — in 9% of patients within the first year after treatment.⁸ With radiation, it is difficult to be sure that the cancer is eradicated, since PSA levels rarely become undetectable. Local recurrence tends to be detected late, if at all, when additional local therapy is hazardous and seldom effective. No randomized trials comparing survival rates after radiation and surgery have been published, but population-based studies show lower overall and cancer-specific survival rates after radiation for all risk groups.¹⁵

Given this patient's low PSA level and small-volume cancer on biopsy, it is highly likely (probability, 88%) that his cancer is confined to the prostate gland, making him an excellent candidate for nerve-sparing surgery. The operative mortality rate in a healthy 63-year-old is less than 0.1%. In a multi-institutional longitudinal study of the quality of life after radical prostatectomy, 2 years after the procedure, 20% of patients reported incontinence requiring the use of one or more incontinence pads daily, but urinary obstruction and irritation improved significantly, and overall distress from urinary symptoms was less than at baseline. Sexual function, especially the quality of erection, deteriorated substantially in the first 3 months but had improved at 2 years, especially in young men with low PSA levels who had undergone nerve-sparing surgery.⁸ Although these side effects are troublesome, they can be

mitigated through treatments that, albeit cumbersome, are widely available. If experienced surgeons perform the surgery, the risks are much lower. Radical prostatectomy provides better long-term cancer-specific and overall survival¹³⁻¹⁵ than expectant management or radiotherapy.

The probability that this patient's PSA level would become undetectable after radical prostatectomy and remain so for over 10 years is 98% (according to the nomogram at www.mskcc.org/mskcc/html/10088.cfm),¹⁶ minimizing the need for further therapy that would adversely affect his quality of life. After radical prostatectomy, unlike radiotherapy or expectant management, any rise in the PSA level signals recurrent cancer, which can be treated safely and effectively with the use of low-dose radiotherapy.¹⁷

Radical prostatectomy is a delicate, technically challenging procedure. Optimal results, attainable with the open retropubic, laparoscopic, or robotic-assisted approaches, depend more on the experience of the surgeon than on the technique itself. I would counsel this patient to find an experienced surgeon with a history of excellent results and to have his cancer treated through radical prostatectomy.

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From the Department of Urology, Memorial Sloan-Kettering Cancer Center, New York.

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