CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 15-2008: A 55-Year-Old Man with an Elevated Prostate-Specific Antigen Level and Early-Stage Prostate Cancer

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PRESENTATION OF CASE

Dr. Donald S. Kaufman: A 55-year-old man was referred to this hospital for management of prostate cancer. He had been well until approximately 1 year earlier, when he noted the progressively decreasing force of his urinary stream, increasing urinary urgency, and nocturia up to four times per night. At that time, he had noted decreased libido for several months, but his erections were adequate for intercourse. His primary care physician obtained a measurement of serum prostate-specific antigen (PSA), which was 6.6 ng per milliliter. The patient was referred to a local urologist. On examination, the abdomen and external genitalia were normal, and the prostate was smooth. Results of urinalysis were normal. Ultrasound-guided needle biopsies of the prostate were performed. Microscopical examination of the biopsy specimens disclosed adenocarcinoma, with a Gleason score of 6 out of 10, in specimens from the left base (involving 10% of the tissue) and the right midzone (involving 1% of the tissue). Biopsy specimens from four other sites were negative. Three weeks later, the patient was seen by a urologist at this hospital.

The patient was very frightened about the diagnosis of cancer and particularly concerned about loss of spontaneous erectile function. He had hypertension, for which he took atenolol (50 mg per day); he had had an appendectomy in childhood and a spontaneous pneumothorax as a young man but had been well otherwise. He worked as a construction supervisor and lived with his girlfriend and her children. There was no family history of prostate disease. Atenolol was his only medication, and he had no known medication allergies.

On examination, the blood pressure was 116/92 mm Hg; other vital signs were normal. The abdomen was soft and was neither tender nor distended. Rectal examination revealed a smooth, moderately enlarged prostate. There was no palpable lymphadenopathy. Computed tomographic (CT) scanning of the abdomen and pelvis showed an enlarged prostate; except for this finding and minimal scarring of the upper pole of the left kidney, the results were normal.

Radical prostatectomy and the management of sexual dysfunction were discussed. Consultation with a radiation oncologist was recommended. Three months

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later, the patient saw a radiation oncologist at this hospital. Conventional external beam radiation therapy, conformal high-dose external beam radiation, and brachytherapy were discussed.

A management decision was made.

PATHOLOGICAL DISCUSSION

Dr. Kaufman: Dr. Wu, may we see the biopsy specimens?

Dr. Chin-Lee Wu: Sextant needle core biopsies of the prostate were performed with ultrasound guidance. On microscopical examination, two of the six needle cores contained Gleason grade 3 adenocarcinoma (Fig. 1). Approximately 10% of the core from the left base (Fig. 1A) and about 1% of the core from the right midportion of the gland (Fig. 1B) were cancerous.

In reporting diagnoses of prostate cancer, we include the Gleason score, the number of cores in which cancer is involved, and the proportion of each core that is cancerous.[1] In the Gleason system for grading prostate cancer, the tumor is graded from 1 (most differentiated) to 5 (least differentiated). Since prostate cancers may be heterogeneous, with more than one grade, the two highest grades are combined to generate the Gleason score on a scale of 2 to 10.[2-4] In this case, the entire tumor was grade 3, making the score 3+3 (6 of 10).

The Gleason score correlates generally but not perfectly with long-term survival in patients with prostate cancer.[2,3,5] The prognostic value of the score on needle core–biopsy specimens, which were obtained in this case, is limited by sampling effect and tumor heterogeneity, resulting in undergrading of cancer in 42% of patients who underwent needle core biopsy in one study.[6] The involvement of cancer in multiple biopsy cores correlates with the presence of extensive cancer at radical prostatectomy, but detection of only a small amount of cancer on needle biopsy, as in this case, does not rule out the possibility that extensive cancer may be found in the prostate gland.[7-9]

DISCUSSION OF MANAGEMENT

Dr. Kaufman: Dr. Barry, would you discuss your view of the options for the treatment of early prostate cancer in this 55-year-old man?

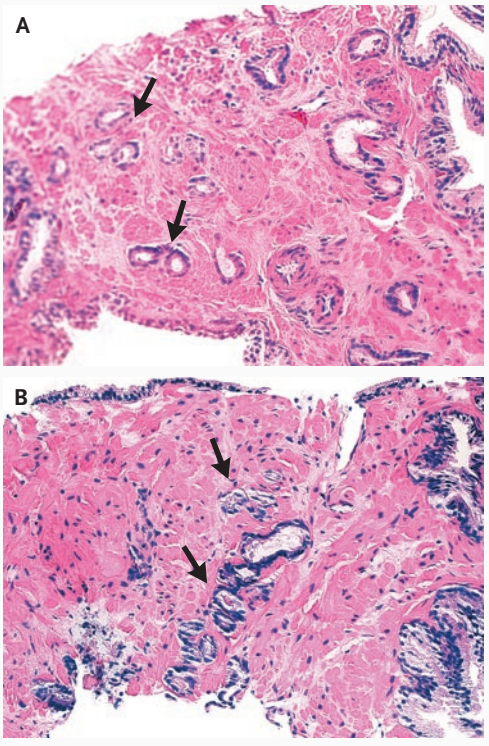

Figure 1. Specimens from Needle Core Biopsy of the Prostate with Gleason Score 6 (3+3) Adenocarcinoma (Hematoxylin and Eosin).

Specimens from the left base (Panel A) and right midportion (Panel B) of the prostate show a small, infiltrating, acinar-type adenocarcinoma (arrows).

IMPORTANT FEATURES OF THE CASE

Dr. Michael J. Barry: This 55-year-old man with clinically localized prostate cancer faces a choice of conservative management, radiation, or surgery. Each of these strategies has multiple variations that may bewilder patients. Key demographic and medical characteristics of this patient appear in Table 1. We also learn that he is frightened about both his diagnosis and the side effects of treatment. Helping him come to grips with these concerns is an important step in helping him make an informed decision about the management of his case. As is true for most men facing early-stage prostate cancer, some knowledge of the patient's values is required for the physician to help him make an optimal decision — in other words, the decision is preference-sensitive.[10]

Table 1. Key Information about the Patient.

Demographic and medical characteristics
55-Year-old man
Stage T1c prostate cancer
Small proportion positive in 2 of 6 biopsy cores (left and right)
Gleason grade, 6
Prostate-specific antigen, 6.6 ng per milliliter
Increasing lower urinary tract symptoms over the past year
Enlarged prostate detected by digital rectal examination and CT
Well-controlled hypertension
Patient's concerns
Very frightened about the diagnosis of cancer
Concerned about loss of spontaneous erectile function

DETERMINING THE PROGNOSIS

A good starting point would be to give the patient a realistic appraisal of his prognosis, considering what we know about him and his cancer. Many patients translate the word "cancer" into an imminent death sentence. Because the natural history of early-stage prostate cancer is so different from what most men expect, it is critical to address this misconception early to obviate the natural tendency to rush into a management decision that may be ill-informed.[11]

Characteristics of the Patient

A key factor to consider in assessing whether this cancer is eventually destined to cause illness and death is the patient's life expectancy, which is a reflection of both his age and coexisting conditions. U.S. life tables indicate that in 2003 the life expectancy for a 55-year-old man with typical coexisting conditions was about 24 years.[12] This patient is relatively healthy, with well-controlled hypertension, so thinking about his prognosis over a 25-year horizon is reasonable. Taking coexisting conditions into account in such projections in day-to-day clinical care is challenging. One simple approach is to have patients rate their current health as excellent, good, fair, or poor. Tables can then be used to estimate a so-called physiological age, based on the patient's chronologic age and self-rated health, which in turn provides the basis for an estimate of life expectancy.[13]

Characteristics of the Cancer

We can then turn to the characteristics of the patient's cancer to assess how it might affect his life expectancy. First, can we assess the extent of his cancer? When the biopsy was performed, was it likely that the cancer was driving the PSA elevation and was therefore extensive enough to be a likely cause of future problems, or was the PSA level elevated because of prostatic hyperplasia or inflammation, meaning that the cancer was probably not extensive enough to cause future problems?[14] It is impossible to choose between these two scenarios with the information at hand. The patient had symptoms of lower urinary tract dysfunction that progressed over the previous year. Neither the presence of symptoms suggestive of benign prostatic hyperplasia nor their rate of progression can reliably predict whether the prostate contains cancer. This patient had a uniformly enlarged prostate according to both digital rectal examination and the CT scan, suggesting that his elevated PSA level may be due to benign prostatic hyperplasia rather than cancer.

Relatively favorable features of this man's cancer that we do know about include the Gleason score of 6, which is, for practical purposes, the lowest value assigned by pathologists today; the PSA level of less than 10 ng per milliliter; the absence of a suspicious palpable abnormality; and involvement of cancer in a small number of core samples and a small proportion of each cancer-containing sample. This last point is controversial. In general, lower proportions of involved cores and smaller percentages of total cores containing cancer have predicted a lower cancer volume at radical prostatectomy and better prognoses, but the predictive value of these findings is far from perfect or consistent.[15,16] How these two variables interact remains uncertain, particularly in the current era of extended-pattern biopsies (12 or more cores).

The rate of increase in the PSA level (PSA velocity) has recently been reported to be of prognostic importance. A PSA velocity of more than 2.0 ng per milliliter in the preceding year has been associated with a higher risk of death after surgery or radiation, despite other favorable prog-

Table 2. Predicted 15-Year Outcomes for Men 55 to 59 and 65 to 69 Years of Age with Clinically Localized Prostate Cancer, Based on Two Sets of Projections.*

Characteristic	Projections by Albertsen et al.	Projections by Parker et al.		
Age (yr)	55–59	55–59		65–69
Gleason score	6	<7	7	<7
Outcome (%)				
Dead from prostate cancer	15	0	31	1
Dead from other causes	25	16	17	38
Still alive	60	84	52	61

* Projections are from Albertsen et al.[19] and Parker et al.[20]

nostic features.[17,18] Unfortunately, we have only one PSA measurement in this patient.

MODELS OF SURVIVAL IN THE PSA ERA

How can we use what we know about this patient and his cancer to estimate his prognosis in the absence of attempted curative therapy? Models based on data from the study by Albertsen et al.,[19] in which a large cohort of men with prostate cancer were not initially treated with surgery or radiation, indicate that for men 55 to 59 years old with clinically localized Gleason 6 tumors, 15% would die from prostate cancer at 15 years (Table 2). However, for men whose cancers are diagnosed because of screening for elevated PSA levels, these estimates are inaccurate; four phenomena come into play: overdiagnosis, lead time, grade inflation, and longer life expectancy.

Overdiagnosis refers to the fact that it is now possible to detect cancers that would not have been detected on the basis of clinical assessment alone and would not have led to symptoms or caused death during the patient's expected lifetime; the estimated average rate of overdetection of prostate cancer for 55-year-old men is 27%.[21] Lead time refers to the fact that cancers that would have eventually presented clinically are now being detected earlier because of screening, leading to longer survival from the time of diagnosis; the average lead time at the age of 55 years is estimated to be approximately 12 years.[21] Grade inflation refers to the tendency of pathologists to assign higher Gleason grades now than in the past. For example, of 366 prostate cancers assigned a Gleason score of 5 by pathologists between 1990 and 1992, 91% were given a Gleason score of 6 or higher in 2002 by a pathologist who reexamined the original slides.[22] The consequences of these three effects are that the predicted likelihood of dying from prostate cancer 15 years after diagnosis by means of PSA screening is lower than the predicted likelihood of dying from a cancer diagnosed clinically a decade or more ago. On the other hand, life expectancy is longer now than in the past because of reductions in mortality from competing causes, leaving more men susceptible to death from prostate cancer.

The Parker model, used to estimate outcomes for men with PSA-detected prostate cancers,[20] predicts that a man 55 to 59 years old with a Gleason score of 6 or lower who is initially treated conservatively would not be expected to die from prostate cancer over a period of 15 years (Table 2). Although the predicted outcomes look favorable, this patient's life expectancy is 25 years, so his eventual risk of dying of prostate cancer would be higher. Moreover, we do not really know whether this model would faithfully represent the outcomes for men like this patient who elect conservative management in the modern era.

Finally, we must remember that the aggressiveness of this man's cancer might be underestimated because of the small portion of the prostate sampled by the needle biopsy. If he has cancer with a Gleason grade of 4 that was not sampled when biopsy specimens were obtained, his actual Gleason score would rise to 7.[23] The natural history of Gleason 7 cancers is considerably less favorable than that of Gleason 6 cancers (Table 2).

THE CASE FOR CONSERVATIVE MANAGEMENT

A strategy of conservative management, without an immediate attempt at curative treatment, is a reasonable choice for a man with a favorable prognosis, especially if he is sufficiently concerned about the side effects of surgery and radiation.

As indicated in Table 3, there are several variants of conservative management. For this 55-year-old man with a 25-year life expectancy, active surveillance, with attempted curative therapy delayed until there is evidence of disease progression, is probably most reasonable. Although some clinicians believe that the probability of cure is always highest at initial presentation, this perspective misses the point that many early-stage prostate cancers do not need to be cured, and it ignores the effect of improvements in surgical and radiation techniques over time. However, some cancers may become incurable during observation, and patients electing this strategy must understand that this is a possibility.

Unfortunately, few data on outcomes are available for men undergoing conservative management since use of the PSA test has become widespread.[24] In the active-surveillance cohort described by Klotz,[25] the criteria for conservative management of early-stage prostate cancer for patients less than 70 years old included a PSA level of less than 10 ng per milliliter, a Gleason score of 6 or less, and stage-T1c or stage-T2a disease. The PSA level is checked every 6 months, and a repeated biopsy, with 10 to 12 specimens obtained, is performed at 1 year and thereafter approximately every 3 years. Attempted curative treatment is recommended when the PSA level doubles in less than 3 years or when a higher grade of cancer is present on repeat biopsy. With a median follow-up of 64 months, the predicted 8-year rate of cancer-specific survival is 99.2%.[25]

Despite these favorable short-term outcomes, concerns about the long-term prognosis and eventual development of incurable cancer, as well as patients' anxiety, have made conservative management a third choice for younger men such as our patient. In the United States, from 2000 to 2002, only 13% of men 55 to 59 years of age in whom cancers with Gleason scores of 5 to 7 were diagnosed were treated with conservative management.[26]

Table 3. Strategies of Conservative Management for Clinically Localized Prostate Cancer.

No curative treatment attempted initially; androgen-deprivation therapy for symptomatic metastases or local complications
No curative treatment attempted initially; androgen-deprivation therapy in anticipation of symptomatic disease on the basis of clinical monitoring, including prostate-specific antigen
Primary androgen-deprivation therapy
Delayed attempted curative treatment for progression (active surveillance or expectant management with curative intent)

SUMMARY OF MANAGEMENT

It is reasonable to give this patient the options of conservative management — particularly, active surveillance — and an immediate attempt at curative treatment with surgery or radiation, with a realistic description of the risks associated with each option. The optimal decision will depend greatly on the patient's preferences after he has been informed about his prognosis and the pros and cons of the various options. In this case, if the patient elects conservative management, I would favor a repeat biopsy with 10 to 12 cores either immediately or after a short period of observation. I would also recommend frequent PSA tests during the first year of observation to obtain a reliable estimate of the PSA velocity as early as possible.

Dr. Kaufman: This patient actually presented in 1996. I would like to ask the radiation oncologist and the urologist who treated him to comment on their initial management of the case.

Dr. Anthony L. Zietman (Radiation Oncology): There are two different discussions one could have with this patient — the discussion we had in 1996, when we first saw him, and the one we might have now. In 1996, I advocated external-beam radiation administered with what were then new three-dimensional conformal techniques that used CT imaging for more accurate delivery of the high radiation doses required for cure. Today, the discussion would entail many different radiation and surgical treatment options, as well as the possibility of not treating him at all.

Dr. W. Scott McDougal (Urology): In 1996, I strongly advocated a radical retropubic prostatectomy, and I still believe that surgery would be the preferable option. The patient was extremely concerned about his sexual dysfunction. I had an honest discussion with him at that time, and his risk of losing his erections was not insignificant.

Dr. Kaufman: In 1996, the patient decided, after careful consideration of the options presented by Drs. Zietman and McDougal, to undergo radical prostatectomy. Six months after the biopsy, he was taken to the operating room, but he abruptly changed his mind and canceled the procedure. He has had continued problems with obstructive urinary symptoms and a large residual volume.

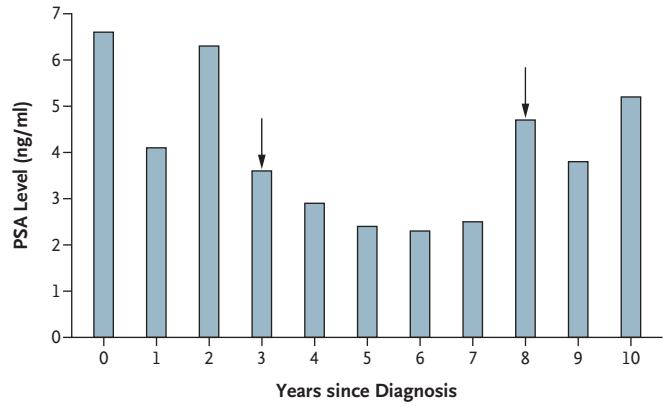

Figure 2. Serum Levels of Prostate-Specific Antigen in This Patient over a Decade.

The level of prostate-specific antigen (PSA) was 4.1 ng per milliliter 6 months after the diagnosis of cancer and 4.6 ng per milliliter 1 year after the diagnosis. Two years after the diagnosis, it was 6.3 ng per milliliter, and 3 years after the diagnosis, it was 3.6 ng per milliliter. At that time, finasteride was begun (arrow at left) because of obstructive symptoms; the PSA level remained between 2.3 and 3.1 ng per milliliter for the next 5 years, until the patient stopped taking finasteride (arrow at right) because of decreased libido. The most recent PSA level was 5.3 ng per milliliter, 11 years after the initial diagnosis.

The PSA level ranged between 3.6 and 6.6 ng per milliliter for the next 3 years. Three years after the diagnosis of prostate cancer, treatment with finasteride was begun because of obstructive symptoms; the PSA level ranged from 2.3 to 3.1 ng per milliliter for the next 5 years, until he stopped taking finasteride because of decreased libido. The most recent PSA level, measured 10 years after the initial diagnosis, was 5.2 ng per milliliter (Fig. 2). The patient feels well.

Dr. McDougal: The results of his prostate examination are unchanged, and a CT scan obtained for the evaluation of urinary retention 10 years after the diagnosis showed no change in the size of the prostate. I have not performed another biopsy in this patient because the results would not have altered my management of the case. The patient remains certain after 10 years that he wants to continue with observation unless the PSA level begins to rise steadily, at which time we might want to convince him to allow us to perform a biopsy. He is in excellent health and is very active both physically and professionally.

Dr. Zietman: Finasteride is a useful drug for men who have both benign prostatic hypertrophy and prostate cancer and are undergoing active surveillance. It suppresses excess PSA production due to benign prostatic hyperplasia. Increases in the PSA level while the patient is taking finasteride are therefore likely to be related to progressive cancer.[27]

Dr. Kaufman: Dr. Young, what is your experience with respect to changes in the Gleason score over time? Have you seen such changes in your department? And do you usually see rising Gleason scores over time in patients who undergo several biopsies?

Dr. Robert H. Young (Pathology): We have followed the national and international trend, recommended by a number of authorities, that one should not diagnose Gleason grade 2 cancer in a needle-biopsy specimen, so most patterns in biopsy material that were previously considered to be grade 2 are now considered to be grade 3. A downside of this trend, in my opinion, is the result that a great number of cases now receive a Gleason score of 6, and we may not be picking up on some prognostic differences.

Dr. Zietman: A recent study examined 38 radical-prostatectomy specimens taken from men with small, low-grade cancers who had received treatment after a long period of active surveillance,[28] and compared them with specimens from men who had elected immediate prostatectomy. There was no difference in the frequency of higher-grade cancers, positive margins, or other adverse features between the two groups. The authors concluded that deferred treatment does not close the window on the chance for cure in selected patients.

Dr. James A. Talcott (Hematology–Oncology): This patient faced an unusually difficult choice. He had to weigh the potential consequences of a usually slow-growing cancer against those of treatments with probably permanent side effects, reconcile the often conflicting recommendations from surgeons and radiation therapists, and accept that he, not the experts, would have to choose the best option available, given his own values and priorities. Choosing initial observation, arguably the best choice for most men, since most cancers are not life-threatening, usually requires that the patient reject the advice of doctors, family members, and even other patients, nearly all of whom choose active treatment. Prostate cancer is a frightening diagnosis for which the treatment is as likely to cause harm as to prolong life. A lowered threshold for

biopsies has the potential to affect many men. In the Prostate Cancer Prevention Trial, in which at least one biopsy was required for participation, prostate cancer was found in 25% of men within 7 years.[29] I believe that evidence of an aggressive cancer, not the anxiety a cancer diagnosis provokes, should trigger an additional biopsy in patients with apparently benign prostate cancer.

Dr. Kaufman: Dr. Barry, what would you now recommend for this patient, who is 65 years old?

Dr. Barry: The first question is whether we can safely assume that he still has a cancer with a Gleason score of 6. Serial biopsies suggest that dedifferentiation over time is relatively uncommon, although long-term data are lacking.[30] His PSA trajectory would further suggest that he has a cancer that is not aggressive. The second question is his life expectancy. It can be estimated at about 17 years with average coexisting conditions, but his physiological age, based on tables using self-rated health as excellent, suggests that his life expectancy is 22 years. According to the Parker model, his risk of dying from prostate cancer within 15 years is only 1% (Table 2). Thus, continued conservative management is reasonable, although information from examination of specimens from repeated biopsies would be helpful in confirming this assessment.

Dr. Kaufman: Are there any last comments from the urologists?

Dr. Douglas M. Dahl (Urology): It is important to counsel patients before PSA testing, but that is not the only opportunity for good judgment to be exercised. Many patients are referred to urologists for consideration of biopsy because of an abnormal PSA test. It is important to consider many variables, including the PSA velocity, the PSA density (the PSA level divided by prostate volume), the results of physical examination, life expectancy, and coexisting conditions. I have a thorough discussion with patients before proceeding to biopsy. I try to prepare them for the possibility of finding a very low-volume, low-grade cancer that may not require immediate treatment. A decision to screen patients with a PSA test should not be understood as the first link in an unstoppable chain of events leading to unwise diagnosis and treatment.

ANATOMICAL DIAGNOSIS

Adenocarcinoma of the prostate, Gleason score 6 of 10, clinical stage T1c.

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