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THE PROSTATE PARADOX

There are new techniques for fighting the cancer. But when should we use them?

BY JEROME GROOPMAN

On a recent spring morning, I spent several hours with Dr. Robert Eyre, a senior urological surgeon at my hospital, in Boston, watching him perform biopsies on men who might have prostate cancer. One patient was a forty-three-year-old office worker, whom I'll call Mr. O'Donnell. A recent physical examination had been entirely normal, but a routine test revealed that the level of the prostate-specific antigen, or P.S.A., in his blood was slightly elevated, which can be an early indication of prostate cancer. An internist had referred him to Dr. Eyre for a biopsy.

First, an ultrasound technician asked Mr. O'Donnell to lie on the examining table on his left side, facing the wall, with his knees flexed to his chest. To the technician's left, there was an ultrasonic probe, which was attached to a screen the size of a portable television. The probe had been covered with a condom and coated with lubricant. "You will feel pressure with the probe," the technician said. "That should be the worst of it." Then he slowly inserted the instrument into Mr. O'Donnell's rectum.

On the screen, a black-and-white picture suddenly became visible. At the top of the image, a large black triangular area indicated Mr. O'Donnell's bladder. Beneath it, one could trace the urethra, which carries urine from the bladder out through the penis. The prostate gland, through which the urethra travels, appeared on the screen as a pale-gray blob. Dr. Eyre studied the image carefully for irregularities, but none were seen. The probe was withdrawn, and Dr. Eyre palpated the gland with his gloved index finger.

"You're young, and the gland is large for your age, so your high P.S.A. may simply be due to a large gland," Dr. Eyre told Mr. O'Donnell. "While your prostate is over all a bit firm, there are no discrete suspicious areas, so I am going to perform random biopsies—four on each side of the gland. It shouldn't take too long." The probe was reinserted into Mr. O'Donnell's rectum while Dr. Eyre picked up a cylindrical, spring-loaded gun and attached a long needle to the top. The gun can deliver a great deal of pressure virtually instantaneously. The bore of the biopsy needle is very small—eighteen-gauge—and it retrieves a sample of tissue roughly the thickness of fishing line and a little more than half an inch in length.

"You'll feel pressure and hear a pop," Dr. Eyre said. "Try not to jump." Mr. O'Donnell drew his knees closer to his chest as Dr. Eyre slid the biopsy gun into the patient, inside the rectal probe. The sharp pop followed, and a white line flashed across the screen as the needle penetrated deep into the prostate gland and retracted. The doctor then removed the biopsy gun as the technician held open a small vial of formaldehyde, into which a pale-white filigree of tissue was deposited.

The entire procedure took less than ten minutes. When Dr. Eyre and I returned to his office, he told me that he was concerned. "Even though Mr. O'Donnell's P.S.A. level is appropriate for the size of his gland," he said, "this is the art of a very educated finger."

The prostate gland is roughly the size and shape of a walnut, and encased in a fibrous sheath called the capsule. We know that it produces proteins that are in seminal fluid, but its function is not fully understood. The nerves and blood vessels to the penis which control erectile function run along the gland's right and left edges.

The cells of the gland depend upon androgens for growth; these hormones also promote the growth of cancer. Most prostate cancers develop along the outer borders of the gland, away from the urinary stream, where they usually grow without causing symptoms. In general, the progress of the disease is extremely slow, possibly spanning decades; the majority of diagnosed cancers are confined to the gland, and are thus potentially curable. On the other hand, the prostate's location—beneath the bladder, around the urethra, and in front of the rectum—makes its treatment and removal particularly tricky.

If the cancer metastasizes, it usually begins by spreading locally, into the fat that surrounds the prostate. Over time, cancer cells can enter the lymph nodes in the pelvis and the bloodstream, most commonly landing in the bones and the spinal cord; advanced stages of the cancer are often marked by severe bone pain and paralysis, as the spinal nerves are strangled. Prostate cancer that has spread beyond the fat surrounding the gland is rarely curable.

Mr. O'Donnell had a fair chance of receiving bad news from his biopsy, even though he is a relatively young man: prostate cancer is the most common non-skin cancer among American men. With the advent of widespread P.S.A. testing, in the late nineteen-eighties, many more cases of prostate cancer are diagnosed yearly; at present, more than a million American men are diagnosed with prostate cancer. A family history of the disease increases your risk. If your father or your brother had prostate cancer, your risk increases twofold; if both had it, your risk is quintupled. An estimated thirty-seven thousand men died of it last year; only lung cancer causes more fatalities among men.

Many men who have not been diagnosed carry nests of "occult" cancer cells in the prostate, which are so slow-growing that they may never cause problems. Autopsy studies show that more than thirty per cent of men carry occult prostate cancer by the age

of fifty; by the age of eighty, nearly fifty per cent of men have some form of prostate cancer.

If Mr. O'Donnell learns that he has prostate cancer and educates himself about his condition, he will make another disconcerting discovery: there is a frustrating lack of consensus among medical professionals on how best to treat the disease. The advice that patients receive is frequently determined by the kind of specialist they consult. In cases where the cancer is confined to the prostate, urologists generally favor surgery to excise the cancer, whereas radiation oncologists may suggest external radiation treatment, or the implantation of radioactive seeds within the prostate. (A few specialists recommend freezing the gland in a treatment called cryotherapy.)One school of thought suggests that prostate cancer is a disease most men die with, rather than from—that only a small fraction of men will have a form of prostate cancer that affects the quality or duration of their lives. This consideration might support "watchful waiting," or observation without treatment, since surgery or radiation often causes impotence, incontinence, or both.

But in which cases is watchful waiting a reasonable response? The odds haven't been properly calculated. Unlike breast-cancer research, in which we have several decades of relatively sound data about the risks and results of various treatments, prostate-cancer research has not been conducted in a sufficiently standardized fashion. There have been no studies in which large comparable groups of patients have been randomly assigned to surgery, radiation, or observation and then followed for a significant period of time. Virtually all the published studies have been retrospective, and have been criticized as biased and methodologically flawed. To promote one therapy over another, some doctors claim success rates that are based on small numbers of favorable outcomes, and cite statistics on potency and continence that are misleading.

As a medical oncologist, I treat patients with metastatic prostate cancer. But recently I set out to learn more about how different specialists respond when a biopsy like Mr. O'Donnell's turns out to be positive, and I interviewed several experts at the forefront of their fields. One was Dr. Peter Scardino, the chairman of the Department of Urology at Memorial Sloan-Kettering Cancer Center, in Manhattan. Dr. Scardino is a firm believer in radical prostatectomy. He has published more than a hundred and seventy scholarly articles on the diagnosis and therapy of prostate cancer, and has performed nearly two thousand prostatectomies.

We spoke in the lounge adjoining the O.R., before we scrubbed for his midday case. Dr. Scardino is in his early fifties, with a full head of black hair, and he speaks with the gentlemanly graciousness of his native Savannah. "We'd all like to understand the biology of prostate cancer, so that we could individualize the treatment and make it fit each man," he said. "But this disease is so variable that we need to understand the science better before we can make definitive recommendations. And we have to refine our techniques of both surgery and radiation to such a degree that we limit complications of erectile dysfunction, bowel difficulties, and incontinence. Then, for the patient, it can become a matter of taste: Do you prefer Italian or Chinese?"

Dr. Scardino readily acknowledged that the field suffers from "turf" battles. For many years, surgeons were reluctant to consider other forms of therapy, and, without reliable data, it is difficult to persuade other specialists to change their favored forms of treatment. But Dr. Scardino also pointed out that the biases of doctors are only part of the picture; the cultural and psychological biases of the patients also play a role.

"I recommend to some of the patients referred to me that we just follow their cases closely and not intervene with surgery or radiation," he said. "But it is hard for men to defer therapy. Maybe one in ten agrees to be followed closely. It is part of the American culture—the way medicine is practiced and the expectations that people have. Some doctors are also concerned about liability. If you follow someone closely and the cancer spreads under your watch, will you be sued?"

Dr. Scardino said that at a medical meeting he attended in Great Britain several years ago the conference chairman had asked which doctors in the audience performed P.S.A. testing routinely. "The Americans raised their hands—the National Health Service in Britain does not endorse P.S.A. screening," Dr. Scardino said. "Then the chairman asked the doctors whether they were treating large numbers of their patients with careful monitoring rather than with active intervention. Now the Brits raised their hands."

We entered the O.R. and met the patient, whom I'll call Mr. Drake. He was fifty-one years old and, like Mr. O'Donnell, had no clinical symptoms and an elevated P.S.A. on a routine physical examination. But Mr. Drake's biopsy had showed cancer with a high Gleason score. (The Gleason score is a calculation that indicates the cancer's level of aggressiveness; the higher the score, the greater the danger that the cancer will spread beyond the prostate.) Dr. Scardino also showed me a nomogram, a graph that predicts the probability of the cancer's returning five years after the operation. We calculated the probability for Mr. Drake at about thirty per cent.

Mr. Drake lay on the operating table, his arms extended in a cruciform posture. Dr. Scardino placed his hand reassuringly on the patient's arm. As the anesthesiologist began to administer the sedative, Mr. Drake said to Dr. Scardino, "Try your best to preserve my nerves."

An incision was made, beginning about an inch below the navel and ending about an inch above the base of the penis. Dr. Scardino operates with a headlight, like a spelunker, and magnifying lenses that resemble jeweller's loupes. "This operation is not forgiving," he said to me. "The margin of error in damaging the nerves to the penis or the sphincters that control the bladder is usually one to two millimeters. Magnifying loupes are used in neurosurgery, and I use them because I want that kind of precision."

In Mr. Drake's case, the area of the prostate thought to be cancerous was at its outer border, right next to the nerve tracts, so the procedure would clearly be a challenge. "You must get clean margins," Dr. Scardino said. "But there is a wide variation among surgeons about what we call margins and whether we dissect out every bit of the gland." Dr. Scardino is well aware that removing less tissue may cause less damage to the nerves;

this means not only a greater likelihood that the patient will retain his potency but a better track record in this area for the surgeon, as well. Still, he considers the risk of leaving cancer behind an unacceptable one.

A plastic surgeon was on call to do a nerve graft from the patient's foot should Dr. Scardino be forced to remove the nerve bundle. "A lot of people think that nerve grafts have not been proved to sustain erectile function," Dr. Scardino said. "They were done years ago, but they were done by urologists, not plastic surgeons, and they didn't work very well. I just submitted a paper on cases where nerve grafts were used in twelve men in whom both left and right nerves had to be cut to remove the cancer. Four of the twelve had return of reasonable erectile functioning, meaning that they achieved erections sufficient for vaginal penetration in about half the attempts."

Dr. Scardino focused intently as he cut deep into the pelvis, searching first for the lymph nodes that surround the prostate gland. I tried to identify the anatomical structures—it was like looking into a shadowed well of blood and bowel and nerves and arteries and muscle. "We are there," Dr. Scardino said to me when he had cut down to the thick grayish-white sheath of the prostate capsule. It resembled a clamshell. He felt the surface of the gland. "It's firm on the right side. We'll have to do a wider dissection to get it all. But maybe we'll be lucky and won't have to take the nerves with it."

As the likelihood increased that a nerve graft would be needed, the plastic surgeon was paged. "I'm encouraged by our pilot study," Dr. Scardino said, "but what we need is a formal randomized prospective study of urologists working with plastic surgeons to prove that grafts are truly valuable in sustaining potency."

A few moments later, Dr. Scardino showed me what looked like a mass of yellow strands that were the thickness of a silk thread: "That's probably the nerve bundle." Most of the strands ran alongside the prostate gland into the penis, but projections of nerves also splayed over the capsule of the gland.

A nurse stood by a new machine called a CaverMap, which looks like a VCR console with a digital display on the front. This device would help confirm the location of the nerve bundle and assess erectile function before and after the prostate gland was removed. A thin plastic tube filled with mercury was fit around the base of Mr. Drake's penis, and attached to a strain gauge. Dr. Scardino took an instrument the size of an electric toothbrush with an electrode at its end. After determining the baseline pressure, he applied the electrode to the bundle of nerves he believed ran to the penis. I watched as the penis jumped slightly and then slowly reddened and engorged. Blue arrows on the CaverMap console raced upward. "That's the nerve bundle, all right," Dr. Scardino said.

Over the next forty minutes, Dr. Scardino performed a series of cuts circumscribing the prostate gland. "We are going to have to take some nerves on the right side," he said. I watched as the fine yellow fibers were sliced away. Finally, the doctor lifted the gland out of the patient and placed it gingerly on a green towel; a bright lamp was focused on it by an assisting nurse. Dr. Scardino examined its surface, showing me again the nerves that had been sacrificed. "Let's check to see whether what we left works."

He positioned the electrode over the remaining bundle of fibers. A dull whine that sounded like a faulty smoke detector emanated from the machine. “Zero,” the CaverMap nurse said. “No sign of movement.” Dr. Scardino moved the electrode further into the pelvis, following the course of the nerves until he had almost reached the place where they were lost in the muscle and entered the penile shaft. Again, there was a whine from the CaverMap, indicating no change in the pulses from the strain gauge. Again, there was no sign of movement.

“Let’s let his blood pressure rise,” Dr. Scardino said to the anesthesiologist. “Bring it up above a hundred and keep it there.” Then he turned to a resident who was assisting him. “Loosen the clamps on those arteries.” (An erection requires blood flow, and the patient had already lost about a litre of blood during the operation.) The monitor near the anesthesiologist showed a gradual return of Mr. Drake’s blood pressure, and Dr. Scardino placed the electrode over the nerve bundle on the right side of Mr. Drake’s pelvis. The CaverMap began its dull whine. Then the noise was interrupted by a series of sharp clicks. “Plus one,” the nurse announced. Seconds passed. “Plus two.” At twenty seconds, the strain gauge had fallen back to plus one. Luminescent blue arrows raced up the display on the CaverMap. The penis swelled to about half its prior breadth. “He is anatomically intact,” Dr. Scardino said. “It was fortunate that his nerves were just far enough away from the capsule. There is no need for a nerve graft.”

Dr. Scardino was pleased, but also cautious. “You get your final report card quickly from the pathologist,” he reminded me, meaning that in the next three days he would learn whether the margins that he had carved were indeed free of cancer cells. “I’ll learn whether we made the right judgments.”

Mr. Drake would have a catheter in his bladder over the next week to ten days. “After we take it out, we’ll see if he is dry,” Dr. Scardino said, referring to the frequent complication of temporary urinary incontinence. Dr. Scardino does extensive follow-up interviewing with his patients after surgery; after a year, the majority of them have fully regained continence. Mr. Drake would be given a prescription for Viagra. If after six weeks he was not having satisfactory spontaneous erections, he would be advised to begin injections of drugs into his penis, which may hasten the return of erectile function.

Shortly after the surgery, Dr. Scardino met with Mrs. Drake. “Things went well,” Dr. Scardino said, reaching for her hand. “We saved about eighty per cent of the nerve on the right. He has an aggressive cancer, and I don’t know yet if this cured him. But we are hopeful.”

For many years, radiation treatment of prostate cancer has been explored as an alternative to surgery. By and large, older men who had serious underlying illnesses, like heart disease or emphysema, were judged to be risky surgical candidates, and thus were referred by urologists to radiation oncologists. So were patients with large, bulky tumors that were judged impossible to remove. But the complications from the therapy were significant, including radiation injuries to the rectum, bladder, and urethra which caused

rectal bleeding and bladder irritation. Erectile dysfunction often appeared months later, after the shrinking and scarring of small blood vessels in and around the nerves of the penis. Although there were few strictly reliable studies comparing prostatectomy and radiation treatment, the informal consensus was that the latter was inferior. (Of course, the patients being referred in the first place were those who were medically frail or had a poor prognosis.) Now, however, advances in technology may make radiation a comparable option to surgery for many more patients.

After watching Dr. Scardino operate, I went to meet Dr. Steven Leibel, who is the chairman of radiation oncology at Memorial Sloan-Kettering Cancer Center. Dr. Leibel has graying hair, horn-rimmed glasses, and a warm laugh. He and his group are developing a form of treatment called "intensity-modulated radiation therapy." It uses high-performance computers and computer-driven radiation machines that can safely deliver intense levels of radiation to the prostate, sculpting the beam to fit the precise anatomy of the gland and largely sparing the rectum and bladder. As in Dr. Scardino's surgery, a miscalculation of a few millimeters can be catastrophic. Before the new technology was developed, Dr. Leibel explained, the dose that could be delivered had been severely limited because of the potentially serious side effects. "Now we give a wish list to the computer regarding the tolerance of the rectum and the bladder and the dose we want to aim at the prostate," he said. Patients' anatomies differ, and each person's anatomy can be reconstructed in three dimensions using a CT scanner. Special radiation machines have been designed with between twenty-six and sixty pairs of tungsten leaves; these leaves move during the therapy, absorbing different levels of radiation and shaping the beam as it is projected to the tissue.

We took the elevator down to the first floor and sat with a group of radiation physicists who were typing commands into computers for different patients that day. Dr. Leibel called up one patient on a screen that was split into two parts. One section of the screen projected a two-dimensional image of the patient's pelvis; the second presented what is called a "wire-frame projection," a three-dimensional representation of the bladder, the prostate, and the rectum which is constructed from multiple CT scans.

Wire-frame projections resemble slinky toys, and the computer can rotate them, so that you can look at them from the top, or from the bottom, or from the side. Different shades representing different doses of radiation can be added to the image; Dr. Leibel typed in a series of commands, and the computer projected a palette of white, red, and blue over the 3-D projection of bladder, prostate, and rectum.

"How do you know that this software actually works?" I asked.

Dr. Leibel explained that the system was initially constructed using customized synthetic parts built from a material whose density corresponded exactly to that of the tissues of the pelvis. Dosimeters were placed in the parts. Only after his group felt confident that the computer was calculating the correct doses in a precise fashion was the system used on patients.

We left the simulation room and moved to the treatment area. Two technicians were operating a bank of computers. Patients in bathrobes and green hospital slippers

were moving in and out of different rooms. “Patients spend fifteen minutes on a machine,” Dr. Leibel said. “First, they must get into a special plastic cast, which has been molded to their anatomy, and which fixes them on the table to receive the beam from the X-ray machine. Then they are radiated for four and a half minutes.”

I watched as a technician flipped a switch and a massive lead door some ten inches thick slowly drifted shut; then she activated the X-ray machine. As the beam was projected, a series of blue rectangles appeared on the computer screen, each one representing a tungsten leaf used to manipulate the beam; the leaves slid back and forth, modulating the radiation in a precise correspondence to the dimensions of the patient’s prostate gland.

The technology has allowed escalation of the standard radiation dose to 81 Gy from the conventional limit of between 65 and 70. Moreover, the incidence of rectal bleeding has fallen from fifteen per cent to three per cent. Initial data from some two hundred and twenty patients, based on prostate biopsies two and a half years after treatment, show that as the radiation dose is increased a larger proportion of men have no residual cancer. The difference can range from fifty-one per cent being free of cancer cells at standard radiation doses to ninety-one per cent at the higher 81 Gy dose. But at least a decade must elapse before the figures are truly meaningful.

“Prospective trials are essential,” Dr. Leibel concluded. “Our goal is to compare the 3-D computer-assisted radiation to standard radiation and to surgery. We’ll also use new biological and molecular imaging technologies to try to show us where the cancer cells are hiding in the gland. That way, we can focus the most intense radiation on those areas.”

This form of treatment generally requires daily sessions that span some nine weeks. Other radiation oncologists are refining a onetime procedure called brachytherapy, which involves the implantation of radioactive seeds in the prostate. I visited Dr. Anthony D’Amico, who is the chief of genito-urinary radiation oncology at the Brigham and Women’s Hospital and Dana-Farber Cancer Institute, in Boston. We met two stories below the ground level of the hospital, in the brachytherapy suite. A wiry thirty-eight-year-old, Dr. D’Amico earned a Ph.D. in physics from M.I.T. before he got his M.D. He is optimistic about the possibilities of brachytherapy, but he is also aware of the lack of data to justify its widespread application, and so he selects his patients carefully: they all have very early-stage, unaggressive cancers confined to the gland. That morning, a sixty-three-year-old man whom I will call Mr. Keller was being treated with a refined technique of seed implantation. “Everyone who comes here under the age of seventy is first offered a radical prostatectomy as the gold standard,” Dr. D’Amico said, “but this patient was fearful about incontinence and chose a non-surgical approach.”

Dr. D’Amico was working with a team of medical experts that included an M.R.I. specialist, radiation physicists, and a urological surgeon. In an anteroom, he showed me Mr. Keller’s earlier M.R.I. scan on a computer screen. Fine shades of gray formed the familiar walnut shape. Commands were typed on the computer keyboard. Red dots

appeared on the M.R.I. image. These indicated where nests of cancer cells were situated in the gland, and where the radioactivity was to be seeded. The computer then superimposed green dots, simulating the trajectories of the needles that would deliver the radioactive seeds.

We entered a cool, cavernous concrete room, where Mr. Keller was lying in a special M.R.I. machine. On each side of him were six-foot magnets, which looked like giant metal doughnuts. He was under general anesthesia, his legs raised and held in stirrups, like a woman undergoing a gynecological examination. A firm coil, called an obturator, had been inserted into his rectum to exert constant outward pressure and prevent motion of the prostate during the procedure.

Behind leaded glass, a radiation specialist was loading titanium-encased Iodine-125 pellets into a needle. Each pellet is two and a half millimeters in length. The dose of radiation to be delivered had also been customized to Mr. Keller's gland by the computer. A plastic template was fixed to the skin between his scrotum and his rectum. Dr. D'Amico's assistant then took the needle and inserted it, through a hole in the plastic template, into Mr. Keller's prostate. As the assistant threaded another long needle loaded with radioactive seeds through the plastic template, Dr. D'Amico told me, "We are currently designing a robotic arm to make the needle insertion even more precise."

During the procedure, the M.R.I. specialist watched the computer screen, where images of the prostate were being generated every three seconds. "We need to move the needle three millimeters to the patient's right," the M.R.I. specialist said. The computer screen with the M.R.I. image showed the line of the needle just missing a virtual marker, a white "T." Dr. D'Amico's assistant repositioned the needle until it corresponded with the target. After forty minutes and twenty-four needles, Mr. Keller had ninety titanium pellets filled with radioactive iodine permanently embedded in his prostate.

"This is all a matter of trying to improve techniques so that patients can be cured and enjoy a better quality of life," Dr. D'Amico explained. Each week, two or three of his patients undergo brachytherapy. A hundred and thirty-eight patients have been treated to date; seventy-four patients have been followed for a year, and fifteen patients for two years. About five per cent have short-term problems with "urinary urgency," but this passes. There has been minimal inflammation of the rectum from the radiation.

As with radical prostatectomy, however, the patient is likely to have difficulties achieving an erection, although these difficulties may take longer to appear. "Our potency outcomes are competitive with nerve-sparing surgery for a young man who is fully potent before the procedure," Dr. D'Amico said. "Again, I emphasize, these are highly selected patients, but, at two and a half years, our small series shows that about twenty-five per cent have significant problems with erections." In his study, there have been no cases of recurrent prostate cancer after the seed radiation, to judge from the patients' P.S.A. levels. But, like Scardino's nerve-graft study, the sample size is still so small as to be almost statistically insignificant, and, like Leibel's studies, much longer follow-ups are needed before conclusions can be drawn.

"The next advance in prostate-cancer diagnosis will be using optics," Dr. D'Amico predicted. He is collaborating with physicists and electrical engineers at M.I.T. on using a fiber-optic scope inserted into the prostate to produce a beam of near-infrared wavelengths. The image that results has a resolution of ten microns, about the size of a cell, to a depth of three millimeters. In the future, Dr. D'Amico believes, the interior of the prostate gland will be visualized this way, and the cancer assessed without the need for biopsy. This would allow a doctor to select a treatment based on a complete knowledge of where his patient's cancer lies and how aggressive it appears.

Despite the serious side effects that can accompany surgery and radiation therapies, most of the doctors I spoke to generally believed in early, aggressive intervention: prostate cancer that does spread is a debilitating, excruciating, and essentially incurable disease. Once the cancer has metastasized, surgery and brachytherapy are no longer treatment options, and the patient must undergo hormone therapy for the rest of his life. Years ago, I cared for a sixty-eight-year-old man, whom I'll call Peter Manuel, suffering from advanced prostate cancer. Three years before he came to see me, Mr. Manuel had developed symptoms of an enlarged prostate. This was ascribed to his age, and a local urologist performed a trans-urethral prostatectomy, shaving away the enlarged parts of the gland which obstructed the outflow of urine through the urethra. Within the shavings were areas of cancer. The cells had a large and distorted shape, aggressive in appearance. Mr. Manuel underwent a second operation, in which the urologist excised several lymph nodes that rested against the back of the pelvis. Deposits of prostate cancer were found within these nodes. The urologist treated Mr. Manuel with a combination of hormone blockers to retard the progress of the disease, but within a year the prostate cancer had spread to his lower spine.

By the time he was referred to me, Mr. Manuel looked like many other aging men with bone metastases from prostate cancer. A short, neatly dressed gentleman, he offered a ready smile, but his eyes seemed heavy and vacant. He was taking large doses of Percodan for the back pain, and I noticed how slow his steps were, and how long it took for him to find a comfortable position lying down. A physical exam showed the effects of his hormonal therapy. His testes were atrophied, the size of two marbles, and there was modest enlargement of his breasts; hormone therapy nearly always leaves the patient impotent. When I pressed firmly on his lower spine, he winced in pain. The cancer in his bones was leaching out calcium, which was now elevated in his blood system. High levels of calcium cause mental dullness, thirst, kidney stones, and disturbed heart rhythm.

After the exam, I explained to Mr. Manuel and his wife that at this stage of the disease we were unable to cure the cancer; we could only attempt to control its growth and minimize the pain it caused. For some four months, the pain was lessened as X-ray therapy burned away the cancer. Several weeks later, however, Mr. Manuel had a gnawing pain in his lower back. An M.R.I. scan showed that the cancer had quickly regrown and was now pressing on the spinal nerves. A neurosurgeon excised some of the cancer from the surrounding nerves, to prevent paralysis.

Three months later, symptoms returned. Mr. Manuel wanted to be treated, as he put it, until there was no hope left. Tumor masses now studded his abdomen and bones, and chemotherapy did little to help. Soon his blood calcium began to rise, and all the measures we attempted to reduce it were to no avail. He drifted into a coma. His wife agreed that nothing more should be done, and he died.

It is terminal cases like Mr. Manuel's that inform the debates among oncologists about P.S.A. testing and encourage doctors to recommend intervention for early-stage disease like Mr. Drake's. But we must recognize that that perspective, too, is only a partial one. The drawbacks of intervention in early-stage prostate cancer may be less drastic and less visible to the medical community, but they may be extremely significant to the patient. Most prostate-cancer patients do not have access to either the technologies or the highly skilled specialists that I encountered in my research. And there remains the vexed problem of how to balance the consequences of intervening with the consequences of not intervening.

Dr. James Talcott is a medical oncologist and the director of the Center for Outcomes Research at the Massachusetts General Hospital Cancer Center, in Boston. He has analyzed different interventions for prostate cancer, weighing issues of quality of life against those of survival. "Assessment of the outcomes of serious diseases like cancer has generally been a process of body counting," he told me. But prostate cancer, he argued, is different.

"Think about it," he continued. "Nearly two hundred thousand men a year are diagnosed with prostate cancer, and annually about thirty-five to forty thousand die. That means that for the vast majority the cancer is not the cause of death. For most, it's like diabetes, chronic and controllable, for one or two decades, and then for the unfortunate minority who die of the disease, during the last six months, it's like lung cancer, with the tumor spreading widely and causing pain and debility."

Does that mean that we need to recast our concept of this particular disease, to start thinking about it differently from the way we think about other common cancers? Given what we know—and don't know—why should we be so eager to treat? The fundamental challenge in recommending what to do after the diagnosis, Dr. Talcott believes, is to "fit prostate cancer in with the life cycle of the man."

Dr. Talcott studies outcomes based on interviews and questionnaires with patients rather than on statistics from surgeons or radiation therapists. "A patient doesn't like to tell a doctor who he thinks saved his life that he is leaking urine or is impotent. It's a magical relationship between patient and doctor—especially among older men, who are reluctant to say things that they fear may be unwelcome by their physician." He and a colleague, Jack Clark, have conducted focus groups among men of different ages and different races to target key issues in assessing quality of life. "Men never give up being sexual people," Dr. Talcott said. "What we learned from the focus groups is that no man ever stops thinking about sex."

Dr. Talcott is also keenly aware that the statistics made available to patients before surgery can be misleading. In a recently published study, conducted among several Harvard hospitals, Dr. Talcott found a high frequency of impotence and incontinence after prostatectomy. This contrasted with some of the studies published over the years by individual surgeons which claimed impotence rates of less than thirty per cent and incontinence rates close to zero. “I explain to patients that these published series select for the nerve-sparing operation the youngest, healthiest men who have the highest level of potency before therapy,” Dr. Talcott said. “These are usually not the men in their sixties or seventies sitting in my office.”

The important questions are who needs treatment and who needs watching. “More than three-quarters of the patients don’t really need to be treated,” Dr. Talcott said. “The whole battle about what is the best treatment targets between three and fifteen per cent of all the men diagnosed with prostate cancer. And if we know whom we need to treat we then have to show how significantly that treatment would extend life.”

This battle over early treatment has intensified with recent data that show a decline in the rate of death from prostate cancer. Dr. Talcott, for one, is not sure that the decline is the result of early diagnosis through P.S.A. screening. “The only certain impact of P.S.A. screening is that patients are being diagnosed earlier and therefore have the best prognosis, since you enlarge the pool of men with small, early, slow-growing cancers not causing symptoms,” he said. It is possible that the improved statistics may be due to other factors entirely—changes in the accuracy of data collection from death certificates, for example, or in the diet of the American male. “Has P.S.A. screening just forced men to make decisions five to ten years earlier than they otherwise would, decisions that change their life with regard to quality?” What’s more, Dr. Talcott points out, the information available to help patients make the right choice is insufficient. “Without randomized prospective trials, we do not know that one approach to prostate cancer is better than another,” he said. And yet, for the patient facing a more than twenty-per-cent chance of ending his life on hormone therapy and in terrible pain, doing nothing seems equally inadequate.

“I tell my patients to do thought experiments,” Dr. Talcott went on. “Try to imagine your life after a radical prostatectomy, where you are impotent. Try to imagine your life after radiation therapy, where you suffer with urinary or bowel irritation. Then imagine that you’ve done nothing, just been closely monitored. In each scenario—surgery or radiation or just observation—then imagine that the cancer has come back. Which bullets are you willing to take?”