

A 64-Year-Old Man With Low-Risk Prostate Cancer

Review of Prostate Cancer Treatment

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DR AMY SHIP: Mr D is a 64-year-old man with newly diagnosed prostate cancer. He lives in the greater-Boston area and has commercial insurance.

Mr D's prostate cancer was diagnosed incidentally. When his PSA [prostate-specific antigen] level was found to be elevated as part of a workup for erectile dysfunction, he underwent prostate biopsy. His pathology revealed adenocarcinoma in the right mid apex, with a Gleason score of 6, involving 10% of a single biopsy core from among a total of 10 cores taken at biopsy (FIGURE). Two other cores revealed high-grade prostatic intraepithelial neoplasia and 1 focus of atypia suspicious for adenocarcinoma. Urological history is notable for nocturia once per night, passage of a ureteral calculus spontaneously once in the past, and bilateral inguinal herniorrhaphy and left hydrocelectomy 2 years ago. He has no family history of prostate cancer.

Mr D's past medical history is otherwise significant for gastric ulcer thought to be due to nonsteroidal anti-inflammatory use, which led to 2 episodes of significant GI [gastrointestinal tract] bleeding, remote paroxysmal atrial fibrillation in the setting of a filariasis infection, intermittent sinusitis, hyperlipidemia, and depression.

His medications include atorvastatin 20 mg per day, duloxetine hydrochloride 20 mg daily, lorazepam 1 mg nightly, and sildenafil 100 mg as needed. He is considered intolerant to nonsteroidal anti-inflammatory drugs because of the gastric ulcer but has no frank allergies to any medications.

Mr D has a history of tobacco use from ages 13 to 23 years. He drinks alcohol daily, 1 to 2 glasses of wine or hard liquor. He works full time as a researcher, lives with his second wife, and has 2 adult children.

Earlier detection of prostate cancer in the past decade has been accompanied by greater reduction in US prostate cancer mortality than that seen with any other cancer. Prostate cancer is usually diagnosed at early stages and is most commonly treated by prostatectomy, radiotherapy, or brachytherapy. For intermediate- and high-risk prostate cancers, randomized clinical trials have shown survival benefit subsequent to prostatectomy or to combined radiation with androgen-suppressive therapy. However, prostatectomy, radiotherapy, and brachytherapy each can lead to distinct adverse effects. Moreover, for the lowest-risk categories of early stage prostate cancer, evidence supporting an intervention is only indirect. New approaches to surveillance of prostate cancer have consequently emerged that do not eschew treatment altogether. Instead "active" surveillance aims to implement definitive intervention effectively for those low-risk cancers that show a propensity for progression as evidenced by histopathological or serological change during the surveillance interval.

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On physical examination at the time of his urological consultation, Mr D appeared well and had normal vital signs. His digital rectal examination showed a benign prostate to palpation, approximately 30 mL in size.

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Mr D's PSA result that prompted a decision for biopsy was 5.3 ng/mL. A year earlier the value had been 3.0 ng/mL. At the time of his consultation for considering his prostate cancer care options (2 months after his prostate biopsy and 4 months after the PSA level of 5.3 that had prompted biopsy), the PSA was 4.5 ng/mL, indicating an inconsistent rate of change or PSA velocity. His testosterone was in the normal range at 362 ng/dL.

MR D: HIS VIEW

I went to see the urologist because my internist had thought that my testosterone levels might be a little low, and he wanted to get that more fully evaluated. I actually thought he would help me very effectively. He was very, very straightforward about it. He made it clear that this was not something immediate and that with watchful waiting, I had the possibility of not being involved in surgery. He confirmed that there was the possibility of someone finally figuring out what might be the best way to go or that there would be some new treatment. It doesn't preclude any options in a year or 2 years, 5 years, whatever.

I thought a lot about the risk of mortality. But I really feel like that was not on the table for me. So the things that bothered me most were the side effects. I was very concerned about impotence. I really did not like that idea at all. The bowel and incontinence thing, well, I didn't like that either.

In meeting with the surgeon and the radiologist, there may have been some change in my thinking about it. At first, I thought that the watch-and-wait approach would be fine. Second, I think I went in to the meeting with the idea that surgery would be the likely option. And then I came out of there thinking maybe the radioactive pellets would be a better choice.

Since I decided on watchful waiting, I then decided that I didn't have to decide. So I talked to a Chinese American friend of mine. Her father was a physician who was very famous and very well-known in our community for using alternative medicines. She prescribed 3 different medications for me starting about 5 weeks before I went to see the surgeon and the radiologist for the consult. She swore that these would lower the level.

At that moment, I saw no harm in taking them, but my surgeon was very negative about it. After a very discouraging meeting with him, I stopped taking the alternative medicines. If he had said, "This isn't going to help or harm," I probably would have continued. But he was pretty clear about saying that he thought it was a really bad idea. Of course 2 days later, my level was lower.

I felt the urologist who brought me the diagnosis was terrific. He understood that this is a surprising thing to hear about. There wasn't an overwhelming amount of information, which I think often happens in serious situations where bad news is delivered. I felt very well cared for and part of a very well-planned process. That's really been very effective.

It's also allowed me to think pretty clearly about where to go and what to do.

QUESTIONS FOR DRS SANDA AND KAPLAN

What is the epidemiology of prostate cancer? What is known about the natural history of prostate cancer? What treatments are available and how effective is each? What are the indications for surgery vs radiotherapy vs medical treatment vs watchful waiting? What are the complications of each treatment? How do you advise patients about their options? What does the future hold? What do you recommend for our patient?

DRS SANDA AND KAPLAN

Prevalence and Natural History of Early Stage Prostate Cancer

Prostate cancer was the most second common cancer in the United States in 2008, excluding skin cancer, with 186 000 new cases.¹ However, in terms of cancer deaths per case diagnosed, prostate cancer is less lethal than many cancers. In 2008, prostate cancer ranked fifth in total annual deaths among all cancers, with 28 600 deaths. A reduction of prostate cancer mortality over the past decade has been accompanied by earlier cancer detection, and so it is increasingly common to see patients like Mr D in the earliest stages of their cancer. Mr D is faced with a range of care options for his clinical stage T1c prostate cancer, including active surveillance, radical prostatectomy, external beam radiotherapy, or brachytherapy. Selecting the best care option for patients with early stage prostate cancer is not straightforward because good-quality evidence directly comparing different treatment options for early stage prostate cancer is sparse. Consideration must be given not only to the survival consequences and acute morbidity of each approach, but also to the possible effects of treatment or surveillance on quality of life.

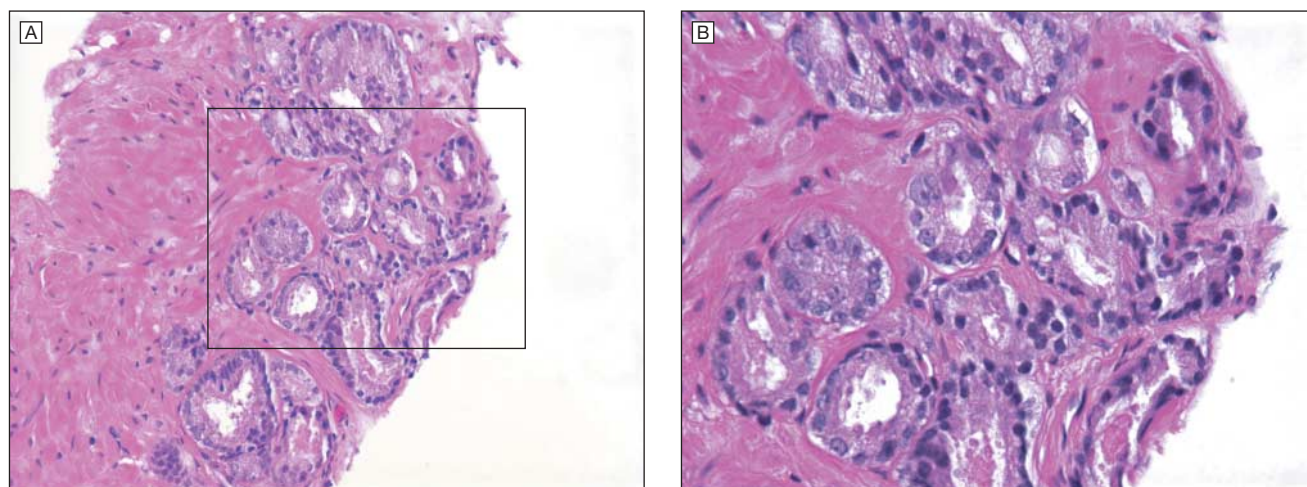
The incidence of prostate cancer is expected to rise concurrently with anticipated increases in life expectancy. Consequently, the burden on the health care system of managing prostate cancer is also expected to increase. Despite increases in prostate cancer incidence, prostate cancer mortality has declined: in 1994, there were 35 000 deaths attributed to prostate cancer, while in 2008, this figure dropped significantly to 28 600 prostate cancer deaths.¹ Prostate cancer mortality reduction during this period has exceeded the mortality rates for any other cancer in US adults, and it coincided with the advent of the prostate-specific antigen (PSA) serum test for screening. During the same interval in Britain, where PSA screening is not commonly used, prostate cancer deaths remained unchanged.² Because of uncertainty over whether the declines seen are due to true mortality reduction, increased diagnosis of prostate cancer that otherwise never would have manifested clinically, stage shift of diagnosed prostate cancer, or a combination, rec-

ommendations regarding the advisability of PSA screening remain mixed (TABLE 1).³ Two large randomized trials of PSA screening in the United States and Europe, were reported.^{4,5} The Prostate, Lung, Colon, and Ovarian Cancer Screening Trial (PLCO) randomized patients to undergo prostate cancer screening via PSA and digital rectal examination and was inconclusive: an interim report showed overwhelming contamination of PSA screening in the control group because at least 52% of patients who had been randomized to not undergo screening instead underwent PSA testing.⁴ A concurrent European Randomized Study Screening for Prostate trial that benefited from a larger sample size and better protocol compliance showed a significant reduction in prostate cancer mortality among men randomized to PSA testing⁵: at 9 years' follow-up, 326 prostate cancer deaths occurred in the control group vs 214 in the group that underwent PSA testing once every 4 years. Notably, 1410 men

needed to be screened to prevent 1 prostate cancer death; however, the number of screenings to prevent 1 cancer death was similar to the numbers reported in studies of mammographic screening for breast cancer and fecal occult blood testing for colorectal cancer.⁵ Most prostate cancer mortality (in the absence of treatment) occurs 10 to 20 years after diagnosis^{6,7} and therefore results from longer follow-up of the European trial are likely to provide more meaningful indications as to mortality reduction consequences of PSA screening. Due to pervasive, noncompliant screening in its control group, the American PLCO trial is unlikely to provide conclusive data regarding effects of PSA screening on mortality even with longer follow-up.

With the debate about screening notwithstanding, PSA testing has been widely adopted in the United States. Subsequent stage migration has led to predominance of asymptomatic, early stage, localized prostate cancer such

Figure. Prostate Biopsy Histopathology of Mr D



Scattered acini are seen with round, rigid outlines that are lined by epithelial cells with mildly eosinophilic cytoplasm, enlarged nuclei, and prominent nucleoli that are consistent with Gleason score 6 (low grade) prostatic adenocarcinoma. The absence of basal cells that typically line the acinar spaces and rigid contours of the acini are clues to the histologic diagnosis. A, Box indicates area of detail in panel B (hematoxylin-eosin, original magnification $\times 200$). B, High-powered view (hematoxylin-eosin, original magnification $\times 400$).

Table 1. Consensus Panel Recommendations for Prostate Cancer Screening

Organization or Consensus Panel	Last Updated	Recommendation	Comment or Special Considerations
US Preventive Services Task Force and American Academy of Family Physicians	2002	Insufficient evidence to recommend for or against screening	Evidence in 2002 indicated that PSA improves early detection, but not health outcome. Predated recent randomized controlled trial results showing survival benefit with treatment
ACS and AUA	2006 to 2009	Offer both PSA and DRE beginning at age 40 y (AUA) or age 50 y (ACS) if life expectancy >10 y and only after informing patients about benefits and limitations	Offer screening at age 45 y for men with family history or if African American Offer screening at age 40 y if multiple risk factors present
National Comprehensive Cancer Network	2007	Offer or discuss screening beginning at age 40 y Not advised after age 75 y Biopsy for PSA >2.5 ng/mL	Consider patient's health and risk factors before screening, biopsy, or both Consider % free PSA and PSA velocity

Abbreviation: ACS, American Cancer Society; AUA, American Urological Association; DRE, digital rectal examination; PSA, prostate-specific antigen

as that found in Mr D. Even among early stage (clinical stage T1 or T2) prostate cancers, there is considerable heterogeneity with respect to cancer aggressiveness, as reflected by the natural history of untreated primary prostate cancer.^{6,7} The main characteristic that predicts primary prostate cancer aggressiveness is the Gleason classification score of the cancer. Among men of Mr D's age at prostate cancer diagnosis, 62% with untreated early stage prostate cancer from the Connecticut tumor registry died of prostate cancer if their Gleason score was 7, whereas 27% died of prostate cancer if the Gleason score was 6.⁶ Serum PSA levels have also been shown to be associated with cancer aggressiveness as measured by risk of cancer recurrence after treatment.⁸⁻¹⁰

Treatment Options

The initial question faced by patients and their physicians is whether interventions are justifiable and desirable after weighing the potential benefits against potential adverse effects or whether treatment should be deferred in lieu of careful monitoring. Decisions regarding care options for patients like Mr D should be made according to the level of

aggressiveness of the primary cancer. Early stage cancers can be categorized as low risk, intermediate risk, or high risk (TABLE 2).

Several multicenter, randomized clinical trials have shown survival benefit when men with intermediate- or high-risk early stage prostate cancer were treated by prostatectomy or radiotherapy (TABLE 3).¹¹⁻¹⁴ In Sweden, participants with low- or intermediate-risk prostate cancer were randomized to either prostatectomy or surveillance (patients randomized to surveillance were allowed to receive radiotherapy or hormonal therapy for symptoms or progression).¹¹ A modest survival benefit was evident at a median follow-up of 8 years for patients randomized to prostatectomy (6% absolute difference), and subset analysis detected the benefit only among men younger than 65 years, which would include Mr D. Randomized trials in higher-risk cancers have focused on the consequence of adjuvant androgen-suppressive therapy, administered either after prostatectomy or concurrently with external radiotherapy.¹²⁻¹⁵ A multicenter randomized trial of men with intermediate- to high-risk prostate cancer conducted by the Eastern Oncology Cooperative

Table 2. Prostate Cancer Aggressiveness Risk Strata and Related Care Options^a

Early Stage Prostate Cancer Aggressiveness Category	Measures of Prostate Cancer Severity			Prostate Cancer Care Options
	Gleason Score	Clinical Stage ^b	Serum PSA	
Low risk	≤6	T1 or T2a	<10	Active surveillance, prostatectomy, brachytherapy, or external radiotherapy
Intermediate risk	≤6	T1 or T2a or b	10-20	Prostatectomy, external radiotherapy with adjuvant androgen suppressive therapy, or brachytherapy
	7	T1 or T2a or b	< 20	
High risk	≤7	T1 or T2a, b, or c	>20	External radiotherapy with adjuvant androgen suppressive therapy or prostatectomy
	8-10	T1 or T2a, b, or c	Any PSA	

Abbreviation: PSA, prostate-specific antigen.

^aBased on National Comprehensive Cancer Network Treatment Guidelines and D'Amico et al.¹⁰

^bClinical stages: T1, normal digital rectal examination; T2a, nodularity or induration involving less than one-half of 1 side of prostate; T2b, nodule involving more than one-half of 1 side of prostate; T2c, nodule involving both sides of the prostate.

Table 3. Randomized Clinical Trials Evaluating Early Stage Prostate Cancer Treatment

Source	Prostate Cancer Aggressiveness or Risk Group	Randomization	Group Observed Survival Benefit	Comment
Bill-Axelsson et al, ¹¹ 2005	Stage T1-T2 N0; low to intermediate risk	Radical prostatectomy vs watchful waiting	8.2 y of follow-up 76% in surgery vs 70% in watchful waiting of prostate cancer	Benefit limited to men <65 y
Bolla et al, ¹² 1997	Stage T1-T3 N0; intermediate to high risk	External radiotherapy alone vs combination with androgen suppressive therapy	3.75 y of follow-up Overall survival for combination group 79% vs 62% for external radiotherapy alone	Androgen suppressive therapy administered for 3 y
D'Amico et al, ¹³ 2004	Stage T1-T2 N0; intermediate to high risk	External radiotherapy alone vs combination with androgen suppressive therapy	4.5 y of follow-up 5-y survival, 88% in combination group vs 78% in external radiotherapy alone	Androgen suppressive therapy administered for 6 mo ^a
Messing et al, ¹⁴ 1999	Stage T1-T3 N1-2; intermediate to high risk	Radical prostatectomy alone vs combination with androgen suppressive therapy	7.1 y follow-up 85% in combination group vs 65% in radical prostatectomy alone	Androgen suppressive therapy administered indefinitely

^aSix months of androgen suppressive therapy in this trial included 2 months of neoadjuvant, 2 months concurrent treatment, and 2 months of adjuvant therapy.

Group found that lifelong adjuvant androgen-suppressive therapy improved overall survival in men found to have microscopic lymph node metastases at the time of radical prostatectomy.¹⁴ Neoadjuvant androgen-suppressive therapy prior to prostatectomy showed reduction in pathological stage after androgen suppression but showed no benefit in cancer-free survival.¹⁵ This has tempered enthusiasm for trials of neoadjuvant therapy before prostatectomy. Conversely, 2 trials involving patients with intermediate- and high-risk prostate cancer undergoing radiotherapy treatment found that patients randomized to 6 months of adjuvant androgen-suppressive therapy in the US multicenter trial¹³ and randomized to 2 years in the international trial¹² had improved overall survival. These randomized clinical trial results constitute evidence that definitive treatment for intermediate- to high-risk early stage prostate cancer, with or without adjuvant systemic therapy, improves overall survival. On this basis, for early stage prostate cancer, decision making for men with intermediate- or high-risk cancer can focus on selecting between various forms of prostatectomy or various forms of radiotherapy.

In contrast, randomized clinical trial data regarding the efficacy of definitive primary treatment in improving overall survival for low-risk prostate cancer are sparse. The Scandinavian Prostate Cancer Group Study 4 (SPCG-4) trial demonstrated improved survival after prostatectomy than for watchful waiting. However, this trial was composed predominantly of intermediate-risk cancers.¹¹ Relevance of the treatment benefit observed in this trial to the lowest-risk cancers, such as those with a Gleason score of 6 that involving only a minute focus of a single biopsy core as in Mr D's case, is uncertain. In the setting of low-risk prostate cancer, no randomized control trials have been completed to demonstrate the efficacy of radiotherapy as measured by overall survival. It is difficult to complete such studies because of the large sample size required and because it is difficult to convince men with newly diagnosed, early stage prostate cancer to undergo randomization between different treatment modalities.¹⁶ The Surgical Prostatectomy vs Interstitial Radiotherapy Intervention Trial (SPIRIT) closed after accruing less than 100 patients in more than 2 years of concerted effort at multiple National Cancer Institute–affiliated networks in the United States and Canada.¹⁷

Active Surveillance

Among patients with low-risk prostate cancers, only a limited subset may harbor the potential for clinical metastasis. Without treatment, the long-term risk of cancer death from Gleason 6 cancers, like that of Mr D, is 27%.⁶ Coupled with a paucity of class I evidence to justify treatment of low-risk cancers, this has provided rationale for optimizing deferred management of low-risk, early stage prostate cancer. In early studies of watchful waiting, surveillance

entailed intent to treat only if, or when, metastases or symptomatic progression appeared. Contemporary active surveillance instead aims to treat, with curative intent, those cancers that develop more aggressive features while being monitored and while the cancers are still susceptible to surgery or radiotherapy.¹⁸⁻²³

The contemporary rationale for deferring definitive primary therapy was first supported by 2 population-based observational studies that showed a low rate of cancer mortality for patients with primary tumors and a Gleason score of less than 7, or moderate grade, who did not undergo treatment of their primary prostate cancer.^{6,7} These findings suggested that many cancers with a Gleason score of 6 or less may have an indolent natural history. However, 3 reports that showed survival benefit of prostatectomy over watchful waiting—the SPCG-4 trial,¹¹ an analysis of outcomes in the US SEER registry,²⁴ and long-term follow-up of the initial nonrandomized Swedish surveillance cohort that at earlier follow-up had not detected treatment benefit⁷—indicate that indiscriminant watchful waiting in moderate risk cancers carries significant risk of cancer mortality.

Based on the paucity of evidence of treatment benefit for low-risk cancers, a new paradigm for deferred primary treatment emerged, initially led by several academic centers, and subsequently adopted in community urology practice and endorsed by urology and oncology consensus panel clinical guidelines.^{18-23,25,26} In contrast to earlier approaches to watchful waiting, this new model is both more selective in identifying candidates for whom treatment can be deferred and more vigilant in subsequent monitoring. A focus on low-risk cancers (eg, Gleason score of 6, low PSA level, and limited tumor volume on biopsy) as targets for active surveillance was proposed in 1993.¹⁸ Subsequently, institutions reported results from prospective series of men with low-risk prostate cancer who undergo active surveillance (that, based on consensus, may include periodic PSA testing and repeated biopsy),²⁵ wherein progression in tumor volume or grade leads to consideration of definitive treatment.¹⁹⁻²³ With contemporary active surveillance, one-third to one-half of men remain free of primary treatment 5 years after diagnosis (TABLE 4). When histopathological or PSA progression does occur, the intent of subsequent treatment is definitive. Accordingly, no difference in adverse pathology findings at prostatectomy (such as presence of extraprostatic extension) was detected between low-risk patients undergoing active surveillance and patients concurrently undergoing prostatectomy at the same institution.¹⁹ However, the sample size of this single institutional study was small and analysis of such outcomes in community-based cohorts is needed.

The contemporary approach of active surveillance is potentially suitable for men irrespective of age or functional status.²⁵ However, this active surveillance approach

has not been evaluated prospectively in multicenter studies and is the subject of an ongoing randomized clinical trial (START).¹⁶ Whether adverse effects of treatment are worse after active surveillance than they would have been at the outset is an important consideration, and such outcome data are not yet available.

Definitive Treatment for Early Stage Prostate Cancer

Radical Prostatectomy. Class I evidence demonstrated that prostatectomy is an effective method of improving overall survival for low- to intermediate-risk prostate cancer,¹¹ a unique outcome among local-regional treatment options that target the primary tumor. Other treatment modalities have shown survival benefit, but only when combined with systemic adjuvants.^{12,13} However, radical prostatectomy is a major surgery that requires inpatient hospitalization and restricted activity during a period of postoperative recovery. It also is associated with potentially acute perioperative adverse events and longer-term treatment-related symptoms and adverse effects.

Acute adverse events associated with radical prostatectomy include bleeding, infection, and urinary retention. Serious adverse events, such as life-threatening hemorrhage, thromboembolic events, or rectal injury, are uncommon.²⁷ Other serious perioperative adverse events (eg, myocardial infarction or sepsis that may be encountered with any major abdominopelvic operation) are rare. As long as judicious criteria are used to identify surgical candidates, treatment-related deaths during prostatectomy are rare.

Urinary incontinence is common in the first few months after prostatectomy; however, most patients recover continence (TABLE 5). Long-term incontinence persists in 2% to 22% of patients, depending on the definition of continence (moderate or severe), and patient age (older men are at greater risk of long-term incontinence).^{27,28} Erectile dysfunction is the most common long-term adverse effect of radical prostatectomy, affecting 20% to 90% of men, depending on factors such as patient baseline sexual function, age, and use of nerve-sparing technique (Table 4).²⁷⁻³³ Even among men who recover erections sufficient for

Table 4. Treatment-Free Survival During Active Surveillance of Early Stage Prostate Cancer in the Era of PSA Screening

Source	No. of Participants	Prostate Cancer Aggressiveness or Risk Group	Treatment-Free Interval Duration ^a	Comment
Warlick et al, ¹⁹ 2006 ^b	407	Low risk and <3 biopsy cores having cancer, PSA density <0.15	75% Treatment-free at 2.8 y	20% Locally advanced on pathology ^c
Zeitman et al, ²⁰ 2001	199	Low, intermediate, and high risk	56% Treatment-free at 5 y	2 Deaths from prostate cancer (after treatment)
Klotz et al, ²² 2006 ^b	299	Low or intermediate risk	66% Treatment-free at 5 y	2 Deaths from prostate cancer
Meng et al, ²³ 2003	457	Low, intermediate, and high risk	49% Treatment-free at 5 y	Not uniformly monitored by repeat biopsy
Carter et al, ²¹ 2003	315	Low risk, <4 biopsy cores with cancer	27% Treatment-free at 4 y	2 Prostate cancer deaths

Abbreviation: PSA, prostate-specific antigen.

^aFollow-up testing on active surveillance may detect cause-to-treat due to either initial understaging of Gleason score or tumor extent or to change or progression of aggressiveness of the primary tumor.

^bProspective, single-institution protocols that included repeat biopsy at regular intervals. Other tabulated studies were retrospective and multi-institutional.

^cNot significantly different from the rate of adverse pathology among an institutional control group composed of men undergoing immediate prostatectomy; 2 men with nodal involvement at delayed prostatectomy did not meet the PSA density entry criterion.

Table 5. Quality-of-Life Effects of Primary Prostate Cancer Treatment^a

Primary Treatment	Prevalence of Moderate to Severe Problems in Specific Health-Related Quality-of-Life Domains, % ^a			
	Urinary Incontinence	Urinary Irritation or Obstruction	Bowel or Rectal	Sexual
Early: 2 to 6 months after primary treatment				
Prostatectomy	15-50	5-15	1-5	>50
External radiation	1-5	15-50	5-15	15-50
Brachytherapy	5-15	15-50	5-15	15-50
Late: 24 months after primary treatment				
Prostatectomy	5-15	1-5 ^b	<1	15-50
External radiation	1-5	1-5 ^b	5-15	15-50
Brachytherapy	5-15	5-15	5-15	15-50

^aBased on Sanda et al.²⁷

^bFive percent to 15% of patients reported improvement in obstructive urinary symptoms after prostatectomy, 1% to 5% after external radiation.

intercourse after prostatectomy, maximal recovery usually takes 1 to 2 years.

In an effort to reduce perioperative risk, laparoscopic and robot-assisted laparoscopic approaches to performing prostatectomy have been developed.^{34,35} These approaches have less blood loss than retropubic prostatectomy (transfusion requirement is rare) and have a favorable cosmetic result due to the smaller incision. However, minimally invasive procedures have shown no difference compared with retropubic prostatectomy in either urinary continence or erection recovery.²⁷ Observational community-based data have found minimally invasive prostatectomy to be associated with higher rates of subsequent secondary or salvage therapy, raising some concerns about whether these options are as efficacious as retropubic prostatectomy.³⁶ Patients and urologists alike have nevertheless gravitated to the appeal of minimally invasive or robot-assisted laparoscopic prostatectomy techniques.³⁶

External Radiotherapy. Modern external radiotherapy for prostate cancer dates to the 1960s.³⁷ By incorporating imaging into the treatment planning for external beam, contemporary techniques enable increased doses to the prostate, while limiting radiation to adjacent normal tissues. Three-dimensional conformal radiation uses images obtained from a computed tomographic scan to shape the radiation beams to the target tissues. Intensity-modulated radiation therapy is a form of conformal radiation in which the radiation energy of small areas in each beam is modulated, allowing refined shaping of the radiation dose around the target structure. Devices such as transabdominal ultrasound and real-time imaging of implanted markers (eg, imaged guided radiation therapy) can be used to further facilitate guiding radiation delivery. Although commonly used, multicenter data demonstrating superior efficacy or outcomes of these techniques to concurrent standard 3-dimensional conformal radiotherapy controls are lacking.

Randomized trials showed that increasing the radiation dose improved recurrence-free survival from 79% to 91% at 5 years,³⁸ and from 59% to 78% at 8.7 years.³⁹ Furthermore, the addition of concurrent androgen-suppressive therapy during radiation improved 5-year survival in randomized trials from 62% to 79% when 3 years of hormone therapy was given, and from 78% to 88% when 6 months of hormone therapy was given.^{12,13} However, the optimal timing and duration of concurrent androgen-suppressive therapy has not yet been established. A recent trial showed that the survival benefit of combining radiotherapy with hormone therapy is not attributable to the hormonal therapy component alone because patients randomized to receive radiation with hormone therapy showed improved survival compared with those randomized to hormonal therapy alone.⁴⁰ The addition of radiation to the pelvis to treat pelvic lymph nodes has been evaluated in patients with high-risk cancers without a definitive survival benefit.^{41,42}

No large randomized studies have been completed that compare treatment with external radiotherapy with other definitive modalities. Prospective, single-institution studies have demonstrated similar PSA recurrence-free survival 5 years after for radiotherapy compared with prostatectomy, although brachytherapy monotherapy was followed by higher risk of PSA recurrence than was prostatectomy in intermediate risk categories (RR, 3.1; $P = .003$).¹⁰

Toxic reactions to radiotherapy can occur immediately after treatment or after many years (Table 5).^{27,33,43-45} Acute toxic effects of radiotherapy include urinary frequency, urgency, or dysuria reported by 11% to 18% of patients (without such problems at baseline) and rectal urgency, frequency, or pain in 13% to 15%. By 1 to 2 years after treatment, urinary symptoms typically subside, but 1 in 10 men report rectal symptoms as becoming a persistently moderate or big problem.^{27,33,43} Erectile dysfunction persists long-term for one-third of men who had reliable erections before undergoing treatment, with more men affected if hormonal adjuvant is used.²⁷ Moreover, even limited courses of hormonal therapy combined with radiotherapy are associated with increased risk of later cardiac events.⁴⁶ Given the reduction of acute surgical morbidity (such as blood loss requiring transfusion) in laparoscopic or robot-assisted prostatectomy, this suggests that the traditional practice of steering older patients toward combinations of hormone therapy and radiotherapy (rather than surgery) may need to be reconsidered.

Recent progress in external radiotherapy has included use of proton beam radiotherapy³⁸; use of novel technology for administering hypofractionated schedules, which consist of fewer and larger fractions of radiation delivered in shorter time intervals^{47,48}; and advanced technologies using image guidance for ultracontoured dose delivery.^{49,50} Due to its unique physical properties, it is hypothesized that proton-based external beam therapy can be used to escalate dosages safely and improve treatment efficacy. Proton-based prostate radiation has been evaluated in a trial in which patients were randomized to a conventional dose of radiation with conventional photons vs a high dose that administered conventional dose radiation with a proton boost. Biochemical-free survival in the high-dose group had improved PSA recurrence-free survival (91% vs 79% 5 years after treatment) but with an accompanying increase in toxic effects of the gastrointestinal tract.³⁸ However, whether proton-based treatment would be different from standard photon-based radiation using highly conformal delivery techniques alone to administer the high-dose boost is not known.

Brachytherapy. Brachytherapy, the placement of radioactive sources into the prostate,⁵¹ is typically an outpatient procedure, during which the seeds are introduced into the prostate percutaneously via a transperitoneal

approach under transrectal ultrasonographic guidance. These sealed sources contain radioactive iodine 125, palladium 103, or cesium 131 and emit low-energy radiation with doses limited to within millimeters of the seeds; none of these isotopes has been shown to be superior.⁵² A national, prospective phase 2 trial showed that brachytherapy for low-risk prostate cancer was followed by 94% biochemical progression-free survival 5 years after treatment.⁵³

Brachytherapy alone cannot reliably achieve therapeutic radiation dose to the seminal vesicles. Therefore, intermediate-risk category prostate cancers, some of which may harbor occult involvement of the seminal vesicles, have been treated with combination therapy composed of low-dose external beam radiotherapy combined with a low-dose brachytherapy. In this way, the extraprostatic tissues receive a higher dose than with brachytherapy monotherapy. A national phase 2 study of external beam radiation combined with brachytherapy showed that 15% of patients experienced grade 1 to 3 urinary or rectal toxicity, while 81% remained free of biochemical progression 4 years after treatment.⁵⁴ The relative efficacy of brachytherapy as monotherapy compared with its combination with external beam is not known, but it is being evaluated in an ongoing randomized clinical study.⁵⁵

The spectrum and time course of acute radiation-related symptoms following prostate brachytherapy are shown in Table 5. As with prostatectomy and radiotherapy, erectile dysfunction is the most commonly reported adverse effect, reported by 30% of patients who did not have erectile dysfunction at baseline.²⁷ Irritative and obstructive urinary symptoms affect one-third of patients early after brachytherapy, and 9% to 10% of patients who did not have problems with urination at baseline report troublesome urinary frequency persisting long-term. Symptoms of radiation proctitis and problematic fatigue are reported by 10% of men early after treatment and 5% to 6% long-term.²⁷

Brachytherapy is contraindicated in prostates larger than 60 mL in size due to anatomic constraints of the pubic arch that preclude delivery of a sufficient distribution of seeds for adequate radiation dose.⁵⁶ In addition, men with significant obstructive lower urinary tract symptoms prior to treatment may require long-term catheterization and are not optimal candidates for brachytherapy.⁵⁷

A limitation of either radiotherapy or brachytherapy is occasional persistence of cancer within the prostate itself and subsequent progression, seen in 12% to 16% of patients biopsied after external radiotherapy with hormonal adjuvant (42% without adjuvant) and 8% after brachytherapy.⁵⁸⁻⁶⁰ Positive postradiotherapy treatment prostate biopsy is clinically significant because 73% to 97% of patients with positive biopsy progress by 10 years of follow-up.^{58,60} This scenario can be avoided when prostatectomy is administered as the initial primary intervention.

Choosing Treatment

Selecting a treatment poses dilemmas for patients and physicians alike. Specialists in urology, oncology, and radiation oncology may harbor unintentional, specialty-specific biases that may manifest as divergent recommendations to patients. Patients may turn to their primary care physicians as objective arbiters to help choose treatment.

Class I evidence has shown that prostatectomy prolongs survival, without a need for concurrent androgen suppressive therapy.¹¹ On the other hand, radiotherapy avoids inpatient hospitalization and the week or 2 of indwelling urinary catheterization that are required with prostatectomy, but it has known survival benefit (vs conservative management) only when combined with hormonal therapy.⁴⁰ Brachytherapy enables radiation treatment to be implemented through a single outpatient procedure but lacks class I evidence showing survival benefit. The long-term morbidity profiles of these treatments do not deem 1 treatment superior to the other 2 because one-half of surgical patients and one-third of radiotherapy or brachytherapy patients develop erectile dysfunction *de novo*. One in 10 prostatectomy patients develop long-term urinary incontinence, while a similar proportion of radiotherapy patients develop long-term proctitis. Among brachytherapy patients, 5% have reported long-term proctitis and 5% long-term urinary irritative problems. After they have been led to understand these morbidity risks, patients with intermediate- or high-risk cancers who otherwise have a life expectancy of more than 10 years can be encouraged to proceed with treatment instead of active surveillance based on class I evidence of survival benefit.

Low-risk prostate cancers, such as that of Mr D, can alternatively be managed by active surveillance. Class I evidence of survival benefit from primary treatment of low-risk cancers is limited to a subset of the prostatectomy group of SPCG4, and this benefit was limited to men younger than 65 years.¹¹ For low-risk prostate cancer, baseline function and quality-of-life consequences merit greater emphasis in decision making. Lack of erections or interest in sex can sway decisions toward definitive treatment in general, while presence of problematic obstructive urinary symptoms indicates possible functional benefit from prostatectomy. However, Mr D lacks baseline urinary symptoms, and he values sexual activity highly. Patients like Mr D may opt for active surveillance to avoid possible adverse effects of primary treatment. Others may default to active surveillance because they simply cannot choose between treatment options that each carry risk in the face of marginal benefit. Providing patients with an evidence-based information source may facilitate appropriate decision making. A patient education tool developed by input from a community-based sample of prostate cancer survivors and practitioners has been posted on the Internet and published as a pamphlet,

and when tested was found to effectively inform patients about the pros and cons of different prostate cancer treatment options.^{61,62}

We would recommend that Mr D consider active surveillance based on the low-risk profile of his cancer, the absence of preexisting urinary obstructive symptoms, and the importance that he attributed to retaining erectile function. We would advise that he review an evidence-based brochure written to inform patients about their prostate cancer care options.^{61,62} If he agrees to undergo active surveillance, we would recommend reassessment of PSA 2 to 3 times annually and prostate biopsy annually to determine whether his tumor is indolent or whether it is showing propensity for becoming more aggressive, as by progression of biopsy Gleason score or amount of cancer on biopsy (in which case converting to primary treatment would be advisable).

QUESTIONS AND COMMENT

QUESTION: My understanding is that there are 2 downsides to radiation: it may not be quite as effective as it is in other cancers and adverse effects other than erectile dysfunction, especially bowel dysfunction, can be more prevalent over time. Would using either brachytherapy or newer forms of radiotherapy (such as image-linked hyperfractionation or proton beam) reduce the incidence of complications?

DR IRVING KAPLAN: Your first question compares radiation to surgery. That has been tested in retrospective series but not in a randomized study.¹⁰ If you stratify patients according to certain risk groups, the evidence for or against a statistically different incidence of relapse or survival between radiation and surgery patients is not strong.

As for the toxicity profile, innovations like brachytherapy and radiotherapy using hypofractionated image-guided techniques or proton beam radiation have emerged to try to limit the dose to the rectum. Patient-reported quality of life after brachytherapy were not significantly better than standard external (intensity-modulated or 3-dimensional conformal) radiotherapy. How standard therapy compares with newer energy-based therapies, like high-intensity focused ultrasound therapy or hyperfractionated image-guided external radiotherapy, requires collection and reporting of patient-reported outcomes from ongoing IRB [institutional review board]-approved multicenter studies.

DR MARTIN SANDA: I think it is difficult to compare surgery and radiation; however, we always point out that the possibility of tumor persistence, recurrence, or secondary cancer within the prostate is more easily avoided with surgery. Though rates vary between studies, approximately 5% to 10% of patients treated with radiotherapy or seed implants develop intraprostatic persistent or recurrent cancer.

QUESTION: It appears that watchful waiting might be an option for this patient. Are there any alternative or complementary therapies that might benefit him during this period?

DR SANDA: There is some troublesome information on complementary and alternative therapies in prostate cancer. The PC-SPES formulation is something that was widely used over the counter about 10 years ago. When PC-SPES was studied in a bona fide prospective interventional trial,⁶³ it was found to be associated with significant thromboembolic events. Experience with PC-SPES has tempered many practitioners' enthusiasm for nonprescribed, over-the-counter remedies in prostate cancer, which might contain estrogenic compounds. Furthermore, the consumer market of over-the-counter, so-called "prostate health" supplements, continues to be linked to thromboembolic events.⁶⁴ On the other hand, there are conservative medical management approaches that look promising. For example, the potential benefit of statins in reducing prostate cancer mortality, as described in *Journal of the National Cancer Institute* from the Physicians' Health Study.⁶⁵ There is also increasing evidence, both from prospective cohorts and other prospective epidemiological data, suggesting that lower body mass, minimized obesity, and lower cholesterol or lipids could be beneficial.⁶⁵

QUESTION: As an internist, I have observed an incidence of morbidity with sexual function that is far higher than 49%. Do you have many studies asking patients about sexual function are conducted by surgeons or radiotherapists as opposed to lay observers?

DR SANDA: The biases inherent to who asks the questions about side effects was considered by study designers. The data presented about sexuality and erection outcomes came from a multicenter, national study where patients' sexuality was assessed by third-party interviewers. During patient enrollment and interviewing, we emphasized that the interviews be anonymous and independent from their care.

There are 3 more factors to consider. First, the definition of erectile dysfunction. Obviously having a penis that is hard enough to penetrate the vagina is entirely different than having great sex. As such, there is range of definitions used depending on the study.

Second, the consideration of patient baseline functioning. One-third to one-half of patients we see with prostate cancer already has substantial erectile dysfunction. Often this does not come up until after treatment, so we try to bring it up before.

Third, the practitioner effect. There is anecdotal evidence that a practitioner's expertise can affect sexual outcome. There is often a discrepancy in a patient's quality of life that correlates with the physician's level of experience. This has been formally demonstrated in the context of urinary outcomes.⁶⁶

QUESTION: The more we learn about different types of prostate cancer, the more difficult it has become to compare

groups in studies. How will this heterogeneity affect the interpretation and design of future studies?

DR SANDA: The key to this question is determining how data collected from a heterogeneous population can inform individual patients' decision making. Outcomes data from multicenter, studies^{27,33,67} where this heterogeneity was captured well need to be re-analyzed to generate predictive models that would enable physicians to tell patients, based on weight, prostate size, and baseline sexual functioning, their likely outcomes. This is a very important direction for physicians treating patients with prostate cancer.

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