

Selecting Treatment for High-Risk, Localized Prostate Cancer: The Case for Radical Prostatectomy

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The most common treatment options for men with clinically localized prostate cancer include radical prostatectomy and radiation therapy. The choice between these options is often controversial, and selecting the optimal treatment poses a great challenge for patients and physicians. Factors important to the decision include age and life expectancy of the patient, the natural history of the prostate cancer, how curable the disease is, and the morbidity of treatment. Use of these criteria to select treatment for a healthy, 70-year-old man presenting with a non-palpable tumor, stage T1c disease, serum prostate-specific antigen of 12 ng/mL, and an adenocarcinoma with a Gleason score of 8 that is present in 2 of 12 biopsy cores would lead to the choice of radical prostatectomy over radiation therapy. Data show that such a patient has a life expectancy of more than 12.3 years if the prostate cancer can be cured and a high probability of dying from the disease if it is not cured. Data further show that radical prostatectomy in such a patient would confer a survival advantage over radiation therapy without resulting in greater complications or reduction in quality of life.

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Radical prostatectomy, radiation therapy, and watchful waiting represent the most common treatment options offered to men with clinically localized carcinoma of the prostate. The optimal treatment for these patients is often controversial, and selecting a treatment represents a tremendous challenge both for patients and for health care providers. The decision-making process would be more straightforward if the results were available from a trial comparing various quality-of-life and survival outcomes for men randomized to radical prostatectomy, radiation therapy, and watchful waiting and followed up for 15 years.

Unfortunately, a definitive trial of this design has never been conducted. Moreover, even if such a study had been initiated 15 years ago, advances in diagnosis and management of prostate cancer and the development of validated methods to assess quality-of-life outcomes would render the findings virtually irrelevant today. Specifically, over the last 15 years there has been significant stage migration due to the widespread acceptance of prostate-specific antigen (PSA) screening,¹ lower treatment-

treatment for a healthy, 70-year-old man presenting with a nonpalpable tumor, stage T1c disease, serum PSA of 12 ng/mL, and an adenocarcinoma with a Gleason score of 8 that is present in 2 of 12 biopsy cores.

Life Expectancy

The average life expectancy for a 70-year-old American male is 12.3 years.⁵ An average 70-year-old male has a 58%, 34%, and 15% probability of surviving 10, 15, and 20 years, respectively. These life-expectancy

study from Scandinavia in which 301 men with newly diagnosed, clinically localized prostate cancer were managed with a noncurative intent. In this study, 50% of all men who were diagnosed at 70 years of age with clinically localized prostate cancer died from their disease. However, the authors did not stratify the age-dependent death rate for newly diagnosed clinically localized prostate cancer according to Gleason score. The percentage of men dying of prostate cancer would be expected to be greater than 50% for the subset of men with high-grade disease. These studies provide compelling evidence that high-grade prostate cancer has a dramatic impact on the survival of men who are diagnosed at age 70 and provide the rationale to offer treatment intended to reduce this risk.

The fact that untreated prostate cancer leads to death is not, in and of itself, an indication for intervention.

related morbidity due to advances in surgical technique,² improved delivery of both external beam³ and interstitial⁴ radiation to the prostate, and the validation of self-administered instruments to capture quality-of-life outcomes.⁴ Despite the inherent limitations and deficiencies of the available clinical information, we as health care providers are still confronted on a daily basis with the need to guide our patients through decisions regarding the treatment of newly diagnosed, clinically localized carcinoma of the prostate. In the Summer 2000 issue of *Reviews in Urology*, I contributed an article entitled "Selecting Candidates for Radical Prostatectomy," which outlined an evidence-based approach to the process of selecting treatment for men with clinically localized prostate cancer.⁵ The factors relevant to this decision include age and life expectancy of the patient, the natural history of the prostate cancer, the ability to cure the disease, and the morbidity of treatment. In this point-counterpoint discussion, I will outline an evidenced-based approach, based on these criteria, to selecting

statistics must be interpreted based on comorbidities, and the subject of our point-counterpoint discussion is a healthy 70-year-old man. Therefore, the average life expectancy of 12.3 years is likely an underestimate of his true life expectancy.

Natural History of the Disease

Several studies reported in the literature provide insights into the natural history of high-grade prostate cancer in a 70-year-old man. Albertsen and associates⁶ examined the survival of men 65–75 years of age who had clinically localized prostate cancer, comparing those treated with hormonal therapy with aged-matched, untreated controls. The survival expectancy for men with Gleason 8–10 adenocarcinoma of the prostate treated with hormonal therapy was 6–8 years less than that for controls. If one assumes that hormonal therapy does not extend survival, then the difference in survival between the hormonally-treated group versus the control group represents the impact of high-grade, clinically localized prostate cancer on survival.

Aus and associates⁷ reported on a

Curability of Prostate Cancer

The fact that untreated prostate cancer leads to death is not, in and of itself, an indication for intervention. Treatment must lower the risk of death to justify intervention. Walsh and associates recently reported on the long-term survival for men with Gleason 8–10 adenocarcinoma who underwent radical retropubic prostatectomy.⁸ In this series, the 5-, 10-, and 15-year biochemical disease-free survival was 47%, 29%, and 15% respectively. If one considers both the natural-history data previously described and the Walsh survival data for Gleason 8–10 tumors, radical prostatectomy appears to offer a significant survival advantage. It is important to recognize that the majority of those cases in the Walsh series who had 10- and 15-year survival data were diagnosed in the pre-PSA era, and therefore these survival statistics do not reflect the favorable impact of stage migration attributable to PSA screening on survival outcomes. In addition, biochemical recur-

rence does not always imply systemic disease, and some cases with biochemical recurrence may be effectively treated with adjuvant radiotherapy.⁹ The biochemical disease-free survival data presented by Walsh do not take into account the potential benefit of adjuvant radiotherapy.

Historically, the finding of a Gleason 8 prostate cancer was associated with an ominous prognosis because these tumors were palpable and invariably associated with a large tumor volume. However, the case under discussion has features that suggest a better prognosis than those of the entire group of Gleason 8–10 cancers reported by Walsh and associates since the Gleason score is an 8, the tumor is not palpable, and there is reason to believe the tumor volume is small because of the low-volume disease on the biopsy.

Radical Prostatectomy Versus Radiation Therapy

The natural history of the disease, life expectancy of the patient, and potential for cure provide compelling reasons to treat the patient presented in this point-counterpoint discussion aggressively, with the intent to cure the prostate cancer. The next question, and the primary subject of this point-counterpoint discussion, is whether to offer radical prostatectomy or radiation therapy. The decision to offer one treatment or the other must reflect a critical analysis of benefits (ie, survival) and risks.

Survival

The only randomized study comparing radical prostatectomy and radiation therapy was performed within the Veteran's Administration system.¹⁰ At 8 years follow-up, surgery was shown to have a significant survival advantage. This study has been criticized by radiotherapists who argue that the randomization favored the

radical prostatectomy arm, even though the protocol for randomization was not violated.

A recent study presented at the 2002 American Urological Association Annual Meeting in Orlando also suggests a survival advantage of radical prostatectomy for high-grade disease. Leak and associates¹¹ reported on a group of 460 men with Gleason 8–10, clinically localized adenocarcinomas who underwent radical prostatectomy, radiation therapy, or conservative therapy between 1980

and 1997. After adjusting for age, race, grade of tumor, comorbidity, local status, and year of diagnosis, a Cox proportional hazards model was used to compare long-term survival therapy among the three treatment groups. Relative to conservative therapy, radical prostatectomy and radiation therapy gave a 10.4-year and 1.7-year increase in length of survival, respectively. The authors concluded that radical prostatectomy had the greatest impact on decreasing cancer-specific mortality in men with high-grade prostate cancers.

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Complications

Radical prostatectomy performed by experienced surgeons in the modern era is associated with minimal morbidity. Lepor and associates¹² recently reported on the outcomes of 1000 consecutive men with clinically localized prostate cancer who underwent radical retropubic prostatectomy between April 1994 and July 2000. The intraoperative and in-hospital mortality was 0. Only 8 (0.8%) men experienced an intraoperative complication. None of these intraoperative complications resulted in any long-

term disability or sequelae. The incidence of medical complications during the hospitalization and over a 30-day postoperative interval included deep vein thrombosis (0.1%), pulmonary embolism (0.2%) and myocardial infarction (0.5%). The risk of allogeneic transfusion was 9.7%. The mean length of hospital stay was 2.3 days. Only 5 (0.5%) patients underwent reoperation.

Maximal continence and potency are typically obtained within 1 and 2 years, respectively. It is well recog-

nized that reliable outcomes data regarding continence and potency can only be obtained using validated self-administered questionnaires. Beginning in October 2000, I embarked on a project to prospectively determine baseline and 3-, 12-, and 24-month continence and potency outcomes using such instruments. We have recently examined our continence outcomes at 1 year.

At baseline, 85% of men leaked urine not at all; 9%, less than once a week; 4%, about once a week; and 2%, every day. Of those men who were continent at baseline, 78% wore no pads, 15% wore one small pad, 5% wore 2 pads, and 2% wore at least 3 pads 1 year following radical prostatectomy. Fifty percent of these same men indicated that their bother due to incontinence was no problem; 31% indicated it was a very small problem; 10%, a small problem; 5%, a moderate problem; and 4%, a big problem. If the definition of continence is the requirement for one or fewer small pads or none or slight bother, then 91%–93% of continent men undergoing radical prostatectomy maintain continence 1 year following

Table 1
Radiation Therapy Oncology Group Scale for Classification of Complications Following Radiation Therapy

Grade	Description
0	No complication
1	Minor symptom requiring no treatment
2	Minor symptom requiring medication
3	Symptom requiring minor surgical intervention
4	Symptom requiring major surgical intervention
5	Death

surgery. Walsh and associates¹³ have recently reported that 95% of men had no or small bother due to incontinence 18 months following radical retropubic prostatectomy.

We have insufficient follow-up data at this time to assess our potency outcomes. However, Walsh and associates¹³ have recently assessed potency outcomes following radical retropubic prostatectomy using a validated disease-targeted, quality-of-life survey. The median age of this group was 57 years. Eighty-six percent of these men were potent 18 months following nerve-sparing radical retropubic prostatectomy.

Assessment of intermediate-term quality-of-life outcomes of radiation therapy is essential because the consequences of radiation therapy on continence, bowel function, and potency are often not realized for up to 2 years. Long-term studies are also important to address issues such as radiation cystitis, proctitis, and other sequelae. However, it is difficult to define the morbidity associated with radiation therapy because of the grading scale that is widely accepted for quantifying outcomes and the lack of long-term follow-up studies.

Complications following radiation

therapy are typically classified using the Radiation Therapy Oncology Group (RTOG) scale shown in Table 1. This outcomes scale is misleading because a man with severe lower urinary tract symptoms secondary to a contracted bladder may receive no medical therapy or surgical intervention because there is no treatment

It is difficult to define the morbidity associated with radiation therapy because of the grading scale that is widely accepted for quantifying outcomes and the lack of long-term follow-up studies.

that has proven utility in this setting. The decision to offer intervention is left up to the discretion of the radiation therapist. Therefore, despite the likelihood that the patient is seriously bothered and even disabled by the contracted bladder, the complication is a Grade 1 complication because no therapy was offered.

Michalski and associates¹⁴ recently reported on the toxicity following three-dimensional conformal radiotherapy (3D CRT) for prostate cancer in 592 men randomized to an RTOG study comparing different dosing regimens. Approximately 50% of men experienced acute bladder or bowel

toxicity, and 40% developed a Grade 2 morbidity, respectively.

Zelevsky and associates¹⁵ recently reported the late complications following 3D CRT in 137 men and brachytherapy in 145 men with favorable-risk prostate cancer who were treated between 1988 and 1997 at Memorial Sloan-Kettering Cancer Center. This report represents a small proportion of the men actually treated there during this time period. Late treatment complications were defined as events developing 90 days after completion of radiation therapy or those events persisting beyond 90 days after completing radiation therapy. Patient questionnaires were not used to capture complications. Following 3D CRT and brachytherapy, 9% and 38% of men, respectively, developed Grade 2 or 3 genitourinary toxicity, and 6% and 4% of men, respectively, developed Grade 2 rectal toxicity. Five years following treatment, 43% of men who underwent 3D CRT

and 53% of men who underwent brachytherapy complained of erectile dysfunction.

Talcott and associates¹⁶ recently reported the first long-term outcome assessment following brachytherapy for early prostate cancer using a validated patient questionnaire. One hundred five men who had been treated with brachytherapy at Northwest Hospital at least 2 years and 9 months responded to a mailed questionnaire assessing urinary and bowel function. Fifteen percent of men who underwent seed implantation alone and 19% who underwent a combination of seed implantation and external beam ther-

apy complained of frequent diarrhea, mucus per rectum, or rectal bleeding. Forty percent of men who underwent seed implantation alone and 55% who underwent combination therapy

improves throughout the first postoperative year and potency improves throughout the first 2 postoperative years, whereas sexual dysfunction and urinary incontinence are late

prostatectomy or control groups. Sexual function was equivalent in the brachytherapy and radical prostatectomy groups, and both treated groups were worse than controls. Based upon the UCLA comparative experience¹⁷ and the composite experience reported in the literature, it appears that, overall, radical prostatectomy, 3D CRT, and brachytherapy have a similar impact on quality of life.

Sexual function was equivalent in the brachytherapy and radical prostatectomy groups, and both treated groups were worse than controls.

complained of urinary leakage. However, the use of pads is a better indicator of level of continence and its impact on quality of life. Eighteen percent of men who underwent seed implantation alone and 13% who underwent combination therapy required pad use for their incontinence. Sexual dysfunction was a significant problem following brachytherapy. Sixty-eight percent of men who underwent seed implantation alone and 82% who underwent combination therapy indicated that their erections were inadequate for penetration without manual assistance.

Brandeis and associates¹⁷ reported a study comparing quality-of-life outcomes following radical prostatectomy and brachytherapy using a validated patient questionnaire for men treated at a single institution. Follow-up ranged between 3 and 17 months. An obvious limitation of this study is that continence status following radical prostatectomy

complications following radiation therapy. Therefore, the relatively short follow-up interval significantly underestimates the complications of brachytherapy and overestimates the complications of surgical intervention. In this study, patients in the radical prostatectomy group suffered more from incontinence than did those in the brachytherapy group or healthy controls. (Interestingly, an assessment of both continence and voiding dysfunction showed that

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brachytherapy had a greater negative impact than radical prostatectomy, and radical prostatectomy was equivalent to controls.) Bowel function was a greater bother in the brachytherapy group than in either the radical

Summary

A healthy, 70-year-old man with a low-volume, high-grade, clinically localized prostate cancer has a life expectancy exceeding 12.3 years if the prostate cancer can be cured. The available natural history data for clinically localized prostate cancer demonstrates that a healthy 70-year-old man has a high probability of dying from high-grade disease if treated with a noncurative intent.

In select cases, men with nonpalpable, high-grade, clinically localized prostate cancer have disease that is amenable to cure. The available data demonstrate that for men with high-grade prostate cancer, radical prosta-

Main Points

- When selecting the best treatment for patients with clinically localized prostate cancer, one should consider the life expectancy of the patient, the natural history of the prostate cancer, the curability of the disease, and the morbidity of treatment.
- High-grade prostate cancer managed with noncurative intent greatly reduces life expectancy.
- Radical prostatectomy appears to offer a significant survival advantage over radiation therapy.
- Overall, radical prostatectomy, three-dimensional conformal radiotherapy, and brachytherapy appear to have a similar impact on quality of life.
- A healthy, 70-year-old with low-volume, high-grade, clinically localized prostate cancer is best treated with radical prostatectomy because it offers the best chance for cure without greater reduction in quality of life.

tectomy has a survival advantage compared with radiation therapy. In the hands of experienced surgeons, the complications associated with radical prostatectomy and radiation therapy are minimal, and recovery is typically uneventful. The valid quality-of-life outcomes data suggest that the better survival achieved by radical prostatectomy does not come at the expense of quality of life. Therefore, the healthy, 70-year-old man presented in this point-counterpoint discussion is best treated with radical prostatectomy because this option provides the best probability for cure without further compromising quality of life. ■

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Announcement

We are pleased to announce that Dr. Alan W. Partin, Contributing Editor to *Reviews in Urology*, has been awarded the 2002 Gold Cystoscope Award for his outstanding work in BPH and prostate cancer.

The Gold Cystoscope Award is presented annually to a urologist who has distinguished himself through outstanding contributions to his profession within ten (10) years of completing his residency training.