Original Article

Counterpoint: The Case for Immediate Active Treatment

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Abstract
Active monitoring strategies recently have received attention as possible treatment options for men with low-risk prostate cancer who have a life expectancy of more than 10 years. However, no current criteria sufficiently predict outcomes for individuals with clinically localized disease and an otherwise long life expectancy who undergo either immediate or delayed treatment, or no treatment. This article describes the available evidence regarding treatment outcomes in men with low-risk prostate cancer and presents the case for immediate active treatment. (*JNCCN* 2007;5:699–702)

An estimated 218,890 men will be diagnosed with prostate cancer in the United States in 2007.[1] The widespread use of prostate-specific antigen (PSA)–based screening has led to a striking migration to early-stage disease at diagnosis. From 1985 to 1989, 16% of men were diagnosed with metastatic disease, whereas the most recent statistics from 2002 show this proportion had decreased to 4% (a 75% reduction); the proportion presenting with metastatic disease is probably even lower today.[2] Moreover, the 32.5% decline in the age-adjusted prostate cancer mortality rate reported from 1993 to 2003 would not have occurred if widespread PSA-based screening detected only harmless prostate cancers. Similar trends were reported in Austria, where the implementation of free PSA-based screening in Tyrol led to an even larger reduction in prostate cancer-specific mortality compared to the rest of the country where screening was not readily available.[3] Despite these favorable trends, concern exists that prostate cancer is being overdiagnosed and overtreated.

As a result, active monitoring for low-risk men has been implemented at many institutions, even for men with a long life expectancy. These programs are designed to delay definitive treatment until there is evidence of disease progression, and then, hopefully, intervene with curative therapy. One important limitation of this approach is that there is no consensus or validated criteria to identify appropriate candidates for active monitoring or to trigger intervention while the "window of curability" is still open.

The increased likelihood of worse outcomes with delays in treatment is concerning. For example, Freedland et al.[4] examined whether a delay of more than 180 days between diagnosis and treatment would affect cancer control outcomes in men with low-risk prostate cancer (PSA < 10 ng/mL and biopsy Gleason score ≤ 6). They found that an increasing interval between biopsy and surgery conferred a significantly greater risk for biochemical progression. On multivariate analysis of age, race, clinical stage, PSA, percentage of biopsy cores involved with cancer, and year of surgery, treatment delays remained a significant independent predictor of biochemical progression (relative risk, 2.73; $P = .002$). Although this study was designed primarily to evaluate whether surgeon availability and other scheduling delays adversely influence treatment outcomes, the results have important implications for active monitoring protocols with curative intent that typically involve far longer delays between diagnosis and treatment.

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Active Monitoring Protocols

In 1995, Choo et al.[5] initiated a large active monitoring program in Canada. Their protocol included men with clinical stage T1b to T2b N0 M0 prostate cancer with a Gleason score 7 or less and PSA 15 ng/mL or less. Initially, the trigger for intervention was a PSA doubling time (PSADT) of less than 2 years or progression to Gleason score 8 or more on repeat biopsy. In 2001, after initially unfavorable results, Klotz[6] revised the trigger for intervention to a PSADT of less than 3 years or progression to a Gleason score 4 + 3 = 7 or higher. For example, among 24 men who discontinued surveillance and underwent radical prostatectomy for a PSADT of less than 2 years, 58% had pathologic stage T3 disease, 8% had lymph node metastases, and only 42% still had pathologically organ-confined disease.

In contrast, in the senior author's radical prostatectomy series, 72% of men who would have met the inclusion criteria for Klotz's protocol had organ-confined disease with clear surgical margins (unpublished data). The disparity between these percentages suggests that, without a more accurate way to identify apparently low-risk patients with a more aggressive phenotype, undue delays in treatment may lead to less-favorable outcomes, at least to the extent that adverse pathology affects clinical outcomes.

Another active monitoring program led by Carter et al.[7] includes men with clinical stage T1c, a PSA density less than 0.15 ng/mL/cm^3, Gleason score less than 7 (with no pattern 4 or 5), fewer than 3 positive biopsy cores, and 50% or less involvement of any core. In addition to the more strict inclusion criteria, this program involves a different follow-up protocol with different triggers for intervention. Warlick et al.[8] recently reported on the results of this study in 38 men who discontinued surveillance and underwent delayed radical prostatectomy. Using nomogram predictions for a more than 75% probability of 10-year disease-free survival, they reported that 9 (23%) men in the delayed intervention group had noncurable cancer at surgery, compared with 24 of 150 (16%) men in an immediate radical prostatectomy group treated at the same institution. Although the difference was not statistically significant (P = .266 unadjusted), this may be a result of the small sample sizes. In addition, comparisons of actuarial survival data may be more meaningful than nomogram predictions. Applying the same nomogram to men from the author's surgical database with biopsy Gleason score 3 + 3 = 6 and 2 or fewer positive biopsy cores, 100% of the patients treated with immediate radical prostatectomy had a greater than 75% chance of 10-year disease-free survival (unpublished data). Moreover, 27% of these men were upgraded to Gleason score 7 or higher on the final pathology report, representing a population in whom active treatment is undeniably warranted.

Are We Overtreating?

Miller et al.[9] recently reported on management trends from 2000 to 2002 in low-risk men, including those aged 70 years or younger with Gleason sum 2 to 4 and men aged 70 years or older with Gleason sum 7 or less. Using Surveillance, Epidemiology, and End Results (SEER) data, they estimated that 2564 (10%) and 10,973 (45%) low-risk patients were overtreated with radical prostatectomy and radiation therapy, respectively. Unfortunately, because men were classified exclusively based on Gleason score, this analysis did not account for many other clinical variables that affect management decisions in daily practice. Moreover, most of the men they claimed were "overtreated" with radical prostatectomy were younger than 65 years. Because all cancers have the potential to acquire further mutations that are associated with more aggressive characteristics, proving that any prostate cancer detected in a young man does not have the capability to cause future morbidity or mortality is difficult.

Loeb et al.[10] previously performed a similar analysis, attempting to determine the true extent of possible overtreatment in patients from the senior author's surgical series treated from 1989 to 2001. Of the 1410 patients with data on volume from the pathology report, 93 (6.6%) met the Ohori criteria[11] for "unimportant" cancer (volume ≤ 0.5 cm^3, confined to the prostate, and no primary or secondary Gleason pattern 4 or 5). Substituting the criteria by Epstein et al.[12] (< 0.2 cm^3, confined to the prostate, Gleason sum < 7), only 6 (0.4%) tumors would be considered "insignificant."

Despite the limitations of using pathological definitions to assess overdiagnosis, these numbers suggest that a small proportion of men have a possibly insignificant tumor based upon the findings in the radical prostatectomy specimen. Unfortunately,

reliable means to identify these men preoperatively are currently not available. For example, Epstein et al.[12] suggested that men with a PSA density of less than 0.15 ng/mL/g, biopsy Gleason score 6 or less, fewer than 3 positive biopsy cores, and 50% or less involvement of any core are likely to have insignificant prostate cancer at radical prostatectomy. However, in testing these criteria in 237 men, Bastian et al.[13] found that 8.4% of the tumors that met these preoperative criteria had non–organ-confined disease based on the final pathology report.

The Case for Immediate Therapy

Several reports have shown that early definitive therapy produces better outcomes than watchful waiting. In a randomized controlled trial, Bill-Axelson et al.[14] reported that 14.9% of men managed with watchful waiting had died from prostate cancer at 10 years follow-up, compared with 9.6% of men who underwent early radical prostatectomy (P = .01). It is noteworthy that the patients in this study were primarily diagnosed before the PSA era. In this population, radical prostatectomy decreased the absolute risk for local progression by 25.1%, distant metastases by 10.2%, and overall mortality by 5.0%. Finally, although the power to perform subset analysis was inadequate, these data suggested that men younger than 65 years of age experienced the greatest survival advantage with radical prostatectomy.

To test whether active therapy is advantageous exclusively in younger men, Wong et al.[15] recently used SEER Medicare data to compare the results of treatment versus observation in 44,630 men aged 65 to 80 years. At 12 years follow-up, overall mortality was significantly higher in older men who underwent observation than those who underwent radiation therapy or radical prostatectomy within 6 months of diagnosis (37% vs. 23.8%; P < .001). Even after adjusting for age, geographic location, year of diagnosis, tumor size and grade, marital status, residence in an urban setting, race, income, education level, and comorbidities, active treatment was associated with better survival in the overall population and all predefined subgroups assessed. In addition to the 30% improvement in overall survival, cancer-specific survival was significantly higher in the active-treatment group (hazard ratio, 0.67; 95% confidence interval, 0.58–0.77). Because this was an observational study, additional prospective randomized evidence would be useful to further examine these issues.

Conclusions

In the future, advances in molecular profiling may enhance the ability to quantify the true extent of disease and tumor aggressiveness preoperatively. The reduction in prostate cancer–specific mortality rates strongly suggests that potentially overtreating a small proportion of prostate cancer, if it occurs, may be justified. After all, prostate cancer is a leading cause of cancer deaths and its behavior remains unpredictable. However, with informed patient selection and high-quality treatment, such as nerve-sparing radical prostatectomy, the adverse consequences of possible overtreatment can be minimized. The alternative approach, using currently available clinical variables to select young patients for active monitoring protocols and deferring definitive therapy in good-risk men with a long life expectancy, may eliminate the possibility for cure in the very population that is most likely to benefit from treatment.

References

1. American Cancer Society. Cancer Facts and Figures 2007. Available at: http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf. Accessed January 28, 2007.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence - SEER 17 Regs Public-Use, Nov 2005 Sub (1973-2003 varying), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2006, based on the November 2005 submission. Available at: www.seer.cancer.gov. Accessed August 28, 2006.
3. Oberaigner W, Horninger W, Klocker H, et al. Reduction in prostate cancer mortality in Tyrol, Austria, after introduction of prostate-specific antigen testing. Am J Epidemiol 2006;164:376–384.
4. Freedland SJ, Kane CJ, Amling CL, et al. Delay of radical prostatectomy and risk of biochemical progression in men with low risk prostate cancer. J Urol 2006;175:1298–1302; discussion 1302–1293.
5. Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol 2002;167:1664–1669.
6. Klotz L. Active surveillance for prostate cancer: for whom? J Clin Oncol 2005;23:8165–8169.
7. Carter HB, Walsh PC, Landis P, Epstein JI. Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. J Urol 2002;167:1231–1234.

8. Warlick C, Trock BJ, Landis P, et al. Delayed versus immediate surgical intervention and prostate cancer outcome. J Natl Cancer Inst 2006;98:355–357.
9. Miller DC, Gruber SB, Hollenbeck BK, et al. Incidence of initial local therapy among men with lower-risk prostate cancer in the United States. J Natl Cancer Inst 2006;98:1134–1141.
10. Loeb S, Gonzalez CM, Roehl KA, et al. Pathological characteristics of prostate cancer detected through prostate specific antigen based screening. J Urol 2006;175:902–906.
11. Ohori M, Wheeler TM, Dunn JK, et al. The pathological features and prognosis of prostate cancer detectable with current diagnostic tests. J Urol 1994;152:1714–1720.
12. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994;271:368–374.
13. Bastian PJ, Mangold LA, Epstein JI, Partin AW. Characteristics of insignificant clinical T1c prostate tumors. A contemporary analysis. Cancer 2004;101:2001–2005.
14. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005;352:1977–1984.
15. Wong YN, Mitra N, Hudes G, et al. Survival associated with treatment vs observation of localized prostate cancer in elderly men. JAMA 2006;296:2683–2693.