Models of Care and NCCN Guideline Adherence in Very-Low-Risk Prostate Cancer

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Abstract

NCCN Guidelines recommend active surveillance as the primary management option for patients with very-low-risk prostate cancer and an expected survival of less than 20 years, reflecting the favorable prognosis of these men and the lack of perceived benefit of immediate, definitive treatment. The authors hypothesized that care at a multidisciplinary clinic, where multiple physicians have an opportunity to simultaneously review and discuss each case, is associated with increased rates of active surveillance in men with very-low-risk prostate cancer, including those with limited life expectancy. Of 630 patients with low-risk prostate cancer managed at 1 of 3 tertiary care centers in Boston, Massachusetts in 2009, 274 (43.5%) had very-low-risk classification. Patients were either seen by 1 or more individual practitioners in sequential settings or at a multidisciplinary clinic, in which concurrent consultation with 2 or more of the following specialties was obtained: urology, radiation oncology, and medical oncology. Patients seen at a multidisciplinary prostate cancer clinic were more likely to select active surveillance than those seen by individual practitioners (64% vs 30%; \(P<.001\)), an association that remained significant on multivariable logistic regression (odds ratio [OR], 4.16; \(P<.001\)). When the analysis was limited to patients with an expected survival of less than 20 years, this association remained highly significant (72% vs 34%, \(P<.001\); OR, 5.19; \(P<.001\), respectively). Multidisciplinary care is strongly associated with selection of active surveillance, adherence to NCCN Guidelines and minimization of overtreatment in patients with very-low-risk prostate cancer. (JNCCN 2013;11:1364–1372)

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer form the basis of oncologic practice in the United States (to view the most recent version of these guidelines, visit NCCN.org).\textsuperscript{1} NCCN Guidelines indicate active surveillance to be a standard option for all men with very-low-risk prostate cancer, and the only option for men with very-low-risk prostate cancer and an expected survival of less than 20 years. Under an active surveillance regimen, immediate treatment for prostate cancer is deferred while patients undergo close monitoring for disease progression, with initiation of curative therapy at the time of convincing evidence of progression.\textsuperscript{2,3} The NCCN recommendations for patients with very-low-risk prostate cancer reflect both the extremely favorable prognosis for these men and the lack of perceived benefit to immediate, definitive treatment. Based on data from the 2007 Social Security Life Table, which indicates that the life expectancy for an average 61-year-old man is 20.2 years, the NCCN recommendations imply that active surveillance is the optimal option for many patients with very-low-risk prostate cancer aged 61 years or older. Although the incidence of very-low-risk prostate cancer has not been explicitly described, the belief is that approximately 70% of newly diagnosed patients have low-risk prostate cancer,\textsuperscript{3} and a sizeable proportion of low-risk patients have very-low-risk classification.

Consultation at a multidisciplinary prostate cancer clinic, in which patients meet concurrently with
urologists, radiation oncologists, and medical oncologists specializing in prostate cancer, is thought to reduce physician bias and has been associated with increased selection of active surveillance in patients with prostate cancer when compared with sequential consultation with one or more individual providers. Whether this association exists in patients with very-low-risk prostate cancer has not been described. Given the improved quality of life and decreased health care costs associated with active surveillance as opposed to definitive therapy, factors associated with the pursuit of active surveillance are of clinical and economic importance. In addition, for very-low-risk patients with an expected survival of less than 20 years, active surveillance avoids overtreatment of a disease that is of minimal threat to survival.

The purpose of this study was to test the hypothesis that multidisciplinary care is associated with selection of active surveillance in men with very-low-risk prostate cancer, and to examine the presence or absence of this association in the subset of men with an expected survival of less than 20 years.

Patients and Methods

Study Design and Patient Population

The authors identified 630 consecutive patients with low-risk prostate cancer (Gleason score ≤6, pretreatment prostate-specific antigen [PSA] <10, and clinical stage of ≤T2a) managed at 1 of 3 academic hospitals affiliated with Harvard Medical School in 2009 (Massachusetts General Hospital, Brigham and Women’s Hospital, and Beth Israel Deaconess Medical Center); 274 were considered to have very-low-risk disease, as defined by the NCCN criteria of Gleason score of 6 or less, pretreatment PSA less than 10 ng/mL, PSA density less than 0.15 ng/mL/cm, clinical stage T1c, fewer than 3 positive cores, and 50% or more tissue involvement by prostate cancer within each positive core. Low-risk patients not meeting criteria for very low-risk disease (n=356) were excluded from the cohort. Patients were identified through a review of prostate biopsies or new patient registries housed at each institution.

Before a modality of management was chosen, all patients underwent a history and physical examination, including a digital rectal examination, PSA measurement, and transrectal ultrasound-guided prostate biopsy. Additional staging studies were performed infrequently.

Patients either underwent consultation at a multidisciplinary clinic or were seen sequentially by individual practitioners. A multidisciplinary clinic was defined as a setting in which concurrent consultation with at least 2 of the following specialties was obtained: urology, radiation oncology, and medical oncology. In some cases, the administrative staff scheduled the initial consultation with a new patient in a multidisciplinary clinic. In other instances, patients requested to be seen in a multidisciplinary clinic. Patients who were seen at a multidisciplinary clinic and who also saw individual practitioners at another time were included in the multidisciplinary clinic cohort. All providers participating in a multidisciplinary clinic also had clinic days on which they saw patients individually.

All patients underwent either active surveillance or definitive therapy using radical prostatectomy, external-beam radiation therapy, or brachytherapy, as recommended by NCCN. No patient underwent cryotherapy, high-intensity focused ultrasound, primary androgen deprivation therapy, or a combination of any of these therapies.

Statistical Methodology

Continuous baseline patient characteristics were compared with either the 2 sample t test or a nonparametric k-sample test on the equality of medians using the Fisher exact approach. Categorical baseline patient characteristics were compared using Fisher exact test. Univariable and multivariable logistic regression was performed to determine the association between consultation at a multidisciplinary clinic and other variables of interest, and the selection of active surveillance as an initial management strategy. Variables of interest included demographic factors, such as age, race, marital status, and income; clinical characteristics, such as Charlson comorbidity score, family history of prostate cancer in a first-degree relative, PSA level at diagnosis, the percentage of positive cores (i.e., the number of positive cores divided by the total number of cores obtained at biopsy, multiplied by 100), and the greatest percentage of individual core involvement; and provider factors, such as...
mean experience of physicians (since completing medical school) and the institution of management. Income was estimated using ZIP codes and Census 2000 data (zip-codes.com and census.gov). Standardized betas were calculated to determine the relative magnitude of the association between each variable, and selection of active surveillance. Given the concern about an inherent selection bias wherein men consulting with individual practitioners had already decided on a particular treatment before consulting with a specific physician, the authors repeated the analysis on the 177 men who consulted with more than 1 physician (given the presence of multiple consultations, it is less likely that a patient would have already decided to pursue a specific therapy before the initial consultation with the first provider).

The analysis was also repeated in patients aged 61 years and older (n=154), given that these patients have a life expectancy of 20.2 years based on data from the 2007 Social Security Life Table. Additional methodologies for estimating life expectancy, such as the National Vital Statistics, were used to ensure reproducibility. All P values are 2-sided, with a threshold for significance of .05. Statistical analysis was performed using SAS version 9.3 (SAS institute, Cary, NC, USA). The study was approved by the Institutional Review Board at Dana-Farber/Harvard Cancer Center.

Results

Patient Characteristics

Of the 630 patients with low-risk prostate cancer that were identified, 274 (43.5%) had very-low-risk disease. Demographic, clinical, and provider-related characteristics for patients with very-low-risk prostate cancer seen in a multidisciplinary clinic versus those seen by individual practitioners are provided in Table 1. No significant differences were seen in age, race, income, Charlson comorbidity score, family history of prostate cancer, the number or percentage of positive cores, and the greatest individual core involvement between the 2 cohorts. Patients who were seen in a multidisciplinary clinic were more likely to be unmarried (P=.01), had a slightly higher PSA level (P=.008), and were managed by slightly more-experienced physicians than patients seen by individual practitioners (P=.002).

Management Selection

Patients obtaining consultation at a multidisciplinary prostate cancer clinic, including those with a life expectancy of less than 20 years based on the 2007 Social Security Life Table, were more likely to undergo active surveillance than those seen by individual practitioners (all patients: 64% vs 30%; P<.001; patients with a life expectancy <20 years: 72% vs 34%; P<.001). Rates of selection of radical prostatectomy, external-beam radiation therapy, brachytherapy, and active surveillance in patients seen at a multidisciplinary clinic versus by individual practitioners are presented in Figure 1. Table 2 depicts the characteristics of patients selecting radical prostatectomy, external-beam radiation, brachytherapy, and active surveillance. Table 3 displays the 30 genitourinary oncologists (14 urologists, 9 radiation oncologists, 7 medical oncologists) in the study who consulted on at least 5 patients. For each provider, the number of patients opting for definitive treatment versus active surveillance has been provided.
association between multidisciplinary care and selection of active surveillance remained highly significant on both univariable (OR, 3.69; 95% CI, 1.97–6.89; \(P<.001\)) and multivariable (OR, 3.44; 95% CI, 1.49–7.93; \(P=.004\)) analysis.

When the population was limited to patients with an expected survival of less than 20 years based on the 2007 Social Security Life Table,\(^{11}\) the association between multidisciplinary care and pursuit of active surveillance remained highly significant on multivariable logistic regression (OR, 5.19; 95% CI, 1.97–13.65; \(P<.001\)). This association remained unchanged when life expectancy was estimated using the 2009–2010 National Vital Statistics,\(^{12}\) which indicate a life expectancy of less than 20 years in patients approximately 62 years of age or older (OR, 4.84; 95% CI, 1.75–13.39; \(P=.002\)).

**Discussion**

This contemporary, large, multi-institutional study showed that consultation at a multidisciplinary prostate cancer clinic is strongly associated with selection of active surveillance in men with very-low-risk prostate cancer. The magnitude of this association was greater than that of any demographic, clinical, or provider-related variable also included in the multivariate model. In addition, the adjusted OR for
the association between multidisciplinary care and active surveillance seems to be greater in the very-low-risk population than that seen in prior reports of other patients with prostate cancer.\textsuperscript{14} Despite the benefits of active surveillance with regard to quality of life\textsuperscript{3,13} and cost-containment in men with prostate cancer,\textsuperscript{6,7} it remains underused.\textsuperscript{14} Causes for the limited use of active surveillance are numerous, but likely include reimbursement schemes,\textsuperscript{15} physician bias (in which specialists recommend the therapy that they are capable of delivering),\textsuperscript{16} and overestimation of the benefit of definitive therapy, particularly in patients with limited life expectancy.\textsuperscript{17}

Although variation in compliance with NCCN Guidelines exists nationwide, adherence to these guidelines has been shown to improve outcomes within certain oncologic subsites.\textsuperscript{18} Given that the lifespan of a typical 61-year-old man is approximately 20 years,\textsuperscript{11} and that NCCN Guidelines list active surveillance as the preferred option for these men,\textsuperscript{1} it is reasonable to conclude that consultation at a multidisciplinary clinic may be associated with improved adherence to NCCN recommendations and minimization of overtreatment in men with prostate cancer. Prior studies have indicated that physicians are poor at estimating life expectancy.\textsuperscript{19–22} It is possible that the multidisciplinary care setting, in which multiple providers concurrently evaluate and discuss a given patient, allows physicians to better estimate the prognosis and potential benefit of definitive ther-
apy in those with limited life expectancy, resulting in more appropriate management decisions.

A recent study from William Beaumont compared patients seen in a newly instituted multidisciplinary clinic versus historical controls. The investigators found increased adherence to NCCN Guidelines in intermediate-risk patients who underwent multidisciplinary care, although adherence patterns in low- and high-risk patients were not statistically different; the very-low-risk group was not examined. This study is therefore part of a growing body of literature indicating an association between multidisciplinary care and differences in care patterns for patients with prostate cancer. When placed into the context of other literature that indicates very high provider satisfaction with multidisciplinary care and differences in care patterns for patients with prostate cancer. When placed into the context of other literature that indicates very high patient satisfaction with multidisciplinary care, one may conclude that, when feasible, multidisciplinary clinics offer a highly appealing approach to the management of patients with prostate cancer. Moreover, experts continue to advocate for use of multidisciplinary care in the management of patients with prostate cancer. Given the potential benefits that multidisciplinary clinics seem to impart on the health care system, it is reasonable to suggest that the reimbursement schema should acknowledge the value provided by multidisciplinary models of care.

It is important to note that active surveillance in the management of prostate cancer remains controversial. Although several important and high-impact trials have compared definitive therapy with watchful waiting in the management of prostate cancer, watchful waiting (in which patients are not screened for progression of disease and often do not receive therapy with curative intent at the time of clinical progression) has not been recognized as an option by NCCN for these patients (although it is important to note that the PIVOT trial did not identify a survival difference between patients with low-risk prostate cancer treated with either prostatectomy or watchful waiting). The benefit of definitive therapy relative to active surveillance remains unknown. Investigators from Johns Hopkins recently reported outcomes from a prospectively followed population of patients with predominantly very-low-risk prostate cancer managed with active surveillance. At 10 years, approximately 40% of patients remained free from intervention. No prostate cancer–related deaths were reported. Similarly, investigators from Europe have shown a 10-year prostate cancer–specific survival rate of 100% in patients with largely very-low-risk disease managed with active surveillance. These results constitute part of a growing body of evidence indi-

<table>
<thead>
<tr>
<th>Table 2 Characteristics of Patients Selecting Given Modality of Management</th>
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<tbody>
<tr>
<td>Radical Prostatectomy (N=124)</td>
</tr>
<tr>
<td>Age (mean, y)</td>
</tr>
<tr>
<td>Race (% white)</td>
</tr>
<tr>
<td>Marital status (% married)</td>
</tr>
<tr>
<td>Annual income (median, in thousands of US$)</td>
</tr>
<tr>
<td>Charlson comorbidity score (% with score 0)</td>
</tr>
<tr>
<td>Family history (% positive)</td>
</tr>
<tr>
<td>PSA at diagnosis (median, ng/mL)</td>
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<tr>
<td>PSA density at diagnosis (median, ng/mL/cm³)</td>
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<tr>
<td>Percentage with 1 positive core (%)</td>
</tr>
<tr>
<td>Percentage of positive cores (median)</td>
</tr>
<tr>
<td>Greatest percentage of individual core involvement (median)</td>
</tr>
<tr>
<td>Experience of consulting physicians (median, y)</td>
</tr>
<tr>
<td>Seen in multidisciplinary clinic (%)</td>
</tr>
</tbody>
</table>

Abbreviation: PSA, prostate-specific antigen.
cating extremely low rates of prostate cancer–spe

cific mortality in appropriately selected patients

managed with active surveillance at 10 years.9,30

Whether prostate cancer–specific mortality rates

will increase with longer follow-up, which has been

reported in men managed with watchful waiting,31

remains to be determined. Ultimately, the ProtecT

trial (ClinicalTrials.gov identifier: NCT00632983),

which randomizes patients to active surveillance,

radical prostatectomy, or radiation therapy, will

provide more definitive conclusions regarding the

comparative effectiveness of active surveillance in

the management of patients with prostate cancer,

with preliminary results expected in 2015.

Several limitations of this study warrant men

tion. It is possible that patients who seek care at a

multidisciplinary clinic are different from those seen

by individual practitioners. In this study, however,

| Table 3 Selection of Definitive Treatment and Active Surveillance by Patients Seen by Each Provider in the Studya |
|-----------------|-----------------|-----------------|
| Urologist 1     | 57              | 51 (89)         | 6 (11)         |
| Urologist 2     | 48              | 33 (69)         | 15 (31)        |
| Urologist 3     | 24              | 7 (29)          | 17 (71)        |
| Urologist 4     | 23              | 17 (74)         | 6 (26)         |
| Urologist 5     | 21              | 11 (52)         | 10 (48)        |
| Urologist 6     | 20              | 10 (50)         | 10 (50)        |
| Urologist 7     | 18              | 13 (72)         | 5 (28)         |
| Urologist 8     | 14              | 2 (14)          | 12 (86)        |
| Urologist 9     | 13              | 3 (23)          | 10 (77)        |
| Urologist 10    | 12              | 6 (50)          | 6 (50)         |
| Urologist 11    | 8               | 3 (37.5)        | 5 (62.5)       |
| Urologist 12    | 7               | 3 (43)          | 4 (57)         |
| Urologist 13    | 6               | 6 (100)         | 0 (0)          |
| Urologist 14    | 5               | 4 (80)          | 1 (20)         |
| Radiation oncologist 1 | 32 | 12 (37.5) | 20 (62.5) |
| Radiation oncologist 2 | 28 | 23 (82) | 5 (18) |
| Radiation oncologist 3 | 24 | 10 (42) | 14 (58) |
| Radiation oncologist 4 | 23 | 7 (30) | 16 (70) |
| Radiation oncologist 5 | 22 | 8 (36) | 14 (64) |
| Radiation oncologist 6 | 13 | 8 (62) | 5 (38) |
| Radiation oncologist 7 | 10 | 6 (60) | 4 (40) |
| Radiation oncologist 8 | 8 | 7 (87.5) | 1 (12.5) |
| Radiation oncologist 9 | 8 | 3 (37.5) | 5 (62.5) |
| Medical oncologist 1 | 36 | 15 (42) | 21 (58) |
| Medical oncologist 2 | 21 | 13 (62) | 8 (38) |
| Medical oncologist 3 | 14 | 4 (29) | 10 (71) |
| Medical oncologist 4 | 12 | 5 (42) | 7 (58) |
| Medical oncologist 5 | 11 | 3 (27) | 8 (73) |
| Medical oncologist 6 | 10 | 1 (10) | 9 (90) |
| Medical oncologist 7 | 7 | 1 (14) | 6 (86) |

aOnly includes providers who consulted on at least 5 patients.
demographic, clinical, and provider characteristics were similar between the 2 cohorts, as shown in Table 1, and therefore it does not appear that any measurable factor could have accounted for the main findings of this study. In addition, when the analysis was limited to patients who saw more than 1 physician (thereby minimizing the likelihood that patients consulted with a physician after already selecting a specific therapy), the main findings remained unchanged. However, this multivariable analysis cannot account for an unmeasured confounder, nor can it appropriately adjust for selection bias that may be present. In addition, preconsultation interviews/questionnaires were not conducted for patients in this study, and therefore the degree of selection bias, if present, cannot be quantified. More recently, the authors’ group has been investigating the value of a Web-based decision aid in patients with newly diagnosed prostate cancer as part of a prospective observational cohort study (ClinicalTrials.gov identifier: NCT01673581). Second, approximately 90% of patients in this study were white, and the results may not be generalizable to other races. Third, the authors cannot state with certainty the degree to which physicians included in this study were aware of the NCCN Guidelines for Prostate Cancer at the time of initial consultation with their patients. Lastly, all patients in this study were seen at tertiary care centers within a major metropolitan center, an environment that allows for multidisciplinary clinics to be implemented with greater ease than in communities where specialists may be separated by great distances or limited by other constraints. However, despite these limitations, the results do suggest that multidisciplinary care can be associated with tangible benefits to the patient and the health system at large, and should be considered a modality of care when possible. Regardless of the setting in which patients are seen, however, improved physician ability to estimate life expectancy may spare patients with limited life expectancy the toxicity associated with treatment.

In conclusion, multidisciplinary care is associated with increased rates of active surveillance, im-

Table 4 Univariable and Multivariable Logistic Regression for Choice of Active Surveillance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable OR (95% CI)</th>
<th>P</th>
<th>Multivariable OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year increase)</td>
<td>1.08 (1.04–1.11)</td>
<td>&lt;.001</td>
<td>1.08 (1.03–1.13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race (AA vs white; ref=white)</td>
<td>1.16 (0.30–4.41)</td>
<td>.83</td>
<td>1.87 (0.34–10.41)</td>
<td>.47</td>
</tr>
<tr>
<td>Marital status (married vs single; ref=married)</td>
<td>2.39 (1.27–4.49)</td>
<td>.007</td>
<td>1.95 (0.91–4.16)</td>
<td>.09</td>
</tr>
<tr>
<td>Charlson comorbidity index (0 vs ≥1; ref=0)</td>
<td>1.84 (1.03–3.28)</td>
<td>.04</td>
<td>1.68 (0.84–3.37)</td>
<td>.14</td>
</tr>
<tr>
<td>Family history (yes vs no; ref=no)</td>
<td>0.87 (0.48–1.57)</td>
<td>.64</td>
<td>0.97 (0.46–2.02)</td>
<td>.92</td>
</tr>
<tr>
<td>PSA (per ng/mL increase)</td>
<td>1.12 (0.97–1.29)</td>
<td>.13</td>
<td>0.92 (0.77–1.10)</td>
<td>.37</td>
</tr>
<tr>
<td>% positive cores (per 1% increase)</td>
<td>0.89 (0.84–0.95)</td>
<td>&lt;.001</td>
<td>0.91 (0.85–0.98)</td>
<td>.02</td>
</tr>
<tr>
<td>Greatest individual core involvement (per 1% increase)</td>
<td>0.95 (0.92–0.97)</td>
<td>&lt;.001</td>
<td>0.95 (0.92–0.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean experience of physicians met (per year increase)</td>
<td>1.06 (1.03–1.09)</td>
<td>&lt;.001</td>
<td>1.04 (1.00–1.07)</td>
<td>.03</td>
</tr>
<tr>
<td>Multidisciplinary clinic (no vs yes; ref=no)</td>
<td>4.11 (2.43–6.95)</td>
<td>&lt;.001</td>
<td>4.16 (1.98–8.75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Institution*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIDMC</td>
<td>1.0 (ref)</td>
<td></td>
<td>1.0 (ref)</td>
<td></td>
</tr>
<tr>
<td>MGH</td>
<td>2.22 (1.09–4.54)</td>
<td>.03</td>
<td>1.89 (0.76–4.73)</td>
<td>.17</td>
</tr>
<tr>
<td>BWH</td>
<td>0.82 (0.38–1.74)</td>
<td>.60</td>
<td>1.60 (0.64–4.01)</td>
<td>.31</td>
</tr>
</tbody>
</table>

Abbreviations: AA, African American; BIDMC, Beth Israel Deaconess Medical Center; BWH, Brigham and Women’s Hospital; CI, confidence interval; MGH, Massachusetts General Hospital; OR, odds ratio; PSA, prostate specific antigen; ref, reference.

*If MGH is set as reference, BWH vs MGH has a multivariable OR of 0.85 (95% CI, 0.38–1.89; P=.68).
proved adherence to guidelines set forth by NCCN, and minimization of overtreatment in patients with very-low-risk prostate cancer. These findings are part of a growing body of literature indicating the potential benefits associated with multidisciplinary care in the management of oncologic conditions.

References