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# Risk Assessment for Prostate Cancer Metastasis and Mortality at the Time of Diagnosis

Matthew R. Cooperberg, Jeanette M. Broering, Peter R. Carroll

**Background**     Although many tools for the assessment of prostate cancer risk have been published, most are designed to predict only biochemical recurrence, usually after a single specified treatment. We assessed the accuracy of the Cancer of the Prostate Risk Assessment (CAPRA) score, which was validated previously to predict pathological and biochemical outcomes after radical prostatectomy, to predict metastases, prostate cancer–specific mortality, and all-cause mortality.

**Methods**     We studied 10 627 men with clinically localized prostate cancer in the Cancer of the Prostate Strategic Urologic Research Endeavor registry, who underwent primary radical prostatectomy, radiation therapy (external beam or interstitial), androgen deprivation monotherapy, or watchful waiting/active surveillance, and had at least 6 months of follow-up after treatment. CAPRA scores were calculated at diagnosis from the prostate-specific antigen level, Gleason score, percentage of biopsy cores that were positive for cancer, clinical tumor stage, and age at diagnosis. Survival was studied with Kaplan–Meier analyses. Associations between increasing CAPRA scores and bone metastasis, cancer-specific mortality, and all-cause mortality were examined by use of proportional hazards regression, with adjustment for primary treatment; for all-cause mortality, the analysis also included adjustment for age and comorbidity. Accuracy of the CAPRA score was assessed with the concordance (c)-index.

**Results**     Among the 10 627 patients, 311 (2.9%) men developed bone metastases, 251 (2.4%) died of prostate cancer, and 1582 (14.9%) died of other causes. Each single-point increase in the CAPRA score was associated with increased bone metastases (hazard ratio [HR] for bone metastases = 1.47, 95% confidence interval [CI] = 1.39 to 1.56), cancer-specific mortality (HR for prostate cancer death = 1.39, 95% CI = 1.31 to 1.48), and all-cause mortality (HR for death = 1.13, 95% CI = 1.10 to 1.16). The CAPRA score was accurate for predicting metastases (c-index = 0.78), cancer-specific mortality (c-index = 0.80), and all-cause mortality (c-index = 0.71).

**Conclusions**     In a large cohort of patients with clinically localized prostate cancer who were managed with one of five primary modalities, the CAPRA score predicted clinical prostate cancer endpoints with good accuracy. These results support the value of the CAPRA score as a risk assessment and stratification tool for both research studies and clinical practice.

In 2008, an estimated 28 660 deaths from prostate cancer were expected in the United States; although this figure makes prostate cancer the second leading cause of cancer death among men after lung cancer, it is eclipsed by the estimated 186 320 men who were expected to be diagnosed (1). Most men diagnosed with prostate cancer will ultimately die of other causes, and the natural history of the disease is usually protracted even for tumors that are ultimately lethal (2). Given the potential impact of all available treatment modalities on quality of life (3), risk assessment at the time of diagnosis is a key component of clinician–patient decision making with respect to the timing and type of initial therapy, which may include active surveillance, locally directed monotherapy, aggressive multimodal therapy, or immediate systemic treatment.

Numerous multivariable models have been developed in recent years to assess cancer progression risk on the basis of clinical data

available at diagnosis, and many of these have been presented as nomograms (4). Calculation of risks from these instruments for large sets of patients is difficult, however, and the models do not generally include validated thresholds to stratify patients into risk groups for research purposes. Moreover, most models are

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**Table 1.** Calculation of the University of California, San Francisco Cancer of the Prostate Risk Assessment (CAPRA) score*

| Variable | Corresponding points |
|---|---|
| PSA at diagnosis, ng/mL | |
| <6.0 | 0 |
| 6.0–10 | 1 |
| 10.01–20 | 2 |
| 20.01–30 | 3 |
| >30 | 4 |
| Gleason score at biopsy examination, primary/secondary pattern | |
| 1–3/1–3 | 0 |
| 1–3/4–5 | 1 |
| 4–5/1–5 | 3 |
| Age at diagnosis, y | |
| <50 | 0 |
| ≥50 | 1 |
| Clinical tumor stage | |
| T1a–T2c | 0 |
| T3a | 1 |
| % of biopsy cores positive for cancer | |
| ≤33 | 0 |
| >33 | 1 |

\* For calculation of the CAPRA score, up to 4 points were assigned for prostate-specific antigen (PSA) at diagnosis; up to 3 points were assigned for the Gleason score; and up to 1 point each for age, clinical tumor stage, and percentage of biopsy cores that were positive for cancer. The total CAPRA score is the sum of points from each variable, with the range of 0–10 points. Note that in a change from the original CAPRA description (6), patients with a PSA level of 0–2 ng/mL were included in the 0-point level.

designed to predict only biochemical recurrence, usually after a single specified treatment modality (5). To address these limitations, we developed the University of California, San Francisco Cancer of the Prostate Risk Assessment (CAPRA), an easily calculable 0- to 10-point scale based on the prostate-specific antigen (PSA) level, Gleason score, clinical tumor stage, percentage of biopsy core samples positive for cancer, and age at diagnosis (*see* Table 1) (6).

The CAPRA score was developed by use of data from 1439 radical prostatectomy patients from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry (6) and has been independently validated in three studies with data from the Shared Equal Access Regional Cancer Hospital registry (7), a multi-institutional academic cohort in Germany (8), and the John Hopkins Medical Institutes (9). In these three studies, which contained a total of more than 9000 additional radical prostatectomy patients, the score accurately and consistently predicted pathological and biochemical outcomes. However, to date, the CAPRA score has not been assessed for its ability to predict metastasis or mortality, nor has it been tested among patients undergoing other treatments.

Fourteen years since the inception of the CaPSURE registry, substantial numbers of patients are beginning to reach these distant endpoints, including development of bone metastasis, prostate cancer–specific mortality, and all-cause mortality. As yet, no instrument predicts metastasis or mortality from time of diagnosis across multiple treatment strategies. We assessed the ability of the CAPRA score to predict progression from the time of diagnosis to one or more of these three endpoints.

## CONTEXT AND CAVEATS

**Prior knowledge**
Most tools for the assessment of prostate cancer risk are designed to predict only biochemical recurrence, defined as increasing levels of prostate-specific antigen (PSA), usually after a single specified treatment.

**Study design**
Retrospective analysis of data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry, a diverse multi-institutional registry of patients with prostate cancer. Patients with localized prostate cancer were treated with primary radical prostatectomy, radiation therapy (external beam or interstitial), androgen deprivation monotherapy, or watchful waiting/active surveillance. The Cancer of the Prostate Risk Assessment (CAPRA) score was calculated at diagnosis from the PSA level, Gleason score, percentage of biopsy cores that were positive for cancer, clinical tumor stage, and age at diagnosis.

**Contribution**
Each single-point increase in the CAPRA score was associated with increased bone metastases, cancer-specific mortality, and all-cause mortality. The CAPRA score was accurate for predicting all three outcomes.

**Implications**
The CAPRA score warrants validation in independent cohorts of prostate cancer patients.

**Limitations**
The number of metastasis and cancer-specific mortality events was relatively small. Some data for cancer-specific mortality were obtained from death certificates, which may be inaccurate. CaPSURE sites were not chosen at random and so do not reflect the general population.

*From the Editors*

## Patients and Methods

### Patient Cohort
CaPSURE is a national disease registry of men with biopsy-proven prostate adenocarcinoma who are recruited from 40 primarily community-based urology practices across the United States. Men with newly diagnosed prostate cancer are recruited consecutively by participating urologists who report initial and follow-up clinical data, including results of staging tests and treatments. Additional clinical, quality-of-life, and health resource utilization data are collected directly from patients, and hospitalization data are confirmed by medical record audit. All patients provide written informed consent under supervision of local institutional review boards at each practice site.

Patients are treated according to their physicians' usual practices and are followed until their death or withdrawal from the study. Patient mortality is reported by participating clinicians, after which a copy of the state death certificate is obtained and a determination of the cause of death (ie, prostate cancer–specific mortality vs death from another cause) is made by consensus of the study investigators. In general, the death is considered to be prostate cancer–specific mortality if prostate cancer was listed as a primary,

secondary, or tertiary cause of death and no other malignancy was listed as a higher order cause. If the patient has been lost to follow-up or a state death certificate is not available, the National Death Index is queried to identify date and cause of death. Additional details regarding CaPSURE's methodology have been reported previously (10,11).

Of 13 740 men enrolled in CaPSURE as of July 31, 2007, 533 with advanced (clinical stage higher than T3aN0M0) disease at time of diagnosis were excluded; 1045 with less than 6 months of posttreatment follow-up data available were excluded; 1037 with missing data on more than one clinical risk variable needed to calculate the CAPRA score (PSA level, Gleason score, clinical tumor stage, or percentage of biopsy core samples that are positive for cancer) were excluded; and 498 with primary treatment coded as missing, unknown, or other were excluded. Thus, 10 627 (77.3%) of the 13 740 patients with prostate cancer constituted the dataset for this analysis.

## Statistical Analysis

The CAPRA score was calculated for each patient as described previously (Table 1) (6). Briefly, up to 4 points are assigned by PSA level at diagnosis; up to 3 points for Gleason score; and up to 1 point each for clinical tumor stage, age at diagnosis, and percentage of biopsy cores involved with cancer. Points from each variable are added to yield a final score ranging from 0 to 10. For the 2028 men who were missing exactly one of the five clinical risk variables needed to calculate the CAPRA score (usually the percentage of biopsy core samples that were positive for cancer), a best-subset regression analysis was used to impute the CAPRA score, which was rounded to the nearest integer up to 10. The distribution of CAPRA scores among patients requiring imputation was similar to the distribution of scores among those with complete data available. For each outcome of interest (metastasis, cancer-specific mortality, or all-cause mortality), Cox proportional hazards regression was used to analyze the performance of the CAPRA score both as a continuous variable and as an ordinal variable, adjusting for primary treatment as a set of indicator variables, age at diagnosis, and Charlson comorbidity score (12) in a multivariable model, with 95% confidence intervals (CIs) for the Cox models being calculated with bias-corrected and accelerated bootstrap correction. The assumption of proportionality was tested via construction of log-minus-log and smooth Schoenfeld residual plots, both of which demonstrated essentially parallel curves; a LOWESS smooth drawn through the latter plot was horizontal.

Because of the small numbers of patients with very high-risk disease, CAPRA scores of 8–10 were combined into one group for analysis; likewise because of the small numbers of patients with CAPRA score of 0, a CAPRA score of 1 rather than 0 was used as the reference for analyses of the CAPRA score as a continuous variable. For each outcome, Harrell's concordance index ($c$-index) was calculated (13) as a measure of predictive accuracy. Interpretation of the $c$-index is similar to that of the area under a receiver operating characteristic curve for a diagnostic test; a $c$-index of 0.5 indicates that the instrument does no better than random guessing and a $c$-index of 1.0 indicates 100% predictive accuracy. In general, $c$-index values for prostate cancer–predictive instruments range from approximately 0.65 to 0.85, with higher accuracy usually seen in academic series and for instruments incor-

**Table 2.** Characteristics of the patient cohort for this study*

| Variable | No. (%) |
|---|---|
| Age at diagnosis, y | |
| <50 | 274 (2.6) |
| 50–65 | 4642 (43.7) |
| 65–75 | 4204 (39.6) |
| >75 | 1507 (14.2) |
| Ethnicity | |
| White | 9153 (86.1) |
| African American | 1093 (10.3) |
| Latino | 180 (1.7) |
| Other | 201 (1.9) |
| PSA level at diagnosis, ng/mL | |
| <6.0 | 4521 (43.9) |
| 6.01–10 | 3008 (29.2) |
| 10.01–20 | 1773 (17.2) |
| 20.01–30 | 420 (4.1) |
| >30 | 586 (5.7) |
| Gleason score | |
| 2–6 | 6805 (65.5) |
| 3 + 4 | 1750 (16.8) |
| 4 + 3 | 899 (8.7) |
| 8–10 | 935 (9.0) |
| Clinical tumor stage | |
| T1 | 4854 (47.4) |
| T2 | 5133 (50.1) |
| T3a | 250 (2.4) |
| % of biopsy cores positive for cancer | |
| ≤10 | 1180 (11.9) |
| 11–33 | 3753 (37.8) |
| 34–50 | 2785 (28.0) |
| 51–75 | 1021 (10.3) |
| >75 | 1198 (12.1) |
| Charlson comorbidity score | |
| 0 | 1471 (17.8) |
| 1 | 2226 (27.0) |
| 2 | 2084 (25.2) |
| 3 | 1378 (16.7) |
| >3 | 1098 (13.3) |
| Primary treatment | |
| Radical prostatectomy | 5378 (50.6) |
| Cryotherapy | 425 (4.0) |
| Brachytherapy | 1441 (13.6) |
| External beam radiotherapy | 1262 (11.9) |
| Primary androgen deprivation therapy | 1457 (13.7) |
| Watchful waiting/active surveillance | 664 (6.3) |

\* PSA = prostate-specific antigen.

porating postoperative (pathological) data. Kaplan–Meier plots were generated for each outcome as stratified by individual CAPRA score levels or by the CAPRA score grouped into low (0–2 points), intermediate (3–5 points), and high (6–10 points) risk groups; these groupings have been validated repeatedly in previous analyses (7–9).

In the original development of the CAPRA score, patients with a PSA level of less than 2 ng/mL were excluded because they had markedly lower rates of recurrence than other patients. In subsequent validation studies, however, these patients were included with those whose PSA levels were 2–6 ng/mL, with no loss of accuracy (8). Therefore, for this analysis, 409 patients with a PSA level of less than 2 ng/mL were included and assigned 0 points for PSA level toward the CAPRA score.

**Table 3.** Distribution of Cancer of the Prostate Risk Assessment (CAPRA) scores by primary treatment type*

| CAPRA score | No. of patients (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **RP** | **Cryo** | **Brachy** | **EBRT** | **PADT** | **WW** | **Total** |
| 0 | 70 (1.3) | 0 (0.0) | 6 (0.4) | 1 (0.1) | 0 (0.0) | 1 (0.2) | 78 (0.7) |
| 1 | 1295 (24.1) | 57 (13.4) | 367 (25.5) | 105 (8.3) | 122 (8.4) | 174 (26.2) | 2120 (20.0) |
| 2 | 1649 (30.7) | 110 (25.9) | 462 (32.1) | 264 (20.9) | 266 (18.3) | 228 (34.3) | 2979 (28.0) |
| 3 | 1008 (18.7) | 73 (17.2) | 258 (17.9) | 263 (20.8) | 233 (16.0) | 138 (20.8) | 1973 (18.6) |
| 4 | 598 (11.1) | 62 (14.6) | 151 (10.5) | 169 (13.4) | 176 (12.1) | 59 (8.9) | 1215 (11.4) |
| 5 | 374 (7.0) | 47 (11.1) | 83 (5.8) | 142 (11.3) | 178 (12.2) | 26 (3.9) | 850 (8.0) |
| 6 | 230 (4.3) | 33 (7.8) | 63 (4.4) | 142 (11.3) | 163 (11.2) | 22 (3.3) | 653 (6.1) |
| 7 | 114 (2.1) | 25 (5.9) | 34 (2.4) | 99 (7.8) | 145 (10.0) | 12 (1.8) | 429 (4.0) |
| 8–10 | 40 (0.7) | 18 (4.2) | 17 (1.2) | 77 (6.1) | 174 (11.9) | 4 (0.6) | 330 (3.1) |
| Total | 5378 | 425 | 1441 | 1262 | 1457 | 664 | 10 627 |

\*  For each primary treatment, the mean CAPRA score was as follows: radical prostatectomy (RP) = 2.6 (95% confidence interval [CI] = 0 to 5.9), cryotherapy (Cryo) = 3.5 (95% CI = 0 to 7.6), brachytherapy (Brachy) = 2.7 (95% CI = 0 to 6.0), external-beam radiation therapy (EBRT) = 4.1 (95% CI = 0 to 8.4), primary androgen deprivation therapy (PADT) = 4.5 (95% CI = 0 to 9.4), watchful waiting/active surveillance (WW) = 2.5 (95% CI = 0 to 6.2), and total = 3.1 (95% CI = 0 to 6.8).

To ensure that substantial bias had not been introduced by the imputation procedure, we also recalculated hazard ratios (HRs) for each outcome, including only the 8587 patients for whom the CAPRA score could be calculated with no imputation. Finally, subset analyses of prostate cancer–specific mortality were performed for patients undergoing radical prostatectomy, radiation therapy (external beam radiotherapy or brachytherapy), or primary androgen deprivation therapy. Subset analyses were not performed for watchful waiting/active surveillance or cryotherapy patients because of the small numbers of events that have occurred in these groups of patients. All statistical tests were two-sided. All analyses were performed with Stata version 10.1 (Stata Corp., College Station, TX).

## Results

The mean patient age at diagnosis among all patients was 66.1 years (95% CI = 49.2 to 82.9 years). The mean CAPRA score was 3.1 (95% CI = 0 to 6.8). In this cohort of 10 627 patients, 9153 (86%) were white and 5378 (50.6%) were treated with radical prostatectomy, 2703 (25.5%) with radiation therapy, 1457 (13.7%) with androgen deprivation monotherapy, 664 (6.3%) with watchful waiting, and 425 (4.0%) with cryotherapy. Most patients had a PSA level of 10 ng/mL or less and a Gleason score of 6 or less, but a broad range of clinical risk characteristics were represented (Table 2). Overall, 5177 (48.7%) of the 10 627 patients were at low risk, 4038 (38.0%) were at intermediate risk, and 1412 (13.3%) were at high risk, respectively, as indicated by their CAPRA scores in the ranges of 0–2, 3–5, and 6–10. Patients treated with androgen deprivation monotherapy or external beam radiation therapy were more likely to have higher CAPRA scores than those treated with other modalities (Table 3).

A total of 311 (2.9%) of the 10 627 patients developed bone metastases, 251 (2.4%) died of prostate cancer, and 1582 (14.9%) died of any cause; the mean follow-up at time of death was 75.6 months, and the median follow-up was 71.3 months. Surviving patients were censored at a mean of 49.3 months and median of 42.6 months. The results of the Kaplan–Meier analyses (Figures 1–3) indicate that risk for each endpoint increased as the CAPRA

score increased, with generally good separation of the survival curves and consistent progression of risk with increasing score, whether the CAPRA score was treated as a continuous or a grouped three-level score. Actuarial prostate cancer–specific and overall survival at 10 years ranged from 98.2% (95% CI = 93.3% to 99.5%) and 76.7% (95% CI = 69.7% to 82.4%), respectively, for patients with a CAPRA score of 0, to 78.9% (95% CI = 70.0% to 85.4%) and 41.5% (95% CI = 33.1% to 49.8%), respectively, for patients with a CAPRA score of 8–10 (Table 4).

Each point increase in CAPRA score was associated with an increased risk of bone metastases (HR for metastasis = 1.47, 95% CI = 1.39 to 1.56), increased risk of cancer-specific mortality (HR for death = 1.39, 95% CI = 1.31 to 1.48), and increased risk of all-cause mortality (HR for death = 1.13, 95% CI = 1.10 to 1.16). No patient with a CAPRA score of 0 reached either metastasis or mortality endpoints. With increasing score, the hazard for each endpoint rises consistently, with the most substantial increases noted for the bone metastasis and prostate cancer–specific mortality endpoints (Table 5).

The accuracy of the CAPRA score to predict outcome was good (for bone metastases, $c$-index = 0.78; for cancer-specific mortality, $c$-index = 0.80; and for all-cause mortality, $c$-index = 0.71). When the analysis was repeated with only the 8587 patients for whom no imputation was performed, the associations between CAPRA score and all three outcomes were stronger (for bone metastases, HR for metastasis = 1.50, 95% CI = 1.41 to 1.61; for prostate cancer–specific mortality, HR for death = 1.53, 95% CI = 1.43 to 1.64; and for all-cause mortality, HR for death = 1.41, 95% CI = 1.23 to 1.61).

The treatment-stratified analysis of prostate cancer–specific mortality included 74 events among the 5378 radical prostatectomy patients, 79 events among the 2703 radiation therapy patients (62 among the 1262 patients treated with external beam radiotherapy and 17 among the 1441 patients treated with brachytherapy), and 78 among the 1457 patients treated with primary androgen deprivation therapy. Each point increase in CAPRA score was associated with an increased risk of prostate cancer–specific mortality for each treatment group: among radical prostatectomy patients (HR for death = 1.48, 95% CI = 1.30 to 1.68),

A



**Figure 1.** Kaplan–Meier plots of metastasis-free interval. **A**) Stratified by Cancer of the Prostate Risk Assessment (CAPRA) score (ie, CAPRA scores of 0 through 8–10). **B**) Stratified by grouped CAPRA scores (ie, CAPRA scores of 0–2, 3–5, and 6–10). Numbers of patients at risk are given at 4-year intervals. Table 4 presents the numerical results of the same analysis, including the metastasis-free interval estimates with 95% confidence intervals at 5 and 10 years.
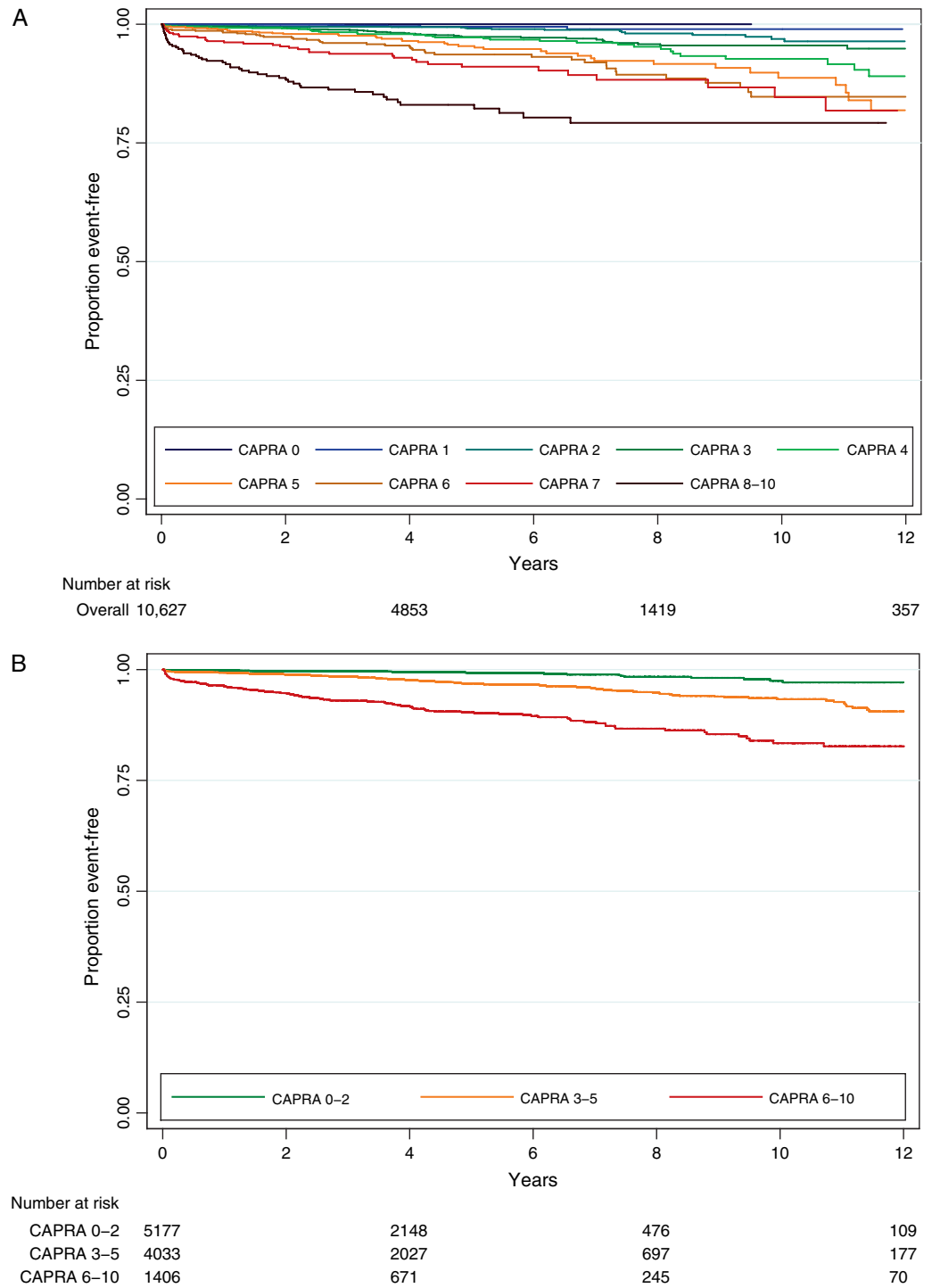
radiation therapy patients (HR for death = 1.34, 95% CI = 1.19 to 1.50), and patients treated with primary androgen deprivation therapy (HR for death = 1.63, 95% CI = 1.39 to 1.89). Accuracy was better among radical prostatectomy patients (*c*-index = 0.72) and primary androgen deprivation therapy patients (*c*-index = 0.79) than among radiation therapy patients (*c*-index = 0.68).

## Discussion

In this study, the CAPRA score was shown to be an accurate predictor of metastasis, cancer-specific mortality, and all-cause mor-

tality across a variety of primary treatment approaches. The strengths of the associations between CAPRA score and metastasis or cancer-specific mortality were similar to those for pathological and biochemical endpoints as calculated in earlier studies. In these studies (6–9), the risk of biochemical recurrence roughly doubled with each 2-point increase in CAPRA score; the present analysis demonstrated a similar increase in the risk of metastasis (HR for metastasis = 1.47) and cancer-specific mortality (HR for death = 1.39), again consistent with a doubling of risk with each 2-point increase in score. The smaller incremental increase in risk for all-cause mortality (HR for death = 1.13) was expected, given the
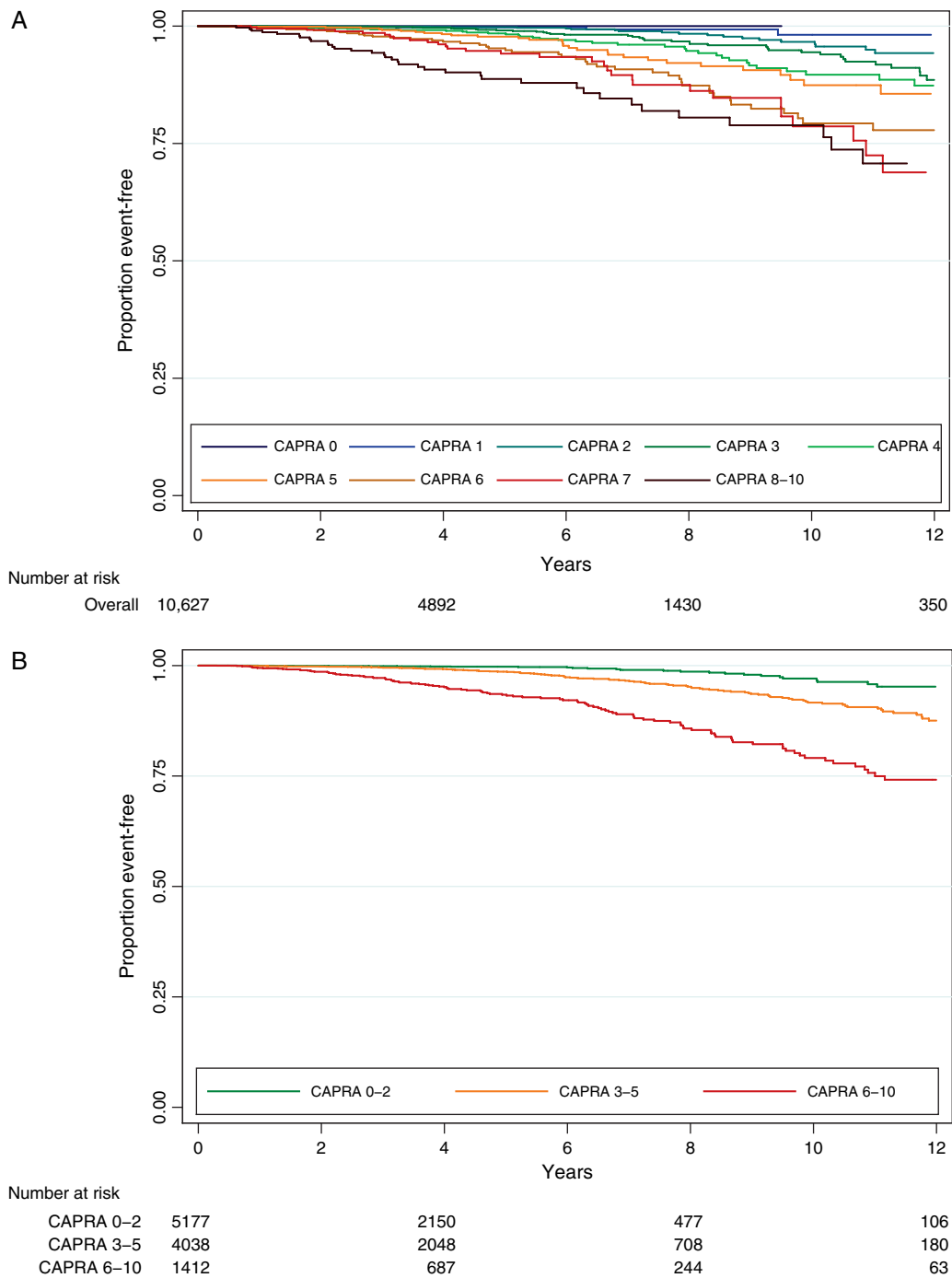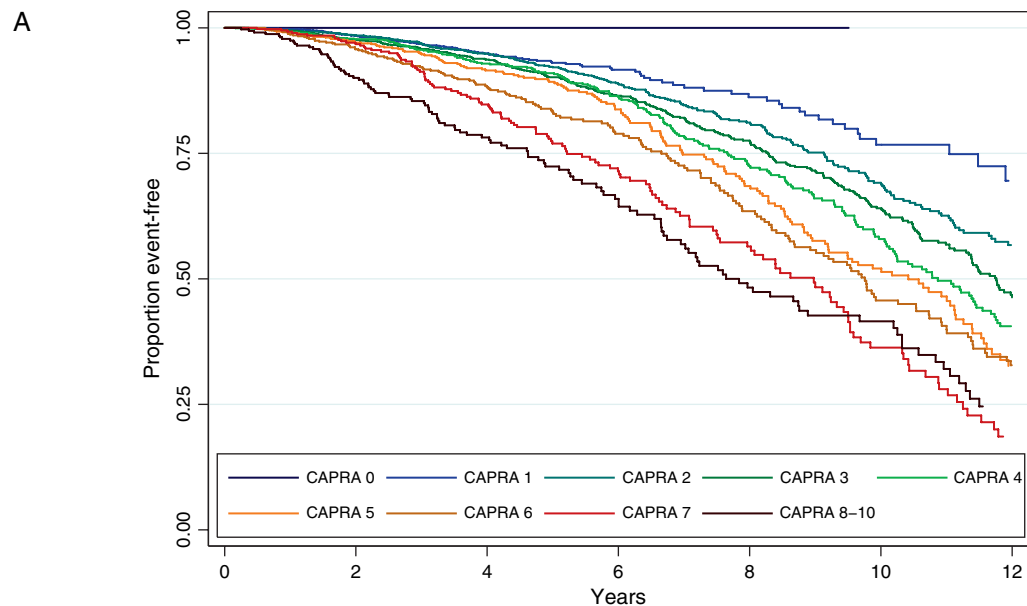
**Figure 2.** Kaplan–Meier plots of prostate cancer–specific survival. **A**) Stratified by Cancer of the Prostate Risk Assessment (CAPRA) score (ie, CAPRA scores of 0 through 8–10). **B**) Stratified by grouped of CAPRA scores (ie, CAPRA scores of 0–2, 3–5, and 6–10). Numbers of patients at risk are given at 4-year intervals. Table 4 presents the numerical results of the same analysis, including the prostate cancer–specific survival estimates with 95% confidence intervals at 5 and 10 years.

impact of patient age and multiple competing causes of mortality among men diagnosed with prostate cancer (14).

The accuracy of the CAPRA score for prediction of all three endpoints in this CaPSURE cohort ($c$-index = 0.78, 0.80, and 0.71 for bone metastases, prostate cancer–specific mortality, and all-cause mortality, respectively) was markedly superior to the accuracy in the original development study for the biochemical recurrence endpoint ($c$-index = 0.66) (6). The accuracy was somewhat lower among patients who were treated with radiation therapy ($c$-index = 0.68) than among those treated with radical prostatectomy ($c$-index = 0.72) or primary androgen deprivation

therapy ($c$-index = 0.79), which likely reflects the heterogeneity of radiation dose and technique over the years and over the multiple treatment sites represented in the CaPSURE registry.

Counseling men with a new diagnosis of prostate cancer entails many challenges, including presentation of realistic likelihoods of disease progression and mortality. These likelihoods, together with patient comorbidity, life expectancy, and preferences for treatment, should help guide planning of a risk-adapted treatment strategy. Men with low-risk prostate cancer are now eligible for at least a trial period of active surveillance at a growing number of institutions (15). Men with low- to intermediate-risk disease are
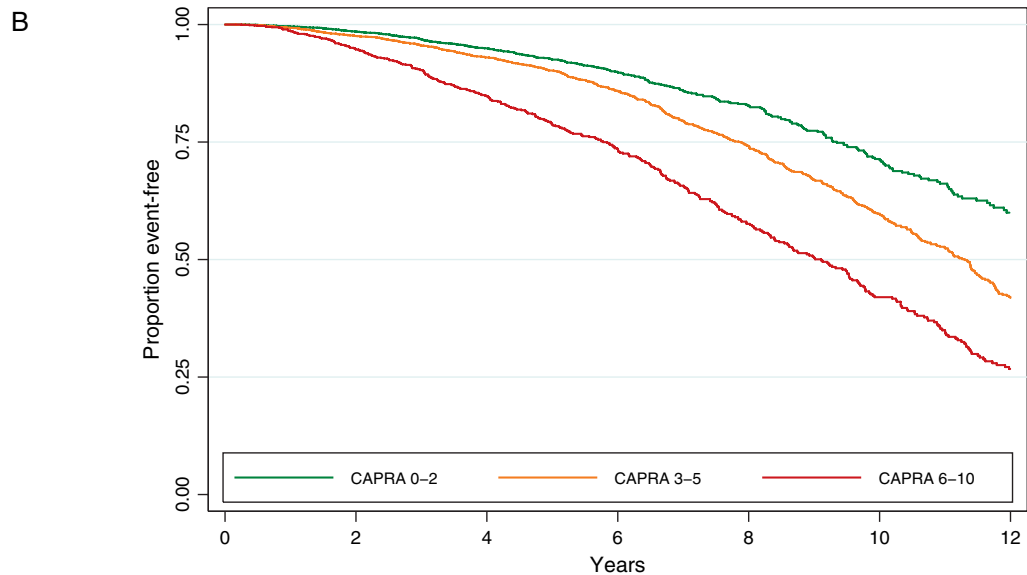
**Figure 3.** Kaplan–Meier plots of overall survival. **A)** Stratified by Cancer of the Prostate Risk Assessment (CAPRA) score (ie, CAPRA scores of 0 through 8–10). **B)** Stratified by grouped CAPRA scores (ie, CAPRA scores of 0–2, 3–5, and 6–10). Numbers of patients at risk are given at 4-year intervals. Table 4 presents the numerical results of the same analysis, including the overall survival estimates with 95% confidence intervals at 5 and 10 years.

well managed by local monotherapy, while those with higher risk disease generally require aggressive multimodal treatment. Finally, men with high-risk tumors are treated systemically for presumptive micrometastatic disease and/or, ideally, should be offered clinical trial enrollment, given the high rates of recurrence and progression with extant standard therapies.

The menu of instruments to help guide decision making has grown rapidly in the 10 years since publication of the original preoperative nomogram by Kattan et al. (16), to 111 instruments for various prostate cancer scenarios by one recent count (4). Most instruments intended for use at time of diagnosis predict bio-

chemical recurrence after one specific form of treatment—for example, radical prostatectomy, external beam radiotherapy, or brachytherapy (4). However, most have not been well validated, and comparison across instruments is difficult, given the concurrent profusion of published definitions of biochemical recurrence (17). Moreover, biochemical recurrence predicts clinical endpoints with various degrees of precision, depending on factors including tumor grade and PSA kinetics after treatment (2). Notable exceptions include a nomogram published by Kattan et al. (18), shown to predict metastases after external beam radiotherapy and the three-level classification by D'Amico et al. (19), which predicts

**Table 4.** Actuarial survival outcomes stratified by Cancer of the Prostate Risk Assessment (CAPRA) score*

| CAPRA score(s) | Metastasis-free interval, % likelihood (95% CI) | | Prostate cancer–specific survival, % likelihood (95% CI) | | Overall survival, % likelihood (95% CI) | |
|---|---|---|---|---|---|---|
| | **5 y** | **10 y** | **5 y** | **10 y** | **5 y** | **10 y** |
| 0 | 100 | 100 | 100 | 100 | 100 | 100 |
| 1 | 99.5 (98.8 to 99.8) | 99.0 (97.1 to 99.6) | 99.7 (99.3 to 99.9) | 98.2 (93.3 to 99.5) | 93.0 (91.2 to 94.5) | 76.7 (69.7 to 82.4) |
| 2 | 99.1 (98.5 to 99.5) | 96.9 (94.7 to 98.2) | 99.8 (99.3 to 99.9) | 96.7 (94.2 to 98.1) | 92.1 (90.7 to 93.4) | 69.1 (64.9 to 73.0) |
| 3 | 97.3 (96.3 to 98.1) | 95.5 (93.7 to 96.8) | 99.1 (98.3 to 99.5) | 94.4 (91.7 to 96.3) | 90.2 (88.4 to 91.7) | 64.1 (59.8 to 68.0) |
| 4 | 97.2 (95.8 to 98.2) | 92.7 (89.2 to 95.1) | 98.4 (97.2 to 99.1) | 89.7 (84.9 to 93.0) | 91.0 (88.7 to 92.8) | 57.9 (52.1 to 63.3) |
| 5 | 95.4 (93.2 to 96.9) | 88.7 (83.3 to 92.4) | 97.8 (95.9 to 98.8) | 87.4 (81.1 to 91.7) | 89.3 (86.3 to 91.6) | 52.1 (45.2 to 58.5) |
| 6 | 93.6 (90.9 to 95.6) | 84.7 (78.4 to 89.3) | 95.3 (92.6 to 97.0) | 79.3 (71.8 to 85.0) | 83.2 (79.2 to 86.5) | 45.7 (38.7 to 52.4) |
| 7 | 91.1 (87.3 to 93.8) | 84.6 (76.7 to 90.0) | 94.1 (90.3 to 96.5) | 78.6 (67.9 to 86.1) | 77.0 (71.4 to 81.6) | 36.3 (28.0 to 44.7) |
| 8–10 | 83.0 (77.9 to 87.1) | 79.2 (72.8 to 84.3) | 88.7 (83.6 to 92.4) | 78.9 (70.0 to 85.4) | 72.4 (66.0 to 77.8) | 41.5 (33.1 to 49.8) |
| 0–2 | 99.3 (98.8 to 99.5) | 97.5 (95.9 to 98.5) | 99.7 (99.9 to 99.5) | 97.1 (98.2 to 95.1) | 92.5 (91.5 to 93.5) | 71.4 (67.8 to 74.7) |
| 3–5 | 96.9 (96.2 to 97.5) | 93.3 (91.7 to 94.6) | 98.6 (99.0 to 98.1) | 91.6 (93.4 to 89.5) | 90.2 (89.0 to 91.3) | 59.7 (56.7 to 62.7) |
| 6–10 | 90.4 (88.4 to 92.0) | 83.4 (79.6 to 86.6) | 93.4 (94.9 to 91.5) | 79.1 (83.1 to 74.3) | 78.7 (75.9 to 81.2) | 42.0 (37.4 to 46.5) |

\* The 5- and 10-year actuarial survival estimates for each endpoint are given as percent likelihoods with 95% confidence intervals (CIs), for each individual and grouped CAPRA score level, across all primary treatment groups.

cancer-specific mortality after radical prostatectomy or external beam radiotherapy.

The CAPRA score is among the most extensively and independently validated risk assessment tools available for localized prostate cancer, and it performs well in terms of accuracy, calibration, generalizability, and parsimony (5). The score has previously been evaluated as a predictor of pathological and biochemical outcomes in community-based and academic cohorts of radical prostatectomy patients in both the United States and the Europe. In these studies, the accuracy of the instrument was generally good ($c$-index range = 0.66 to 0.81) and was higher among the academic validation studies (6–9). The accuracy of the CAPRA score in these studies was consistently comparable with the Kattan nomogram ($c$-index range = 0.68 to 0.78) (9,16,20,21). To our knowledge, however, the CAPRA score has not been assessed before this study as a predictor of distal endpoints or examined in cohorts of non–radical prostatectomy patients. Indeed, no validated multivariable instrument yet published has been demonstrated to predict mortality outcomes from time of diagnosis across multiple primary treatment types.

Yossepowitch et al. (22) recently reviewed the accuracy of eight definitions of high-risk disease in predicting distant outcomes, including cancer-specific mortality after radical prostatectomy. These definitions included several simple definitions of risk grouping and a score of 50% or less on the updated preoperative nomogram of Stephenson et al. (23). None of these measures were able to identify a group with greater than a 12% likelihood of cancer-specific mortality at 10 years after treatment. Of note, in the analysis of Yossepowitch et al., a PSA velocity of greater than 2 ng/mL per year, which was previously identified as a strong predictor of cancer-specific mortality (24), was the weakest indicator of risk (22). By contrast, the high-risk group that was identified by a CAPRA score of 6–10 in this analysis had a cancer-specific mortality at 10 years of 20.9%, compared with 2.9% and 8.4%, respectively, for the low-risk and intermediate-risk groups that were defined by CAPRA scores of 0–2 and 3–5, respectively. Moreover, individuals in the high-risk group that was defined by a CAPRA score of 6–10 can be substratified, with actuarial cancer-specific mortality rates ranging from 16.8% to 27.6%.

A particular strength of the CaPSURE database is its large numbers of patients undergoing different primary treatments with uniform ascertainment of follow-up assessment, PSA levels, and clinical endpoints, regardless of initial treatment. Pooling or

**Table 5.** Regression analysis of outcomes by Cancer of the Prostate Risk Assessment (CAPRA) score*

| CAPRA score | HR (95% CI) | | |
|---|---|---|---|
| | **Bone metastasis** | **Cancer-specific mortality** | **All-cause mortality** |
| Continuous | 1.47 (1.39 to 1.56) | 1.39 (1.31 to 1.48) | 1.13 (1.10 to 1.16) |
| Ordinal | | | |
| 0 | 0 | 0 | 0 |
| 1 | 1.0 (reference) | 1.0 (reference) | 1.0 (reference) |
| 2 | 2.59 (1.14 to 5.87) | 1.79 (0.73 to 4.38) | 1.20 (0.97 to 1.49) |
| 3 | 4.77 (2.15 to 10.60) | 3.29 (1.39 to 7.79) | 1.44 (1.16 to 1.78) |
| 4 | 6.86 (3.06 to 15.37) | 4.78 (2.00 to 11.40) | 1.63 (1.30 to 2.05) |
| 5 | 10.68 (4.78 to 23.85) | 6.32 (2.63 to 15.19) | 1.87 (1.47 to 2.37) |
| 6 | 12.21 (5.44 to 27.40) | 8.78 (3.70 to 20.86) | 1.86 (1.46 to 2.37) |
| 7 | 15.81 (6.96 to 35.93) | 10.07 (4.14 to 24.49) | 2.42 (1.87 to 3.12) |
| 8–10 | 28.85 (12.85 to 64.76) | 13.93 (5.76 to 33.67) | 2.37 (1.81 to 3.10) |

\* Hazard ratios (HRs) with 95% confidence intervals (CIs) are given for each outcome (metastases, cancer-specific mortality, and all-cause mortality), with CAPRA score calculated as both a continuous and a ordinal variable. The calculated $c$-index values for each outcome are as follows: bone metastasis = 0.78; cancer-specific mortality = 0.80; and all-cause mortality = 0.71.

comparing patients undergoing radical prostatectomy and radiation therapy is difficult in studies with biochemical endpoints given variations in the definitions of biochemical recurrence (17). By analyzing metastases, cancer-specific mortality, and all-cause mortality, we circumvented this problem. Moreover, these distant endpoints are ultimately more relevant to patients than either pathological or biochemical outcomes. Finally, the CAPRA score can be calculated without paper nomograms, lookup tables, or computer software, and, therefore, is easily applied in clinical and research settings alike. Better and more consistent application of risk assessment techniques should be expected to reduce overtreatment of low-risk disease and undertreatment of high-risk disease, phenomena that appear to have diminished the potential benefits of prostate cancer screening (25).

This study had several limitations. The number of metastasis and cancer-specific mortality events was relatively small, particularly for the secondary analysis by primary treatment type. Additional follow-up should provide more events, including those from patients managed with watchful waiting/active surveillance or cryotherapy. Ascertainment of cancer-specific mortality from a review of death certificates is inherently limited by the quality of information on the certificates; these may be completed by any physician who may have variable familiarity with prostate cancer and with the patient's history. Mortality that is caused by side effects of treatment, in particular, is likely to be underestimated. For example, the death of a patient with prostate cancer who dies of bladder cancer due to pelvic radiation (26), coronary artery disease accelerated by androgen deprivation therapy (27), or sequelae of a hip fracture attributable to osteoporosis that was accelerated by androgen deprivation therapy (28) will likely not be attributed on the death certificate to prostate cancer. Underestimation of cancer-specific mortality may, in fact, partially explain the better-than-expected success of the CAPRA score in predicting all-cause mortality.

The CaPSURE practice sites are distributed across the United States but were not chosen at random and do not represent a statistically significantly valid sample of the population. Comparing the present cohort with the Surveillance Epidemiology and End Results (SEER) sample (29) reveals some relatively minor demographic differences. The median age at diagnosis of prostate cancer patients in the SEER areas was 68 years in the period from January 1, 2001, through December 31, 2005, compared with 66 years in CaPSURE for the same period. In addition, for the same period, African Americans constituted 12.1% of the prostate cancer patients in SEER but only 10.3% of those in CaPSURE, whereas patients of other ethnicities constituted 12.9% of those in SEER but only 3.6% of those in CaPSURE. CaPSURE patients also tend to have slightly higher socioeconomic status on average than the overall population (11).

A total of 3113 (22.6%) of the cohort of 13 740 patients were excluded from the analysis, with roughly one-third excluded because of missing data. This limitation likely reflects the large number of clinicians contributing data to the registry. Imputation of the CAPRA scores for those with only a single missing variable ameliorated the problem to some extent. The similar distribution of CAPRA scores among those with fully calculated and imputed scores was reassuring, as were results of the sensitivity analysis that

excluded those patients with imputed scores. Furthermore, we had no reason to suspect that the missing data were not missing at random.

Patients in CaPSURE are treated by many clinicians in a variety of practice settings. Details of surgery, radiation therapy, and androgen deprivation therapy vary considerably with time and geographic location, and controlling adequately for this variability was not practical with the data available. However, we expect that this unmeasured variability would tend to artificially weaken rather than strengthen the accuracy of the instrument. Indeed, in previous studies (8,9), the CAPRA score performed better in the academic series with fewer clinicians and more consistent treatment patterns than in CaPSURE and the Shared Equal Access Regional Cancer Hospital database (6,7), both of which include multiple sites and clinicians. Future validation studies of the CAPRA score that use data from these and other databases will be important as more patients in these registries reach distal endpoints. Finally, in this analysis, we analyzed patients across multiple treatment approaches because, to date, outcomes have not been proven to be different between these approaches (3). The question of differential risk-adjusted mortality outcomes across primary treatments will be addressed in future CaPSURE studies.

The CAPRA score, which has been well validated in multiple contexts to predict pathological and biochemical endpoints (6–9), is, to our knowledge, the first instrument that uses information available at time of diagnosis to predict accurately the development of metastases, cancer-specific mortality, and all-cause mortality, irrespective of primary treatment. These findings were obtained by use of data from a diverse multi-institutional registry but should still be validated in other cohorts. The impact of primary and secondary therapy will be investigated in further detail in CaPSURE as more patients reach these distal endpoints. Given its high degree of accuracy and ease of calculation, the CAPRA score may prove an increasingly valuable tool for risk stratification in both the clinical practice and the research setting.

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