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ORIGINAL REPORT

Risk Assessment Among Prostate Cancer Patients Receiving Primary Androgen Deprivation Therapy

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Prostate cancer epidemiology has been marked overall by a downward risk migration over time. However, in some populations, both in the United States and abroad, many men are still diagnosed with high-risk and/or advanced disease. Primary androgen deprivation therapy (PADT) is frequently offered to these patients, and disease risk prediction is not well-established in this context. We compared risk features between large disease registries from the United States and Japan, and aimed to build and validate a risk prediction model applicable to PADT patients.

Methods
Data were analyzed from 13,740 men in the United States community-based Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry and 19,265 men in the Japan Study Group of Prostate Cancer (J-CaP) database, a national Japanese registry of men receiving androgen deprivation therapy. Risk distribution was compared between the two datasets using three well-described multivariable instruments. A novel instrument (Japan Cancer of the Prostate Risk Assessment [J-CAPRA]) was designed and validated to be specifically applicable to PADT patients, and more relevant to high-risk patients than existing instruments.

Results
J-CaP patients are more likely than CaPSURE patients to be diagnosed with high-risk features; 43% of J-CaP versus 5% of CaPSURE patients had locally advanced or metastatic disease that could not be stratified with the standard risk assessment tools. J-CAPRA—scored 0 to 12 based on Gleason score, prostate-specific antigen level, and clinical stage—predicts progression-free survival among PADT patients in J-CaP with a c-index of 0.71, and cancer-specific survival among PADT patients in CaPSURE with a c-index of 0.84.

Conclusion
The novel J-CAPRA is the first risk instrument developed and validated for patients undergoing PADT. It is applicable to those with both localized and advanced disease, and performs well in diverse populations.

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INTRODUCTION

Prostate cancer incidence varies tremendously across the world, depending on ethnic and population genetic factors, dietary and other environmental influences, and local screening and diagnostic practices. Incidence is highest in the United States, where prostate-specific antigen (PSA)–based screening is most intense: the world age-standardized rate (ASR) for diagnosis in the US in 2002 was 113.7 per 100,000, corresponding to a 15.3% lifetime risk of diagnosis. However, the ASR even within the country varies seven-fold with region and ethnic group, from a low of 30.9 among Koreans in Los Angeles county to a peak of 216.0 among African Americans in the Detroit area. Rates in Asia are lower overall, ranging from 1.4 in the Jiashan region of China to 50.2 in Israel; by comparison among Asians in the United States, the ASR is 58.0. ASRs in Japan range from 11.3 to 22, for a lifetime risk of diagnosis of 1.2 to 2.5%.[1]

Disease stage and risk also follow disparate patterns across regions. In the US, downward stage migration over time has been well-documented[2]; among contemporary patients only 5% are found to have nodal or distant metastatic disease at time of diagnosis.[3] In Japan, by contrast, 21% of patients present with distant metastases and 19% with locally advanced disease; other measures of risk likewise tend to be higher than elsewhere in the developed world, although as elsewhere there exists evidence of downward risk migration.[4] With this higher incidence of advanced disease, primary androgen deprivation therapy monotherapy (PADT) is a mainstay

of treatment for prostate cancer in Japan. PADT is commonly used in Japan for lower stage disease as well, accounting for 46% overall of primary treatment among men with clinically localized disease.[4] Growing use of PADT for localized disease is not unique to Japan; large US studies have demonstrated frequent PADT use across risk groups as well.[5,6] While medical androgen deprivation therapy in all contexts has fallen in the US in recent years since the implementation of changes to reimbursement under Medicare,[7] the specific impact on PADT for localized disease has not yet been ascertained.

Given the large experience with PADT in Japan, the Japanese Urological Association authorized the establishment of the J-CaP registry in 2001 as a large, multicenter, population-based database of men undergoing PADT,[8] in order to shed light on outcomes for a treatment modality which is frequently used internationally but has been subjected to relatively little analysis to date compared with other major modalities.[9] Risk assessment in this population entails special challenges related to the high proportion of advanced disease and the absence of risk instruments developed or validated for patients receiving PADT. We developed a collaborative study between Japan Study Group of Prostate Cancer (J-CaP) and the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database, a large, community-based registry of prostate cancer patients in the US,[10] in order to compare patterns of risk and outcomes.

METHODS

J-CaP and CaPSURE

J-CaP includes men diagnosed in Japan with any stage of prostate cancer between 2001 and 2003 and treated with androgen deprivation therapy, as monotherapy or in combination. Three hundred eighty-four institutions contributed patients, comprising approximately 50% of all men diagnosed in Japan during the accrual period, and nearly 95% of those treated with PADT. Eighteen point five percent of the patients were treated in academic medical centers, and the remainder in the community. 1997 TNM stage was reported directly by participating clinicians; detailed biopsy data were not included. Urologists at participating institutions report follow-up every 3 months on an ongoing basis, including information on additional treatments, progression, and all-cause mortality. Clinical progression is determined by the clinicians, and may reflect rising PSA, progression of local symptoms, and/or development of metastases. Twenty-six thousand two hundred seventy-two men were enrolled in J-CaP; of these 19,265 were treated with PADT and were included for analysis in this study. Additional information regarding J-CaP has been published previously.[8,11]

CaPSURE accrued patients from 40 clinical practice sites across the US, with 11.4% of the patients treated at academic centers; 13,740 men were accessioned between 1995 and 2007, fewer than 1% of whom were of Asian ancestry. Patients are treated according to the participating physicians' usual practice; 2,077 (15.1%) were treated with PADT. Rather than reporting clinical stage or progression directly as in J-CaP, CaPSURE clinicians submit data on digital rectal exam and ultrasound findings, initial and subsequent PSA values and imaging results, and secondary treatments. Additional clinical data are acquired through semiannual patient surveys, and hospitalization data are verified by medical record audit. Additional details regarding CaPSURE have been published previously.[10] Analyses were performed both on the CaPSURE cohort as a whole and, to allow better comparability with J-CaP, on the subset of those treated with PADT since 2000. Data in both CaPSURE and J-CaP are collected and managed under local and central institutional review board supervision.

Applying Standard Risk Instruments to PADT Patients

For this study, patient risk was assessed with the three-level risk stratification system published by D'Amico et al[12] and adopted in the American Urological Association's clinical practice guideline for localized prostate cancer.[13] Because J-CaP reports clinical stage under the 1997 TNM system which does not include a T2c designation, the risk classification was modified for both cohorts to stratify patients to high risk based on clinical stage T3a. The original Kattan preoperative nomogram score was calculated for all patients with known PSA, Gleason score, and clinical stage.[14] A Kattan-type nomogram has not been published for patients receiving PADT; the updated preoperative instrument[15] was not used because it requires detailed biopsy data not included in J-CaP.

Finally, the University of California, San Francisco Cancer of the Prostate Risk Assessment (CAPRA) score was calculated for both cohorts.[16] Because detailed biopsy data are not included in J-CaP, a previously published modification of the CAPRA score was used, which omits the percent of positive cores variable and calculates the score on a 0 to 9 rather than 0 to 10 scale.[17] For patients missing exactly one input variable needed to calculate the score, the score was imputed using least squares regression; the distribution of imputed CAPRA scores was similar to the distribution of nonimputed scores. These instruments are all intended to stratify patients with localized disease; in this study those with "advanced" disease (clinical stage > T3aN0M0) were categorized separately as advanced. Univariate comparisons were made between categorized age and other ordinal risk factors in J-CaP versus CaPSURE using Mantel-Haenszel χ^2 analysis.

Development of the Novel J-CAPRA Score

J-CaP data were built into a new Cox proportional hazards regression model to predict likelihood of clinical progression as defined above. Parameter estimates for variables in the model which were statistically significant independent predictors of progression were translated to points, with each increase in parameter estimate (β) up to .25 corresponding to one point. The ability of the new instrument, designated the Japan Cancer of the Prostate Risk Assessment (J-CAPRA) score, to predict clinical progression-free survival (PFS) was assessed with Kaplan-Meier analysis, Cox proportional hazards regression, and calculation of Harrell's c-index. The c-index assesses the accuracy of a predictive instrument. Its interpretation is similar to that of the area under a receiver operating curve for a diagnostic test: a c-index of 0.5 would indicate no improvement over random guessing, whereas a c-index of 1.0 would indicate perfect predictive accuracy.[18]

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. CIs for the Cox model were calculated with bias corrected and accelerated bootstrap correction. The J-CAPRA score was also categorized to identify three groups at low (J-CAPRA 0 to 2), intermediate (J-CAPRA 3 to 7), and high (J-CAPRA 8 to 12) risk of recurrence.

As a validation analysis, the accuracy of the J-CAPRA score was tested in predicting cancer-specific survival (CSS) among 1,718 patients in CaPSURE receiving PADT with sufficient data to calculate the score. Cox analysis was performed, treating the score both as a continuous and a categorized variable, and the c-index was again calculated for the validation cohort.

RESULTS

Comparing the J-CaP and CaPSURE Cohorts

The mean ± standard deviation (SD) for age among all CaPSURE patients was 66.2 ± 8.7, among the subset treated with PADT since 2000 (n = 1,024) 72.3 ± 8.9, and among J-CaP patients 75.0 ± 7.6. Fifteen point nine percent of the CaPSURE PADT patients were African American, compared to 10.8% of all CaPSURE patients. Table 1 summarizes the clinical and risk characteristics for J-CaP, CaPSURE, and the CaPSURE PADT subset. All comparisons between J-CaP and either the full or subset CaPSURE cohorts were significant at $P < .001$. In general, patients in the CaPSURE subset undergoing PADT since 2000 were older and had higher risk features by any metric than the overall CaPSURE cohort, but younger and with lower risk features than the J-CaP patients.

Table 1. Patient Demographic and Clinical Characteristics

	J-CaP		CaPSURE			
			PADT		All	
Variable	No.	%	No.	%	No.	%
Age, years						
< 55	205	1.1	46	4.5	1,641	11.9
55-65	1,764	9.2	173	16.9	4,683	34.1
66-75	7,965	41.3	397	38.8	5,383	39.2
76-85	7,970	41.4	353	34.5	1,905	13.9
> 85	1,362	7.1	55	5.4	128	0.9
Gleason score						
2-6	5,884	35.1	400	40.8	8,119	64.2
3 + 4	2,802	16.7	162	16.5	2,113	16.7
4 + 3	2,019	12.0	151	15.4	1,091	8.6
8-10	6,060	36.2	268	27.3	1,324	10.5
PSA, ng/mL						
0.00-10.00	4,727	24.6	469	48.9	8,848	71.2
10.01-20.00	3,713	19.3	212	22.1	2,093	16.8
20.01-30.00	1,734	9.0	76	7.9	538	4.3
30.01-40.00	1,090	5.7	40	4.2	241	1.9
40.01-50.00	834	4.3	23	2.4	163	1.3
50.01-100.00	2,207	11.5	79	8.2	312	2.5
100.01-500.00	2,929	15.3	39	4.1	174	1.4
500.01-1,000.00	770	4.0	13	1.4	28	0.2
1,000.01-5,000.00	965	5.0	6	0.6	26	0.2
> 5,000.00	237	1.2	3	0.3	4	0.0
Clinical stage						
T1	4,001	20.8	441	47.5	5,953	46.9
T2	6,274	32.6	410	44.2	6,136	48.3
T3	7,048	36.6	65	7.0	557	4.4
T4	1,943	10.1	12	1.3	51	0.4
Risk group						
Low	2,175	12.2	213	24.0	4,869	42.4
Intermediate	2,627	14.8	287	32.4	4,207	36.6
High	5,378	30.2	287	32.4	1,888	16.4
Advanced	7,601	42.8	99	9.7	533	4.6
Kattan score						
91-100	1,113	6.3	96	10.9	2,759	25.1
81-90	1,755	9.9	223	25.3	3,671	33.4
71-80	1,322	7.4	115	13.0	1,500	13.7
61-70	948	5.3	95	10.8	967	8.8
51-60	803	4.5	65	7.4	495	4.5
41-50	735	4.1	42	4.8	319	2.9
31-40	603	3.4	51	5.8	257	2.3
21-30	634	3.6	43	4.9	229	2.1
10-20	669	3.8	30	3.4	153	1.4
0-10	1,598	9.0	24	2.7	104	0.9
Advanced	7,601	42.8	99	11.2	533	4.9
CAPRA score						
0	0	0.0	1	0.1	124	1.0
1	887	4.6	124	12.6	3,261	25.2
2	1,561	8.1	169	17.1	3523	27.2
3	2,094	10.9	130	13.2	2,163	16.7
4	1,674	8.7	113	11.5	1,289	10.0
5	1,469	7.6	114	11.6	916	7.1
6	1,565	8.1	106	10.8	647	5.0
7	856	4.4	47	4.8	229	1.8
8	818	4.3	70	7.1	219	1.7
9	741	3.9	13	1.3	37	0.3
Advanced	7,601	39.5	99	10.0	533	4.1
Total patients	19,265		1,024		13,740	

NOTE. No. and % given for each level of each risk factor for J-CaP, all CaPSURE patients, and the subset of CaPSURE patients receiving PADT since 2000. Advanced indicates clinical stage > T3aN0M0, for which D'Amico risk group, Kattan score, and CAPRA score cannot be calculated.

Abbreviations: J-CaP, Japan Study Group of Prostate Cancer; CaPSURE, Cancer of the Prostate Strategic Urologic Research Endeavor; PADT, primary androgen deprivation therapy; PSA, prostate-specific antigen; CAPRA, Cancer of the Prostate Risk Assessment.

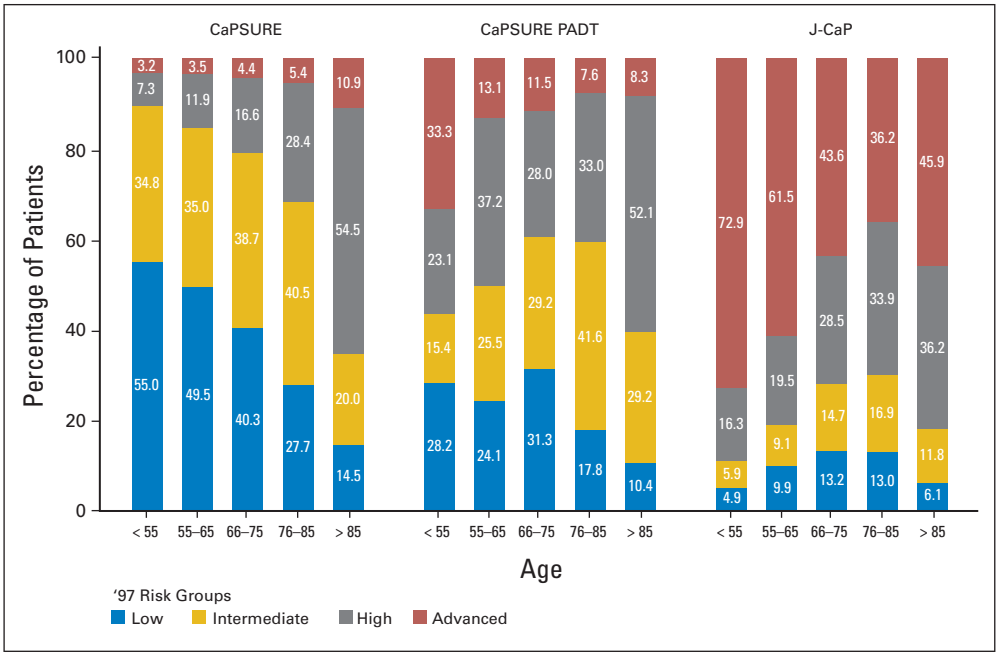

Fig 1. Association of risk and age. Distribution of D'Amico risk groups (modified for 1997 TNM staging) by patient age group is presented for all Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) patients, CaPSURE patients receiving primary androgen deprivation therapy (CaPSURE PADT), and J-CaP patients. Advanced denotes patients with clinical stage higher than T3aN0M0, for whom the D'Amico risk classification does not apply.

The mean ± SD Kattan and CAPRA scores were, respectively, 77.2 ± 19.1 and 2.7 ± 1.8 among the overall CaPSURE cohort, 66.1 ± 24.8 and 3.9 ± 2.2 among the CaPSURE PADT subset, and 53.8 ± 31.7 and 4.6 ± 2.4 among the J-CaP cohort. However, these figures underestimate the risk differences among the cohorts, as 4.1% of the CaPSURE patients overall had advanced disease at diagnosis (> T3aN0M0) for which the D'Amico, Kattan, and CAPRA calculations do not apply, compared to 9.7% of the CaPSURE PADT subset and 42.8% of the J-CaP cohort.

Figure 1 illustrates patterns of risk at diagnosis according to patient age in the different cohorts. In CaPSURE, older patients tend to present with higher risk disease, with rates of high risk or advanced disease increasing from 10.5% among men younger than 55 years to 65.4% of those diagnosed who were older than 85 years. Conversely in J-CaP, 89.2% of men younger than 55 have high risk or advanced disease; with rising age risk falls until after the age of 85, at which point it rises again. The association between risk and age among CaPSURE PADT patients appears similar to that seen among J-CaP patients.

J-CAPRA Score: Assessment and Validation

Among the J-CaP cohort, 5,683 (29.5%) progressed at a median of 16.8 months; median follow-up among those not progressing was 23.7 months. The statistical derivation and calculation of the J-CAPRA score are presented in Table 2. Patients may be assigned 1 point for Gleason score 7 or 2 points for Gleason score 8 to 10; 1 point for PSA 20 to 100 ng/mL, 2 points for PSA 100 to 500 ng/mL, or 3 points for PSA higher than 500 ng/mL; 1 point for stage T2b or T3a, 2 points for T3b, or 3 points for T4; 1 point for N1 disease; and 3 points for M1 disease. Points for each variable are summed to yield a total score with a range of 0 to 12. Due to small numbers of patients at extremely high risk, scores over 10 were combined to 11 to 12.

The distribution of J-CAPRA scores among the J-CaP cohort are listed in Table 3, along with results of the Cox analysis and actuarial 2- and 4-year PFS estimates. The HR (95% CI) for progression with each point increase in J-CAPRA score was 1.25 (1.24 to 1.26) corresponding to roughly a 50% increase in risk of progression with every two-point increase in score ($1.25^2 = 1.56$). The accuracy as measured by the c-index was 0.72. For the categorized J-CAPRA score, relative to low-risk patients (J-CAPRA 0 to 2), the HR for progression was 2.38 (2.21 to 2.56) for intermediate-risk patients (J-CAPRA 3 to 7), and 7.06 (6.55 to 7.61) for high-risk patients (J-CAPRA 8 to 12). Kaplan-Meier plots for both the continuous and categorized scores are presented in Figure 2.

Among 1,718 CaPSURE patients treated with PADT, 178 (10.1%) died of prostate cancer, at a median of 45.6 months. Median follow-up among those not dying of prostate cancer was 40.3 months. The J-CAPRA score distribution, along with results of the Cox analysis and actuarial 2- and 4-year CSS estimates are given in Table 4. The HR (95% CI) for cancer-specific mortality (CSM) with each point increase in J-CAPRA score was 1.46 (1.39 to 1.53), corresponding to roughly a doubling of risk of death from prostate cancer with every two-point increase in score. Relative to J-CAPRA 0 to 2 patients, J-CAPRA 3 to 7 patients had an HR for cancer mortality of 7.34 (4.92 to 10.93), and J-CAPRA 8 to 12 patients had an HR of 30.96 (18.49 to 51.83). Kaplan-Meier curves for CSS among CaPSURE PADT patients are presented in Appendix Figure A1 (online only). The c-index for this validation cohort was 0.84.

DISCUSSION

In the US, incidence and mortality of prostate cancer have been falling steadily since 2001 and 1993, respectively; 5-year CSS from diagnosis now approximates 100% for locoregional disease, and is 32% even for metastatic disease.[3] In contrast, data from the Osaka Cancer Registry demonstrate a 50% increase in prostate cancer incidence in Japan during the 1990s, during which time 5-year

Table 2. Predictors of Progression and Derivation of the J-CAPRA Score

Variable	β	HR	*P*	CI	Points
Gleason score					
3 + 3	Ref				0
3 + 4	.22	1.241	< .001	1.12 to 1.37	1
4 + 3	.26	1.297	< .001	1.17 to 1.44	1
8-10	.49	1.631	< .001	1.50 to 1.77	2
PSA					
0-10	Ref				0
> 10-20	.06	1.064	.276	0.95 to 1.19	0
> 20-50	.16	1.173	.005	1.05 to 1.31	1
> 50-100	.24	1.273	< .001	1.13 to 1.44	1
> 100-500	.42	1.526	< .001	1.36 to 1.71	2
> 500-1,000	.61	1.842	< .001	1.59 to 2.13	3
> 1,000-5,000	.65	1.916	< .001	1.67 to 2.20	3
> 5,000	.76	2.148	< .001	1.77 to 2.61	3
T stage					
T1a	.34	1.402	.115	0.92 to 2.13	0
T1b	.20	1.220	.191	0.91 to 1.64	0
T1c	Ref				0
T2a	.08	1.088	.209	0.95 to 1.24	0
T2b	.17	1.189	.009	1.05 to 1.35	1
T3a	.33	1.390	< .001	1.23 to 1.57	1
T3b	.43	1.534	< .001	1.35 to 1.75	2
T4	.75	2.120	< .001	1.85 to 2.43	3
N stage					
N1	.15	1.162	< .001	1.08 to 1.25	1
M stage					
M1	.70	2.011	< .001	1.87 to 2.16	3

NOTE. Derivation of the J-CAPRA score based on results of Cox proportional hazards analysis of progression among the J-CaP patients. Points from each variable, listed in the right column, are totaled from each category, for a total J-CAPRA score of 0-12.
Abbreviations: PSA, prostate-specific antigen; HR, hazard ratio; J-CAPRA, Japan Cancer of the Prostate Risk Assessment; J-CaP, Japan Study Group of Prostate Cancer.

survival rose sharply from 48% to 64%.[19] Other investigators have likewise documented downward stage and grade migration in Japan as PSA screening has become more widespread.[20] Nonetheless, men in Japan on average, as reflected in the J-CaP cohort, are diagnosed with markedly higher-risk, later-stage disease than those in most other developed countries.

As demonstrated in Figure 1, in CaPSURE, older patients tend to present with higher-risk disease, likely because they have been

Table 3. Assessment of the J-CAPRA Score in J-CaP

						2-Year PFS		4-Year PFS	
J-CAPRA Score	No.	%	HR	95% CI	*P*	HR	95% CI	HR	95% CI
Continuous			1.25	1.24 to 1.26	< .001				
0	2,858	17.1	Ref			90.3	89.0 to 91.5	74.9	72.0 to 77.5
1	2,332	14.0	1.11	0.96 to 1.29	.159	89.2	87.6 to 90.7	70.2	66.5 to 73.6
2	2,253	13.5	1.34	1.17 to 1.54	< .001	87.1	85.3 to 88.6	65.1	61.1 to 68.8
3	1,970	11.8	1.88	1.65 to 2.15	< .001	82.2	80.1 to 84.1	57.3	53.3 to 61.2
4	1,489	8.9	2.03	1.75 to 2.36	< .001	79.9	77.3 to 82.1	56.6	51.8 to 61.1
5	1,022	6.1	3.02	2.60 to 3.51	< .001	71.0	67.5 to 74.1	38.8	32.7 to 44.8
6	854	5.1	3.83	3.32 to 4.42	< .001	64.4	60.5 to 68.0	33.9	28.4 to 39.5
7	798	4.8	4.82	4.21 to 5.52	< .001	55.7	51.7 to 59.5	29.1	24.2 to 34.2
8	849	5.1	6.06	5.26 to 6.98	< .001	46.4	42.5 to 50.2	21.9	17.6 to 26.6
9	820	4.9	8.24	7.26 to 9.37	< .001	39.3	35.5 to 43.1	12.4	9.1 to 16.3
10	752	4.5	9.19	8.03 to 10.53	< .001	33.0	29.1 to 36.9	10.7	7.2 to 14.9
11-12	719	4.3	9.56	8.38 to 10.90	< .001	33.9	30.0 to 37.9	8.2	5.4 to 11.8

NOTE. Cox proportional hazards analysis of J-CAPRA score performance in predicting clinical progression among J-CaP patients.
Abbreviations: J-CAPRA, Japan Cancer of the Prostate Risk Assessment; HR, hazard ratio; PFS, progression-free survival; J-CaP, Japan Study Group of Prostate Cancer.

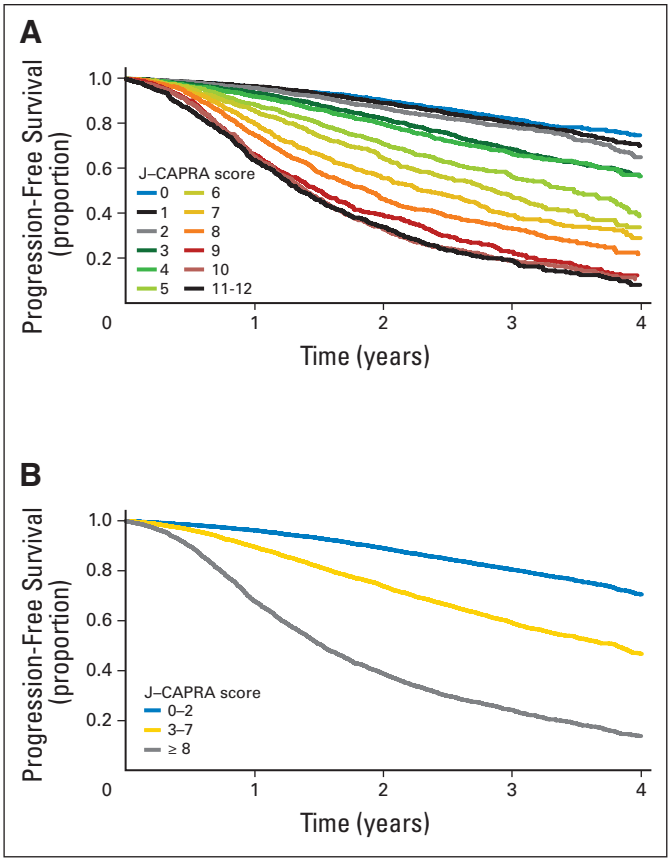

Fig 2. Progression-free survival in J-CaP by J-CAPRA score. Kaplan-Meier survival curves are presented for clinical progression-free survival among (A) J-CaP patients stratified by individual Japan Cancer of the Prostate Risk Assessment (J-CAPRA) scores, and by scores (B) grouped to yield low, intermediate, and high risk strata.

less intensively screened and therefore present later in the disease course.[21] Conversely, in J-CaP, with rising age men present with consistently lower risk until after the age of 85, at which point risk increases again. Of note, the age-risk association among men in CaPSURE receiving PADT mirrors that seen among J-CaP patients—even the age at which the trend reverses—although CaPSURE patients undergoing PADT still have generally lower risk features than J-CaP patients (Tables 1, 3, and 4).

Although PADT is commonly administered as monotherapy for localized prostate cancer in the US,[5,6] outcomes data from US cohorts regarding this approach are sparse.[9] Observational studies often include patients undergoing PADT with those undergoing conservative management,[22] which may bias such studies either for or against conservative management. A recent instrumental variable analysis suggested that men with lower-risk tumors had better survival when followed expectantly than when treated with PADT. The study, however, was restricted in its evaluation of risk by the limitations of administrative databases; data on PSA and appropriate Gleason scoring, for example, were not available.[23] A number of recent articles have raised awareness of the potential adverse metabolic, musculoskeletal, and cardiovascular effects of androgen deprivation[24-26]; given these concerns and the lack of prospective studies, the 2007 American Urological Association practice guideline for prostate cancer did not endorse PADT as a recommended option for clinically localized prostate cancer.[13]

A 1-year registration study of Japanese men diagnosed with prostate cancer was conducted in 2000 before the inauguration of J-CaP. Among 4,529 men, 70% had stage M0 at diagnosis, 81 had clinical T stage T3a or lower, and 30% had a PSA level lower than 10 ng/mL. More than 50% of men across clinical stages received PADT.[4] Analysis of Japanese cohorts have previously produced unique findings regarding the efficacy of PADT[27,28]; J-CaP was initiated to yield better insights into PADT outcomes at the large-scale, population-based level.[8,11]

Risk stratification in the J-CaP population presents unusual challenges. Among 111 entries in a recently updated catalog of published risk instruments for prostate cancer, none had been validated among Japanese patients, nor among those presenting across such a broad range of stages; most instruments intended for use at time of diagnosis explicitly exclude those with locally advanced or metastatic disease.[29]

Table 4. Validation of the J-CAPRA Score Among CaPSURE PADT Patients

						2-Year CSS		4-Year CSS	
J-CAPRA	No.	%	HR	95% CI	*P*	HR	95% CI	HR	95% CI
Continuous			1.46	1.39 to 1.53	< .001				
0	516	30.0	Ref			100		100	
1	396	23.0	2.83	1.09 to 7.36	.033	99.1	97.3 to 99.7	98.1	95.2 to 99.2
2	293	17	4.14	1.62 to 10.57	.003	99.2	96.8 to 99.8	94.9	90.3 to 97.4
3	193	11.2	9.52	3.89 to 23.29	< .001	97.2	92.8 to 99.0	90.1	83.1 to 94.3
4	94	5.5	13.93	5.59 to 34.74	< .001	93.9	86.0 to 97.4	84.6	73.6 to 91.2
5	65	3.8	16.85	6.70 to 42.35	< .001	94.7	84.6 to 98.3	83.7	69.8 to 91.6
6	53	3.1	27.67	11.04 to 69.32	< .001	85.8	71.0 to 93.4	69.3	52.0 to 81.4
7	43	2.5	41.36	16.50 to 103.64	< .001	70.2	52.4 to 82.4	57.9	38.5 to 73.2
8	30	1.7	38.49	14.78 to 100.26	< .001	72.7	50.8 to 86.1	67.9	45.4 to 82.7
9	19	1.1	58.39	20.76 to 164.21	< .001	61.0	32.8 to 80.4	41.9	15.3 to 66.7
10	11	0.6	66.72	23.52 to 189.28	< .001	45.5	16.7 to 70.7	22.7	3.8 to 51.1
11-12	6	0.3	92.79	26.06 to 330.44	< .001	83.3	27.3 to 97.5	33.3	4.6 to 67.6

NOTE. Cox proportional hazards analysis of J-CAPRA score performance in predicting CSS among Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) patients receiving primary androgen deprivation therapy.
Abbreviations: J-CAPRA, Japan Cancer of the Prostate Risk Assessment; PADT, primary androgen deprivation therapy; HR, hazard ratio; CSS, cancer-specific survival.

A Japanese validation study of the Partin tables has recently been published, together with a novel risk instrument for Japanese men undergoing prostatectomy.[30] Other instruments have been published for advanced disease,[31,32] but are intended for patients with castrate resistant disease. No previously published instrument has been intended or validated to predict outcomes for any population of previously untreated patients initiating PADT, nor for cohorts including patients with both localized and advanced disease.

The novel J-CAPRA score, a straightforward instrument requiring neither paper tables nor computer software to calculate, appears to perform well in predicting progression both among the J-CaP development cohort and the CaPSURE PADT external validation cohort, which is both demographically and clinically distinct from J-CaP. These findings highlight the importance of risk stratification even for patients who present with locally advanced or metastatic disease. Patients with multiple adverse risk features at diagnosis may be expected to progress rapidly on PADT, and might benefit from early enrollment in clinical trials of chemotherapeutics, novel targeted agents, or combination therapy.

Several limitations of this analysis should be noted. J-CaP includes only patients receiving androgen deprivation therapy; while these represent roughly half of all prostate cancer patients in Japan, they cannot be assumed to represent the whole Japanese population. Similarly, CaPSURE, while a large community-based US database, is not a random sample of the US prostate cancer population. Although there is moderate representation of African Americans in the CaPSURE PADT cohort, other ethnicities are underrepresented; therefore a comparison of outcomes among patients of Asian descent between the two cohorts is not possible at this time.

Progression in J-CaP is reported directly by clinicians, who may use varied definitions of progression as noted in the Methods section earlier; this heterogeneity could be a source of random error. This variation may explain the substantially higher c-index noted for the validation cohort in CaPSURE, which was tested with the more consistently defined CSM end point. CSM has not yet been ascertained in J-CaP, but as the database reaches further maturity, additional evaluation of J-CAPRA at mortality end points in the J-CaP cohort will be important. Finally, the present analysis does not allow any conclusions to be drawn regarding the merits of PADT relative to other therapeutic modalities.

J-CaP comprises a remarkable group of prostate cancer patients, many of whom presented with far higher risk and more advanced disease than those in other contemporary cohorts reported to date. Despite limited prospective studies reported to date, PADT is used commonly on both sides of the Pacific; with longer follow-up, the J-CaP registry will represent an invaluable source of outcomes data for patients treated with this modality. Care must be taken in applying risk instruments across patient populations and settings for which they have not been validated. The J-CAPRA score is a novel, validated score for predicting outcomes among patients undergoing PADT across the full spectrum of risk and stage, including advanced disease. We hope and expect that future international collaborative studies across disease registries will continue to yield insights into prostate cancer behavior and outcomes independent of local patterns of practice.

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REFERENCES

1. Cuardo MP, Edwards B, Shin HR, et al: Cancer Incidence in Five Continents (vol IX). Lyon, France, IARC Scientific Publications No. 160, IARC, 2007
2. Cooperberg MR, Lubeck DP, Mehta SS, et al: Time trends in clinical risk stratification for prostate cancer: Implications for outcomes (data from CaPSURE). J Urol 170:S21-S27, 2003
3. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2008. CA Cancer J Clin 58:71-96, 2008
4. Cancer Registration Committee of the Japanese Urological Association: Clinicopathological statistics on registered prostate cancer patients in Japan: 2000 report from the Japanese Urological Association. Int J Urol 12:46-61, 2005
5. Cooperberg MR, Grossfeld GD, Lubeck DP, et al: National practice patterns and time trends in androgen ablation for localized prostate cancer. J Natl Cancer Inst 95:981-989, 2003
6. Shahinian VB, Kuo YF, Freeman JL, et al: Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. Cancer 103:1615-1624, 2005
7. Weight CJ, Klein EA, Jones JS: Androgen deprivation falls as orchiectomy rates rise after changes in reimbursement in the U.S. Medicare population. Cancer 112:2195-2201, 2008
8. Akaza H, Usami M, Hinotsu S, et al: Characteristics of patients with prostate cancer who have initially been treated by hormone therapy in Japan: J-CaP surveillance. Jpn J Clin Oncol 34:329-336, 2004
9. Wilt TJ, MacDonald R, Rutks I, et al: Systematic review: Comparative effectiveness and harms of treatments for clinically localized prostate cancer. Ann Intern Med 148:435-448, 2008
10. Cooperberg MR, Broering JM, Litwin MS, et al: The contemporary management of prostate cancer in the United States: Lessons from the cancer of the prostate strategic urologic research endeavor (CaPSURE), a national disease registry. J Urol 171: 1393-1401, 2004
11. Hinotsu S, Akaza H, Usami M, et al: Current status of endocrine therapy for prostate cancer in Japan analysis of primary androgen deprivation

therapy on the basis of data collected by J-CaP. Jpn J Clin Oncol 37:775-781, 2007

12. D'Amico AV, Whittington R, Malkowicz SB, et al: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 280:969-974, 1998

13. Thompson I, Thrasher JB, Aus G, et al: Guideline for the management of clinically localized prostate cancer: 2007 update. J Urol 177:2106-2131, 2007

14. Kattan MW, Eastham JA, Stapleton AM, et al: A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. J Natl Cancer Inst 90:766-771, 1998

15. Stephenson AJ, Scardino PT, Eastham JA, et al: Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst 98:715-717, 2006

16. Cooperberg MR, Pasta DJ, Elkin EP, et al: The University of California, San Francisco Cancer of the Prostate Risk Assessment score: A straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol 173:1938-1942, 2005

17. Zhao KH, Hernandez DJ, Han M, et al: External validation of University of California, San Francisco, cancer of the prostate risk assessment score. Urology 72:396-400, 2008

18. Harrell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15:361-387, 1996

19. Department of Cancer Control and Statistics: Osaka Cancer Registry. http://www.mc.pref.osaka.jp/ocr_e/ocr/index.html

20. Okihara K, Nakanishi H, Nakamura T, et al: Clinical characteristics of prostate cancer in Japanese men in the eras before and after serum prostate-specific antigen testing. Int J Urol 12:662-667, 2005

21. Nguyen PL, Chen MH, Catalona WJ, et al: Biochemical recurrence after radical prostatectomy for prevalent versus incident cases of prostate cancer: Implications for management. Cancer 113:3146-3152, 2008

22. Albertsen PC, Hanley JA, Fine J: 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 293:2095-2101, 2005

23. Lu-Yao GL, Albertsen PC, Moore DF, et al: Survival following primary androgen deprivation therapy among men with localized prostate cancer. JAMA 300:173-181, 2008

24. Keating NL, O'Malley AJ, Smith MR: Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 24:4448-4456, 2006

25. Krupski TL, Smith MR, Lee WC, et al: Natural history of bone complications in men with prostate carcinoma initiating androgen deprivation therapy. Cancer 101:541-549, 2004

26. Tsai HK, D'Amico AV, Sadetsky N, et al: Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst 99:1516-1524, 2007

27. Akaza H: Current status and prospects of androgen depletion therapy for prostate cancer. Best Pract Res Clin Endocrinol Metab 22:293-302, 2008

28. Akaza H, Homma Y, Usami M, et al: Efficacy of primary hormone therapy for localized or locally advanced prostate cancer: Results of a 10-year follow-up. BJU Int 98:573-579, 2006

29. Shariat SF, Karakiewicz PI, Roehrborn CG, et al: An updated catalog of prostate cancer predictive tools. Cancer 113:3075-3099, 2008

30. Naito S, Kuroiwa K, Kinukawa N, et al: Validation of Partin tables and development of a preoperative nomogram for Japanese patients with clinically localized prostate cancer using 2005 International Society of Urological Pathology consensus on Gleason grading: Data from the Clinicopathological Research Group for Localized Prostate Cancer. J Urol 180:904-909, 2008

31. Armstrong AJ, Garrett-Mayer ES, Yang YC, et al: A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: A TAX327 study analysis. Clin Cancer Res 13:6396-6403, 2007

32. Halabi S, Small EJ, Kantoff PW, et al: Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. J Clin Oncol 21:1232-1237, 2003