




Long-term outcomes of androgen deprivation therapy in prostate cancer among Japanese men over 80 years old

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Abstract

This study aimed to analyze the survival rate and to examine the risk of death from prostate cancer when accounting for competing risk of death, in men aged ≥ 80 y treated with primary androgen deprivation therapy (ADT). Data of patients with prostate cancer who had received ADT were extracted from a nationwide community-based database established by the Japan Study Group for Prostate Cancer. Prognostic variables, including progression-free survival, cancer-specific survival, overall survival, and death rates were compared between men stratified by prostate cancer risk. Overall, 4760 patients older than 80 y were included. The proportion of low-, intermediate-, high-, or very high-risk, regional, and metastatic prostate cancer among super-elderly men was 9.5%, 14.6%, 48.8%, 9.0%, 3.2%, and 24.9%, respectively. Survival rates decreased with increasing risk stratification. The cumulative 5-y death rate by prostate cancer for low-, intermediate-, high-, or very high-risk, regional, and metastatic prostate cancer, was 0.92% (95% confidence interval [CI]: 0.2%-3.6%), 1.6% (95% CI: 0.8%-3.4%), 5.75% (95% CI: 4.25%-7.75%), 15.6% (95% CI: 11.6%-23.3%), 20.7% (95% CI: 13.1%-31.7%), and 36.9% (95% CI: 32.8%-41.4%), respectively. Our findings support that there is no need for immediate ADT for low- and intermediate-risk groups. Conversely, in high- or very high-risk, regional, and metastatic prostate cancer, more efforts for curative therapy and intensive therapy are needed in selected patients.

KEYWORDS

androgen deprivation therapy, elderly, Japan Study Group for Prostate Cancer, overtreatment, prostate cancer

1 | INTRODUCTION

Worldwide, prostate cancer is the second most common malignant tumor after lung cancer in men. In 2020, there were an estimated

1.4 million new cases diagnosed with prostate cancer and 375 thousand deaths worldwide. It is the most frequently diagnosed cancer in men in over one-half of countries of the world.¹ In people over 60 y of age, it is the second leading cause of cancer death and it is estimated

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that 1 in every 6 men will suffer from it during his lifetime.¹ Prostate cancer prevalence increases in the elderly population. Therefore, as life expectancy increases, so does the incidence of prostate cancer. The number of men older than 80 y (super-elderly men) is expected to increase 3.5-fold to 2050 worldwide.^{2,3} In Japan, in 2020 prostate cancer was the most diagnosed cancer in men with a projected 95.6 thousand new cases, followed by stomach and colon/rectum, and was the 6th cause of death by cancer in men, with 12.7 thousand deaths.⁴

Prostate cancer diagnosis is based on prostate biopsy, usually triggered by an abnormal prostate-specific antigen (PSA) value (which is mostly recommended in men older than 50 y) or abnormal prostate examination. The majority of guidelines for prostate cancer diagnosis do not recommend PSA screening in men older than 70 y.^{5,6} Conversely, Japanese guidelines do not set a limit for age to recommend PSA screening.⁷

Primary androgen deprivation therapy (ADT) is the gold standard in the management of metastatic prostate cancer, to delay or palliate the symptoms by disease progression.⁸⁻¹¹ In high-risk prostate cancer, guidelines recommend ADT alone or combined with radiotherapy.^{8,9} In Japan, endocrine therapy for prostate cancer takes a more important position compared with the United States and Europe, given that ADT has been also the treatment of choice in localized and locally advanced prostate cancer.¹²

Treatment for men with prostate cancer aims to reduce local and distant progression, mortality and achieve a better quality of life, depending on the scenario. However, in super-elderly men, it is important to consider the risk of death from comorbidities rather than prostate cancer. Therefore, there is a need to accumulate survival data in super-elderly men to assess whether treatment is necessary or not. Our objective is to analyze the survival rate and to examine the risk of death from prostate cancer when accounting for competing risk of death, in men aged ≥ 80 y treated with primary ADT using the database of the Japan Study Group of Prostate Cancer (J-CaP).

2 | MATERIALS AND METHODS

2.1 | Patients

This is an observational retrospective study, with a prospective dataset. From January 2001 to December 2003, men treated with hormone therapy as first-line treatment for prostate cancer were enrolled.¹³ This database includes follow-up data up to 30 September 2014. Approval of data collection was obtained by the institutional review board. All data were anonymized. The initial sample size was $n = 19\,250$.^{14,15} Patient were stratified by prostate cancer group as follows: low-risk included Gleason score ≤ 6 and PSA < 10 ng/mL and clinical T1-2; intermediate-risk included Gleason score 7 and/or PSA 10-20 ng/mL and clinical T1-2; high-risk included Gleason score ≥ 8 and/or PSA ≥ 20 ng/dl and/or Clinical T3-4; regional prostate cancer included any T, N1, M0; and metastatic prostate cancer included any T, any N, and M1. A further subgroup

comparing high-risk and very high-risk prostate cancer as T3b-T4 and/or primary Gleason pattern 5 was performed.⁸ The 1977 version of Gleason score and the UICC 5th edition clinical TNM stage were used.^{16,17} After excluding by unknown data for categorization in risk ($n = 835$), no follow-up ($n = 93$) patients, 18 322 patients were analyzed.

2.2 | Analysis of survival

Progression was diagnosed by the patients' physicians in accordance with the Japanese guideline¹⁸; progressions were defined as PSA progression, radiological progression, or death caused by prostate cancer. PSA progression was defined as 3 consecutive PSA increments, the first date of consecutive PSA increases being defined as the date of PSA progression. Radiological progression was defined as regrowth of known tumor or the development of new lesions.

2.3 | Statistical analysis

Baseline values were expressed as the median and interquartile range (IQR), and the baseline was defined as the date of initial hormone therapy. Progression-free survival (PFS) was defined as the time during which there was no recurrence. Overall survival (OS) was defined as the time from initial hormone therapy to death or last contact with the patient. Cancer-specific survival (CSS) was defined as the time between initial hormone therapy to death by prostate cancer. Survival rates were estimated using the Kaplan-Meier method with the Rothman 95% confidence interval (CI) and compared between groups using the log-rank test method. Associations between patient death and clinicopathological characteristics were evaluated using the Cox proportional risk model. Death cause was divided into death by prostate cancer and death due to any cause was defined as the respective events. To analyze competitive risk, a Fine-Gray model was performed. All statistical analyses were performed with Stata v.14. All tests were two-sided, and a P -value $< .05$ was considered as statistical significance.

3 | RESULTS

The median age for all patients was 75 y (IQR: 71-80 y). The patients' background characteristics at initial hormone therapy are summarized in Table 1. Of 18 322 men included, 4760 (26.0%) were older than 80 y. The proportion of low-, intermediate-, high- or very high-risk, regional, and metastatic prostate cancer among super-elderly men was 9.5%, 14.6%, 38.8%, 9.0%, 3.2%, and 24.9%, respectively. The proportion of high-risk prostate cancer increased by age, in addition, the proportion of low-risk prostate cancer diagnosis decreased with increasing age. Median PSA for low-, intermediate-, high- or very high-risk, regional, and metastatic prostate cancer were 6.3 ng/mL (IQR: 5-8 ng/mL), 12.2 ng/mL (IQR: 10-15.3 ng/mL),

TABLE 1 Patients' background by age categories

	Total (n = 18 322)	<75 (n = 8327)	75-79 (n = 5235)	≥80 (n = 4760)	P- value
Initial PSA value, ng/mL, n (%)					
<10	6513 (36.3%)	3027 (37.2%)	1944 (37.8%)	1542 (33.2%)	
10-20	2963 (16.5%)	1170 (14.3%)	968 (18.8%)	825 (17.7%)	
≥20	8444 (47.2%)	3939 (48.5%)	2228 (43.4%)	2277 (49.1%)	<.001
NA	402	191	95	116	
Gleason score, n (%)					
≤6	5826 (35.0%)	2527 (33.6%)	1836 (38.2%)	1463 (33.9%)	
7	4775 (28.7%)	2145 (28.6%)	1390 (28.8%)	1240 (28.8%)	
8-10	6029 (36.3%)	2836 (37.8%)	1589 (33.0%)	1604 (37.3%)	<.001
NA	1692	819.00	420	453	
Clinical T-stage, n (%)					
T1-2	8982 (49.3%)	3689 (44.4%)	2885 (55.4%)	2408 (51.1%)	
T3-4	9226 (50.7%)	4604 (55.6%)	2318 (44.6%)	2304 (48.9%)	<.001
NA	114	34	32	48	
Clinical N-stage, n (%)					
N0	14 236 (83.4%)	6197 (78.7%)	4291 (87.3%)	3748 (87.4%)	
N1	2833 (16.6%)	1675 (21.3%)	621 (12.7%)	537 (12.6%)	<.001
NA	1253	455	323	475	
Clinical M-stage, n (%)					
M0	12 317 (70.3%)	5277 (65.1%)	3840 (76.3%)	3200 (73.0%)	
M1	5210 (29.7%)	2832 (34.9%)	1194 (23.7%)	1184 (27.0%)	<.001
NA	795	218	201	376	
Risk categories, n (%)					
Low-risk	2122 (11.6%)	951 (11.4%)	718 (13.7%)	453 (9.5%)	
Intermediate-risk	2626 (14.3%)	1047 (12.6%)	881 (16.8%)	698 (14.6%)	
High-risk	6239 (34.1%)	2514 (30.2%)	1877 (35.9%)	1848 (38.8%)	
Very high-risk	1362 (7.5%)	547 (6.6%)	389 (7.4%)	426 (9.0%)	
Regional	763 (4.1%)	436 (5.2%)	176 (3.4%)	151 (3.2%)	
Metastatic	5210 (28.4%)	2832 (34.0%)	1194 (22.8%)	1184 (24.9%)	<.001
Treatment, n (%)					
Anti-androgen	1392 (7.6%)	620 (7.4%)	350 (6.7%)	422 (8.9%)	
Castration	3712 (20.3%)	1422 (17.1%)	1134 (21.7%)	1156 (24.3%)	
CAB	10 847 (59.2%)	5228 (62.8%)	3048 (58.2%)	2571 (54.0%)	
Other	2371 (12.9%)	1057 (12.7%)	703 (13.4%)	611 (12.3%)	<.001

Abbreviations: CAB, combined androgen blockade; NA, not available; PSA, prostate-specific antigen.

34 ng/mL (IQR: 21-68.4 ng/mL), 45.4 ng/mL (IQR: 17-108 ng/mL), 99 ng/mL (IQR: 26-390 ng/mL) and 170 ng/mL (IQR: 51-464 ng/mL), respectively.

The median follow-up was 2.33 y (IQR: 1.01-4.40 y). PFS at 5 y was 59.1% (95% CI: 56.8%-61.1%) for all super-elderly men. In low-, intermediate-, high- or very high-risk, regional, and metastatic prostate cancer groups, PFS at 5 y was 84.1% (95% CI: 78.4%-88.5%),

75.6% (95% CI: 70.6%-79.9%), 63.7% (95% CI: 60.1%-67.1%), 45.6% (95% CI: 38.1%-52.7%), 46.6% (95% CI: 35.1%-57.4%), and 35.5% (95% CI: 31.3%-39.7%), respectively ($P < .0001$, Figure 1A). CSS at 5 y was 86.8% (95%CI: 85.3-88.1) for all super-elderly men. In low-, intermediate, high or very high-risk, regional, and metastatic prostate cancer groups, CSS at 5 y was 99.1% (95% CI: 96.5%-99.8%), 98.4% (95% CI: 96.6%-99.3%), 94.2% (95% CI: 92.3%-95.7%), 84.3%

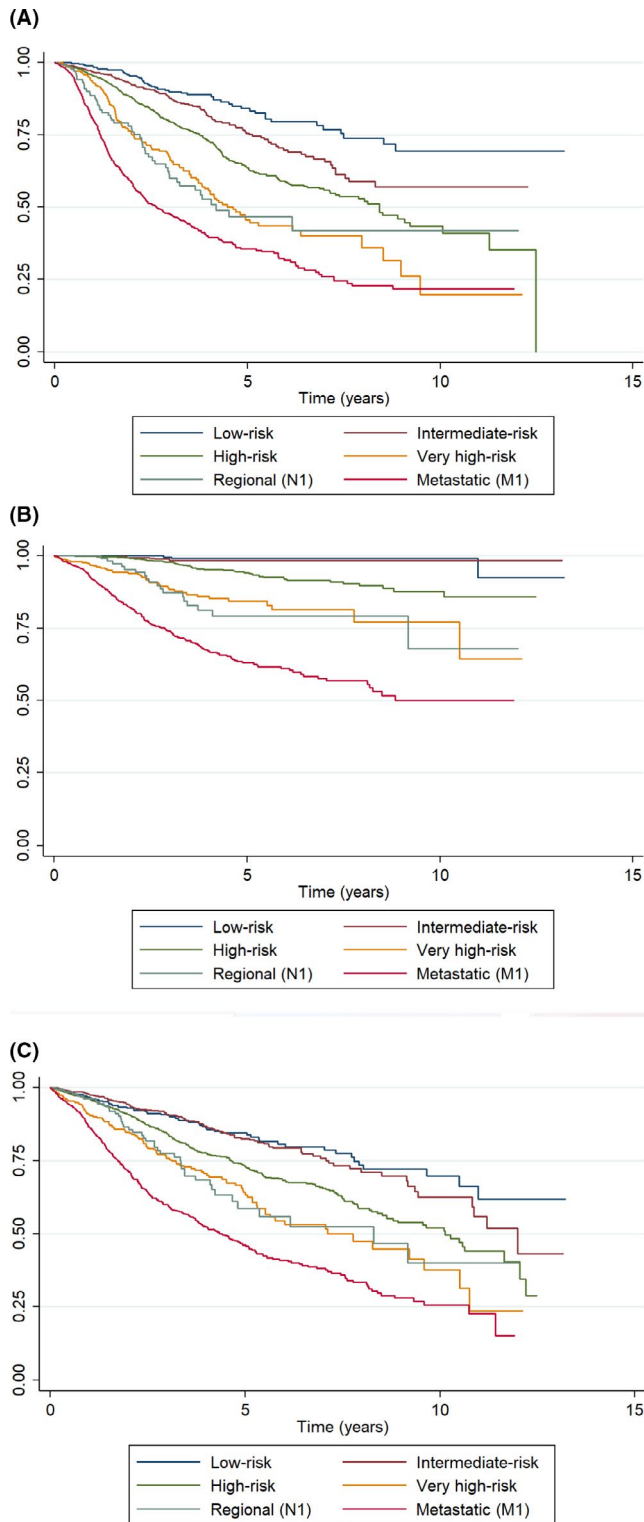


FIGURE 1 Prognosis in patients stratified by risk criteria. A-C, Kaplan-Meier survival curves of progression-free survival (A), cancer-specific survival (B), and overall survival (C) in patients stratified by risk criteria

(95% CI: 78.7%-88.6%), 79.3% (95% CI: 68.2%-86.8%), and 63.1% (95% CI: 58.7%-67.2%), respectively ($P < .0001$, Figure 1B). OS at 5 y was 67.8% (95% CI: 65.9%-69.6%) for all super-elderly men. In

low-, intermediate-, high- or very high-risk, regional, and metastatic prostate cancer groups, OS at 5 y was 84.5% (95% CI: 79.5%-88.4%), 82.6% (95% CI: 78.4%-86.1%), 73.2% (95% CI: 70.2%-75.8%), 63.3% (95% CI: 56.4%-69.6%), 58.7% (95% CI: 46.5%-69.1%), and 46.1% (95% CI: 41.2%-50.1%), respectively ($P < .0001$, Figure 1C).

Univariate Cox-model analysis showed a statistically significant increased hazard risk for recurrence or death by any cause or death by prostate cancer for men with PSA ≥ 20 ng/mL at diagnosis, Gleason score ≥ 8 , clinical T3-4, regional and metastatic prostate cancer (Table 2). On multivariate analysis incorporating these variables PSA ≥ 20 ng/mL at diagnosis, Gleason score ≥ 8 , clinical T3-4, and metastatic prostate cancer showed that each parameter is a significant prognostic factor for PFS, CSS, and OS (Table 3).

During the follow-up, 1114 men were reported as died from any causes. The cause of death and demographics are shown in Table 4. For all super-elderly men, 23.4% (1114/4760) died during follow-up. In the low- and intermediate-risk prostate cancer groups, very few deaths were observed caused by prostate cancer, corresponding to 0.7% (3/389) and 1.7% (7/389), respectively. Conversely, regional, and metastatic prostate cancer accumulated 71.2% (277/389) of deaths by prostate cancer. Among patients with low- and intermediate-risk prostate cancer, only 0.6% (3/453) and 1.0% (7/698) died from prostate cancer, respectively. Conversely, among patients with high- or very high-risk, regional, and metastatic prostate cancer, death from prostate cancer occurred in 3.2% (60/1848), 9.8% (42/426), 11.9% (18/151), and 21.8% (259/1184), respectively. The cumulative 5-y death rate by prostate cancer for low-, intermediate-, high-, or very high-risk, regional, and metastatic prostate cancer, was 0.92% (95% CI: 0.2%-3.6%), 1.6% (95% CI: 0.8%-3.43%), 5.8% (95% CI: 4.3%-7.8%), 15.6% (95% CI: 11.6%-23.3%), 20.7% (95% CI: 13.1%-31.7%), and 36.9% (95% CI: 32.8%-41.4%), respectively ($P < .0001$, Figure 2A). Conversely, the cumulative 5-y death rate by non-prostate cancer for low-, intermediate-, high-, or very high-risk, regional, and metastatic prostate cancer, was 14.7% (95% CI: 11.0%-19.6%), 16.0% (95% CI: 12.6%-20.2%), 22.5% (95% CI: 19.9%-35.4%), 25.8% (95% CI: 19.1%-35.4%), 25.9% (95% CI: 16.4%-35.9%), and 26.9% (95% CI: 23.3%-31.4%), respectively ($P < .0001$, Figure 2B). When compared with men aged < 80 , mortality risk from prostate cancer in super-elderly men was not lower than that in men aged < 80 in low-risk (hazard ratio [HR], 95% CI: 2.53, 0.63-10.1 $P = .19$), intermediate-risk (HR, 95% CI: 1.93, 0.75-4.94, $P = .17$), high-risk (HR, 95% CI: 1.35, 1.00-1.82, $P = .048$), very high-risk (HR, 95% CI: 1.10, 0.77-1.57, $P = .57$), regional (HR, 95% CI: 1.22, 0.73-2.04, $P = .45$), and metastatic prostate cancer (HR, 95% CI: 1.11, 0.97-1.27, $P = .12$).

The univariate sub-distribution hazard ratios for the cause-specific death by the Fine-Gray model are shown in Table 5. Notably, PSA ≥ 20 ng/mL, Gleason score ≥ 8 , clinical T3-4, regional, and metastatic prostate cancer were associated with an increase of risk of prostate cancer-specific death (Table 5). Furthermore, the multivariate Fine-Gray model showed that Gleason score ≥ 8 , clinical T3-4, regional, and metastatic prostate cancer were robustly associated with an increase of risk of prostate cancer-specific death (Table 5).

TABLE 2 Association between clinicopathological characteristics and prognosis in men older than ≥ 80 y

Variable	n	Progression-free survival			Cancer-specific survival			Overall survival		
		HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Initial PSA value										
<20 ng/mL	2367	Ref	-	-	Ref	-	-	Ref	-	-
≥ 20 ng/mL	2277	1.52	1.36-1.71	<.001	1.37	1.11-1.68	.002	1.36	1.20-1.53	<.001
Gleason score										
<8	2703	Ref	-	-	Ref	-	-	Ref	-	-
≥ 8	1604	2.07	1.84-2.34	<.001	3.36	2.70-4.18	<.001	1.83	1.61-2.07	<.001
Clinical T-stage										
T1-2	2408	Ref	-	-	Ref	-	-	Ref	-	-
T3-4	2304	2.61	2.32-2.95	<.001	7.27	5.49-9.61	<.001	2.41	2.12-2.73	<.001
Risk category										
Low/intermediate	1151	Ref	-	-	Ref	-	-	Ref	-	-
High/very high	2274	2.04	1.71-2.44	<.001	6.37	3.32-12.2	<.001	1.81	1.51-2.16	<.001
Clinical N-stage										
N0	3748	Ref	-	-	Ref	-	-	Ref	-	-
N1	537	2.93	2.53-3.38	<.001	4.45	3.57-5.57	<.001	2.30	1.97-2.68	<.001
Clinical M-stage										
M0	3200	Ref	-	-	Ref	-	-	Ref	-	-
M1	1184	3.18	2.81-3.57	<.001	8.38	6.72-10.4	<.001	2.95	2.61-3.34	<.001
Treatment										
Anti-androgen/other	1033	Ref	-	-	Ref	-	-	Ref	-	-
Castration	1156	0.93	0.81-1.06	.29	0.60	0.46-0.78	<.001	0.82	0.71-0.94	.017
CAB	2571	1.03	0.92-1.16	.50	1.23	1.00-1.50	.043	1.06	0.94-1.12	.27

Abbreviations: CAB, combined androgen blockade; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen.

4 | DISCUSSION

The outcome analysis of 4760 patients showed that those with low and intermediate-risk prostate cancer had a significantly better CSS and OS than high-risk and metastatic settings. In this study, almost one-quarter of super-elderly men were low- or intermediate-risk. Kaplan-Meier survival curves were similar between low- and intermediate-risk. Moreover, since the death rate from prostate cancer was extremely low in low- and intermediate-risk, many of them may have undergone unnecessary treatment. Several studies showed no survival benefit for active treatment including radiation therapy, surgery, and ADT, compared with observations over a 10 y period of follow-up.¹⁹⁻²⁶ Also, men older than 74 y and worse baseline health status have been associated with a smaller benefit in specific mortality and life expectancy of surgery vs. active surveillance.²⁷ Therefore, a life expectancy of more than 10 y is considered mandatory for any benefit from local treatment because of the higher likelihood of death from comorbidities.²⁸ In line with this notion, the EORTC randomized trial 30 891 showed that mortality from prostate cancer did not differ significantly between immediate

ADT and deferred ADT initiated upon symptomatic disease progression or life-threatening complications, at least in patients with non-metastatic cancer who survived more than 5 y.²⁹ Then, National Comprehensive Cancer Network guideline recommends observation for low- and intermediate-risk prostate cancer in men with life expectancy of <10 y.⁸

Despite this, most of the elderly patients chose active treatment and only 20%-35% chose observation as initial therapy, with a possible overtreatment, which led to a detriment in the patient's quality of life due to the adverse effects of active treatment, and also to poor utilization of resources in the healthcare system.³⁰⁻³² This could be due to the lack of good quality studies in elderly men; both (patient and physician) choose an active treatment that could be more harmful than beneficial.³³ Masaoka et al³⁴ estimated overtreatment in super-elderly men in a study including 2693 patients with localized prostate cancer from the Monitoring of Cancer Incidence in Japan project. Patients included were diagnosed between 2006 and 2008. They also calculated that 80% of patients were potentially overtreated in this population. Then, observation would be appropriate rather than active treatment in

TABLE 3 Multivariation analysis on association between clinicopathological characteristics and prognosis in elderly men ≥ 80 y old

Variable	n	Progression-free survival			Cancer-specific survival			Overall survival		
		HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Initial PSA value										
<20 ng/mL	2367	Ref	-	-	Ref	-	-	Ref	-	-
≥ 20 ng/mL	2277	1.57	1.33-1.86	<.001	1.92	1.33-2.78	.001	1.30	1.09-1.56	.002
Gleason score										
<8	2703	Ref	-	-	Ref	-	-	Ref	-	-
≥ 8	1604	1.42	1.24-1.62	<.001	1.83	1.44-2.33	<.001	1.29	1.12-1.49	<.001
Clinical T-stage										
T1-2	2408	Ref	-	-	Ref	-	-	Ref	-	-
T3-4	2304	1.46	1.24-1.70	<.001	1.90	1.37-2.62	<.001	1.46	1.23-1.72	<.001
Clinical N-stage										
N0	3748	Ref	-	-	Ref	-	-	Ref	-	-
N1	537	1.47	1.24-1.75	<.001	1.36	1.05-1.76	.019	1.18	0.98-1.42	.070
Clinical M-stage										
M0	3200	Ref	-	-	Ref	-	-	Ref	-	-
M1	1184	2.04	1.76-2.36	<.001	4.75	3.61-6.26	<.001	2.14	1.82-2.50	<.001
Treatment										
Anti-androgen/ other	1033	Ref	-	-	Ref	-	-	Ref	-	-
Castration	1156	1.02	0.84-1.22	.822	0.67	0.47-0.94	.024	0.83	0.69-1.01	.073
CAB	2571	0.82	0.69-0.96	.019	0.65	0.49-0.86	.002	0.78	0.66-0.93	.005

Abbreviations: CAB, combined androgen blockade; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen.

low- and intermediate-risk localized prostate cancer. Furthermore, active surveillance might be an option in selected cases, in which inclusion criteria for active surveillance should be more flexible to include more patients.³⁵⁻³⁸

In contrast, almost half of super-elderly men in this study had high-risk or very high prostate cancer. Death rates from prostate cancer in high-, and very high-risk were 3.2% and 9.8%, respectively. Survival analysis showed that these groups presented lower CSS and OS than low- and intermediate-risk prostate cancer. In the multivariate Fine-Gray model, clinical T3-4 or Gleason score ≥ 8 increased the risk of death by prostate cancer by 2.2-fold and 1.9-fold compared with clinical T1-2 and Gleason score < 8 , respectively. More than a quarter of super-elderly men in this study had regional or metastatic prostate cancer. As expected, they presented the largest death rates, and almost half of regional and more than half of the men who died had death caused by disease. In the multivariable model, positive nodal, or metastasis increased the risk of death by prostate cancer by 1.2-fold and 4.5-fold compared with not nodal and no metastatic disease, respectively. In addition, more death from other than prostate cancer was also observed in high-, and very high-risk, regional, and metastatic diseases. Although the exact reason for this is unknown, it may be derived from selection bias that health

status in patients with low- and intermediate-risk prostate cancer who underwent primary ADT was better, or treatment-related death by hormonal therapy and chemotherapy. Therefore, actual prostate cancer-related death may be more than that shown in this study, supporting the need for disease control. Moreover, mortality risk from prostate cancer is not lower in super-elderly men in high-, and very high-risk, regional, and metastatic diseases. Given that some super-elderly men suffered from cancer progression and died from prostate cancer, carefully selected patients with high-, and very high-risk, and regional prostate cancer should be treated with local treatment such as radiotherapy to prevent cancer-related symptoms and prolong survival, especially in very high-risk, and regional prostate cancer, as guidelines recommend.^{8,9} Similarly, selected patients with metastatic disease should be treated with more intensive treatment than ADT, such as combination with local radiotherapy or novel androgen receptor pathway inhibitors, which are relatively less toxic and therefore tolerable for super-elderly men to prevent suffering from cancer-related symptoms and prolong survival.^{8,9,39,40}

This study has some known limitations. It is a retrospective design. There was no record on performance status and comorbidities, or information for division into low and high metastatic volume categories. As the patients with worse performance status and more

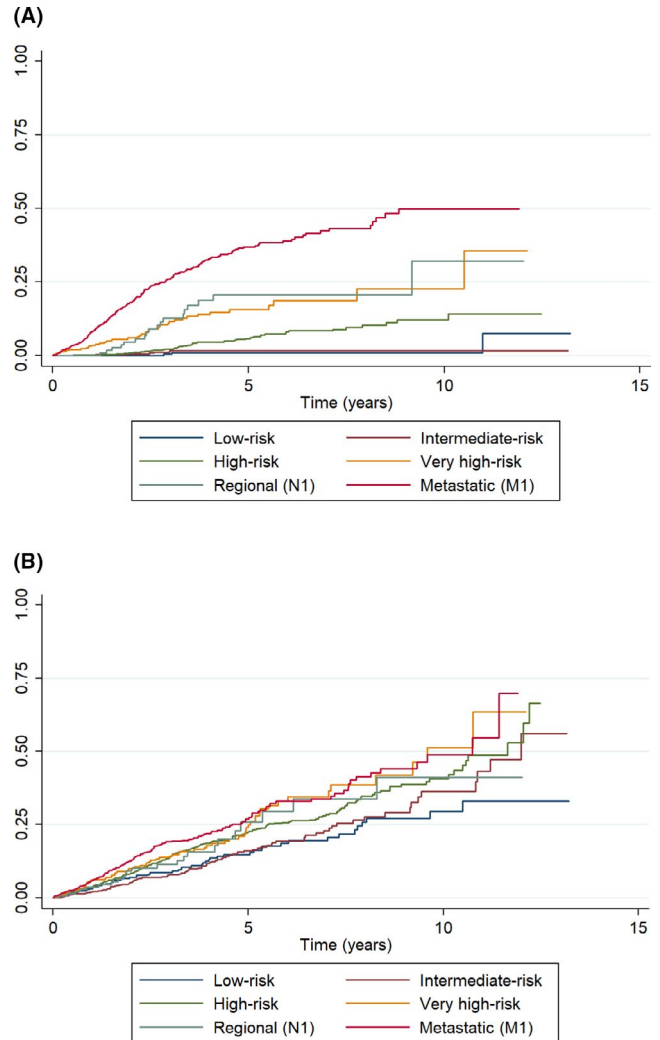
TABLE 4 Death event by prostate cancer and other causes in elderly men ≥ 80 y old

n = 4760	Death by prostate cancer (n = 389)	Death by other cause (n = 725)
Initial PSA value, ng/mL, n (%)		
<10	151 (41.0%)	222 (31.3%)
10-20	18 (4.9%)	110 (15.5%)
≥ 20	199 (54.1%)	377 (53.2%)
NA	21	16
Gleason score, n (%)		
≤ 6	35 (10.0%)	202 (30.6%)
7	93 (26.9%)	197 (29.9%)
8-10	219 (63.1%)	260 (39.5%)
NA	42	66
Clinical T-stage, n (%)		
T1-2	58 (14.9%)	330 (46.1%)
T3-4	329 (85.1%)	385 (53.9%)
NA	2	10
Risk categories, n (%)		
Low risk	3 (0.7%)	57 (7.8%)
Intermediate risk	7 (1.7%)	92 (12.7%)
High risk	60 (15.4%)	291 (40.2%)
Very high risk	42 (10.9%)	71 (9.8%)
Regional	18 (4.7%)	23 (3.2%)
Metastatic	259 (66.6%)	191 (26.3%)
Treatment, n (%)		
Anti-androgen	38 (9.7%)	60 (8.2%)
Castration	69 (17.7%)	189 (26.2%)
CAB	223 (57.3%)	373 (51.4%)
Other	59 (15.3%)	103 (14.2%)

Abbreviations: CAB, combined androgen blockade; PSA, prostate-specific antigen; NA, not available

comorbidity chose primary ADT than curative treatment,⁴¹ this cohort may contain more patients with poor general conditions, leading to possible bias. There were many patient losses to follow-up; therefore, calculation of death by any cause and specific death mortality could be underestimated. As all patients included in the study were treated with ADT, the survival estimation of patients for both low- and intermediate-risk could be overestimated. As there was no observation group, a comparison to show differences between survival and death rate was not possible. Additionally, ADT toxic effect was not recorded. Although changes in life expectancy of super-elderly men over time may affect the results, the expected life expectancy for men of 83 y old (median age of ≥ 80 group in this cohort) was not improved very much (6.69 y in 2001 and 7.48 y in 2019).⁴²

In conclusion, men aged >80 y with low- and intermediate-risk prostate cancer presented a low rate of death by prostate cancer. These findings supported the idea that there was no need for

**FIGURE 2** Cumulative death events in patients stratified by risk criteria. A, B, Cumulative death rate curves for prostate cancer death (A) and non-prostate cancer death (B) in patients stratified by risk criteria

immediate ADT for low- and intermediate-risk groups. Conversely, in the high-, and very high-risk, regional, and metastatic prostate cancer, more effort for curative therapy and intensive therapy are needed in selected patients.

ACKNOWLEDGMENT

We thank Ms Tae Nakano (Research Center for Advanced Science and Technology, University of Tokyo, Tokyo, Japan) for the helpful support.

DISCLOSURE

The authors declare no conflict of interest.

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TABLE 5 Fine-Gray model for competing risk in elderly men ≥ 80 y old

	Prostate cancer-specific death			No prostate cancer death		
	HR	95% CI	P-value	HR	95% CI	P-value
Univariate analysis						
Age (per year)	1.03	1.00-1.06	.012	1.09	1.07-1.12	.005
PSA ≥ 20 ng/mL	1.31	1.06-1.61	.009	1.30	1.13-1.51	<.001
Gleason score ≥ 8	3.22	2.58-3.98	<.001	1.17	1.00-1.36	.045
T3-4	6.77	5.14-8.91	<.001	1.31	1.14-1.52	<.001
N1	4.18	3.35-5.22	<.001	1.10	0.87-1.38	.40
M1	7.61	6.13-9.15	<.001	1.20	1.01-1.42	.032
Multivariate analysis						
Age (per year)	1.01	0.97-1.04	.77	1.09	1.06-1.11	<.001
PSA ≥ 20 ng/mL	1.31	0.82-2.10	.25	1.23	0.90-1.51	.080
Gleason score ≥ 8	1.85	1.45-2.37	<.001	1.00	0.83-1.20	.84
T3-4	2.16	1.37-3.43	.001	1.26	1.02-1.46	.075
N1	1.24	0.71-2.15	.43	0.85	0.61-1.18	.33
M1	4.45	2.66-7.47	<.001	1.10	0.82-1.46	.57

Abbreviations: CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen.

REFERENCES

- Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
- Okonogi N, Katoh H, Kawamura H, et al. Clinical outcomes of helical tomotherapy for super-elderly patients with localized and locally advanced prostate cancer: comparison with patients under 80 years of age. *J Radiat Res*. 2015;56:889-896.
- He W, Goodkind D, Kowal P. An aging world: 2015. <https://www.census.gov/content/dam/Census/library/publications/2016/demo/p95-16-1.pdf>
- Center for Cancer Control and Information Services, National Cancer Center. Cancer Information Service. https://ganjoho.jp/en/public/statistics/short_pred.html
- Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. *J Urol*. 2013;190:419-426.
- Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer—2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2021;79:243-262.
- Takechi Y, Sugimoto M, Taoka R. Evidenced-based clinical practice guideline for prostate cancer (summary: Japanese Urological Association, 2016 edition). *Int J Urol*. 2017;24:648-666.
- Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2019;17:479-505.
- Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II-2020 update: treatment of relapsing and metastatic prostate cancer. *Eur Urol*. 2021;79:263-282.
- Pagliarulo V, Bracarda S, Eisenberger MA, et al. Contemporary role of androgen deprivation therapy for prostate cancer. *Eur Urol*. 2012;61:11-25.
- Yamaoka M, Hara T, Kusaka M. Overcoming persistent dependency on androgen signaling after progression to castration-resistant prostate cancer. *Clin Cancer Res*. 2010;16:4319-4324.
- Akaza H. Trends in primary androgen depletion therapy for patients with localized and locally advanced prostate cancer: Japanese perspective. *Cancer Sci*. 2006;97:243-247.
- 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*. 2004;34:329-336.
- Shiota M, Sumikawa R, Onozawa M, et al. Regional and facility disparities in androgen deprivation therapy for prostate cancer from a multi-institutional Japan-wide database. *Int J Urol*. 2021;28(5):584-591.
- Shiota M, Onozawa M, Hinotsu S, et al. Family history in primary hormone therapy for prostate cancer: analysis from a community-based multi-institutional Japan-wide database. *Int J Urol*. 2020;27:313-318.
- Gleason DF. Histologic grading and clinical staging of carcinoma of the prostate. *Urologic Pathology: The Prostate*. Philadelphia, PA: Lea Febiger; 1977.
- Sobin LH, Fleming ID. TNM Classification of Malignant Tumors, Fifth edition (1997). *Cancer*. 1997;80:1803-1804.
- The Japanese Urological Association and the Japanese Society of Pathology eds. *General Rule for Clinical and Pathological Studies on Prostate Cancer*, 3rd edn. Tokyo, Japan: Kanehara-shuppan; 2001.
- Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375:1415-1424.
- Dell'Oglio P, Boehm K, Trudeau V, et al. Survival after conservative management versus external beam radiation therapy in elderly patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2016;96:1037-1045.
- Lu-Yao GL, Kim S, Moore DF, et al. Primary radiotherapy vs conservative management for localized prostate cancer—a population-based study. *Prostate Cancer Prostatic Dis*. 2015;18:317-324.
- Lu-Yao GL, Albertsen PC, Moore DF, et al. Fifteen-year survival outcomes following primary androgen-deprivation therapy for localized prostate cancer. *JAMA Intern Med*. 2014;174:1460-1467.
- Bill-Axelsson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2011;364:1708-1717.

24. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med*. 2012;367:203-213.
25. Potosky AL, Haque R, Cassidy-Bushrow AE, et al. Effectiveness of primary androgen-deprivation therapy for clinically localized prostate cancer. *J Clin Oncol*. 2014;32:1324-1330.
26. Sammon JD, Abdollah F, Reznor G, et al. Patterns of declining use and the adverse effect of primary androgen deprivation on all-cause mortality in elderly men with prostate cancer. *Eur Urol*. 2015;68:32-39.
27. Liu D, Lehmann HP, Frick KD, et al. Active surveillance versus surgery for low risk prostate cancer: a clinical decision analysis. *J Urol*. 2012;187:1241-1246.
28. Lu-Yao GL, Albertsen PC, Moore DF, et al. Outcomes of localized prostate cancer following conservative management. *JAMA*. 2009;302:1202-1209.
29. Studer UE, Whelan P, Wimpissinger F, et al. Differences in time to disease progression do not predict for cancer-specific survival in patients receiving immediate or deferred androgen-deprivation therapy for prostate cancer: final results of EORTC randomized trial 30891 with 12 years of follow-up. *Eur Urol*. 2014;66:829-838.
30. Aizer AA, Gu X, Chen MH, et al. Cost implications and complications of overtreatment of low-risk prostate cancer in the United States. *J Natl Compr Canc Netw*. 2015;13:61-68.
31. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol*. 2010;28:1117-1123.
32. Hoffman RM, Shi Y, Freedland SJ, et al. Treatment patterns for older veterans with localized prostate cancer. *Cancer Epidemiol*. 2015;39:769-777.
33. Wilt TJ, MacDonald R, Rutks I, et al. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. *Ann Intern Med*. 2008;148:435-448.
34. Masaoka H, Ito H, Yokomizo A, et al. Potential overtreatment among men aged 80 years and older with localized prostate cancer in Japan. *Cancer Sci*. 2017;108:1673-1680.
35. Hirama H, Sugimoto M, Miyatake N, et al. Health-related quality of life in Japanese low-risk prostate cancer patients choosing active surveillance: 3-year follow-up from PRIAS-JAPAN. *World J Urol*. 2020. <https://doi.org/10.1007/s00345-020-03494-4>
36. Thomsen FB, Brasso K, Klotz LH, et al. Active surveillance for clinically localized prostate cancer—a systematic review. *J Surg Oncol*. 2014;109:830-835.
37. Loeb S, Bruinsma SM, Nicholson J, et al. Active surveillance for prostate cancer: a systematic review of clinicopathologic variables and biomarkers for risk stratification. *Eur Urol*. 2015;67:619-626.
38. Klotz L. Active surveillance in intermediate-risk prostate cancer. *BJU Int*. 2020;125:346-354.
39. Sathianathen NJ, Koschel S, Thangasamy IA, et al. Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis. *Eur Urol*. 2020;77:365-372.
40. Burdett S, Boevé LM, Ingleby FC, et al. Prostate radiotherapy for metastatic hormone-sensitive prostate cancer: a STOPCAP systematic review and meta-analysis. *Eur Urol*. 2019;76:115-124.
41. Ueno S, Kitagawa Y, Onozawa M, et al. Background factors and short-term health-related quality of life in patients who initially underwent radical prostatectomy or androgen deprivation therapy for localized prostate cancer in a Japanese prospective observational study (J-CaP Innovative Study-1). *Prostate Int*. 2018;6:7-11.
42. <https://www.mhlw.go.jp/english/database/db-hw/vs02.html>

How to cite this article: Blas L, Onozawa M, Shiota M, et al. Long-term outcomes of androgen deprivation therapy in prostate cancer among Japanese men over 80 years old. *Cancer Sci*. 2021;112:3074–3082. <https://doi.org/10.1111/cas.14974>