Research Square

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Prognosis by initial treatment and baseline risk factors in high-volume metastatic hormone-sensitive prostate cancer: A single-center retrospective study

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Abstract

Background

Treatment intensification is standard for metastatic hormone-sensitive prostate cancer (mHSPC). However, real-world data comparing initial regimens for high-volume disease remain limited, and the prognostic value of baseline factors is unclear. We compared outcomes according to initial treatment and assessed baseline risk factors.

Methods

We retrospectively studied patients with high-volume mHSPC treated at a single center between February 2006 and April 2026. Patients received combined androgen blockade (CAB), upfront docetaxel (DTX), or darolutamide plus DTX (DAR + DTX). Endpoints were overall survival (OS), progression-free survival (PFS), and prostate-specific antigen response. Data were analyzed using Kaplan-Meier method, log-rank tests, and Cox regression analysis in EZR.

Results

We analyzed 114 patients (CAB, 75; upfront DTX, 23; DAR + DTX, 16). The median follow-up was 36.9 months overall and 41.4, 63.1, and 15.4 for the CAB, upfront DTX, and DAR + DTX groups, respectively. OS ($p = 0.012$) and PFS ($p < 0.001$) differed significantly between groups. The DAR + DTX group did not reach the median for either OS or PFS and had zero events. On multivariable analysis, an extent of disease score ≥ 3, hemoglobin ≤ 12 g/dL, Gleason Grade Group 5, and performance status ≥ 2 were independently associated with worse OS, while lactate dehydrogenase ≥ 221 U/L was independently associated with worse PFS. The median OS was 95.4, 38.7, and 18.0 months with 0–1, 2, and 3–4 risk factors, respectively ($p < 0.001$; hazard ratios for death were 2.72 and 9.94).

Conclusions

Baseline clinical factors were independently associated with prognosis in high-volume mHSPC. A simple risk factor count provided a hypothesis-generating prognostic gradient in this single-center cohort and requires external validation before clinical use. No comparative efficacy conclusion can be drawn for DAR + DTX given its zero events and short follow-up.

BACKGROUND

The initial treatment for metastatic hormone-sensitive prostate cancer (mHSPC) has changed substantially. Androgen deprivation therapy (ADT), alone or combined with a first-generation anti-androgen, as in combined androgen blockade (CAB), has long been the standard of care. The CHAARTED

and STAMPEDE trials showed that the addition of docetaxel (DTX) to ADT prolonged overall survival (OS) [1, 2]. Subsequently, the LATITUDE trial demonstrated the benefit of abiraterone [3], and the ARASENS trial showed that triplet therapy with darolutamide (DAR), DTX, and ADT improved OS [4]. Treatment intensification is currently the core strategy for mHSPC management. Because the CHAARTED trial showed the greatest benefit in patients with high-volume disease [5], high-volume mHSPC is a key target for early treatment intensification.

However, the practical application of these trial results remains challenging. Patients with high-volume mHSPC differ widely in age, fitness, and comorbidities, making it unclear which patients benefit most from each treatment intensification strategy. Few studies have directly compared CAB, upfront DTX, and DAR plus DTX for high-volume disease. Moreover, most prognostic data on baseline factors originate from the monotherapy era [6]. These factors include prostate-specific antigen (PSA), lactate dehydrogenase (LDH), hemoglobin (Hb), alkaline phosphatase (ALP), the neutrophil-to-lymphocyte ratio (NLR), and the prognostic nutritional index (PNI). Whether these factors and early PSA responses still stratify prognosis in the treatment intensification era has not been well validated [7, 8].

Therefore, we aimed to identify prognostic factors that may inform treatment choice and risk stratification in patients with high-volume mHSPC. We compared OS and progression-free survival (PFS) after initial treatment and assessed the associations of baseline factors and PSA response with prognosis. Because our cohort spanned two decades (2006–2026), the initial regimens necessarily reflect the evolving standard of care. All consecutive patients were deliberately included to describe real-world prognostication across this period rather than to establish comparative efficacy.

METHODS

Study design

This single-center, retrospective, observational study aims to identify prognostic factors that may inform treatment choice and risk stratification in patients with high-volume mHSPC. Patients with mHSPC who were initially treated at Jichi Medical University Hospital were evaluated. The study period extended from February 2006 to April 2026.

Participants

The eligibility criteria were (1) pathologically confirmed prostate adenocarcinoma; (2) distant metastases at diagnosis or at the start of treatment; (3) high-volume disease according to the CHAARTED criteria [1]; and (4) initial treatment with CAB, upfront DTX, or DAR + DTX. High-volume disease was defined as the presence of visceral metastases and/or at least four bone lesions, with at least one lesion beyond the vertebrae and pelvis. We used the CHAARTED criteria because treatment intensification primarily benefits patients with high-volume disease. Patients who lacked clinical or outcome data were excluded. All eligible patients were included consecutively. As this was a

retrospective comprehensive cohort study, we did not perform an a priori power calculation. Because enrollment spanned 2006–2026, high-volume status for patients imaged before 2014 was reassessed against the CHAARTED four-bone-lesion threshold. Patients diagnosed between January 2016 and March 2023 were treated with upfront DTX, whereas those diagnosed after March 2023 received DAR + DTX.

Data collection and variables

Data were collected through retrospective chart review. Baseline variables included age, Eastern Cooperative Oncology Group performance status (ECOG PS), and body mass index (BMI). We also recorded comorbidities, as well as laboratory parameters including PSA, Hb, albumin (Alb), LDH, ALP, NLR, PNI, and the psoas muscle index (PMI). Additional variables included the extent of disease (EOD) score, Gleason grade, and metastatic stage (M1b/M1c). We also recorded visceral metastases (specifically liver and lung lesions), LATITUDE high-risk status, disease timing, and pain at presentation. The NLR was calculated by dividing the neutrophil count by the lymphocyte count. We calculated the PNI as follows: 10 × Alb (g/dL) + 0.005 × total lymphocyte count (/mm³). For the PMI, the bilateral psoas muscle area on computed tomography (CT) at the lower L3 endplate was measured using the region of interest (ROI) method and divided by the square of the patient's height (m²). The ROI method was chosen because it is readily applicable to routine clinical CT, whereas automated 3D volumetry and validated sarcopenia cutoffs were not used. Tumors were graded using the International Society of Urological Pathology (ISUP) 2014 system. Biopsy specimens obtained before 2014 were reclassified according to this system without central re-review; therefore, Gleason grades assigned by different pathologists across institutions and eras may not be fully equivalent. De novo disease was defined as the presence of metastasis at initial diagnosis, whereas metachronous recurrence was defined as a relapse with distant metastases after treatment for localized or locally advanced disease.

Treatments

CAB consisted of ADT combined with a first-generation anti-androgen. ADT involved surgical castration or the administration of a gonadotropin-releasing hormone agonist or antagonist. Upfront DTX involved the addition of DTX every four weeks for up to six cycles, concurrently with prednisolone. For the DAR + DTX group, DAR 600 mg twice daily was added to ADT and DTX. The treating physician determined the DTX dose, any dose reductions, and the total number of cycles.

Endpoints

The primary endpoint was OS, which was measured from the start of initial treatment until death from any cause. Survivors were censored on the last confirmed date of survival. The secondary endpoints were PFS, PSA response, and the prognostic value of baseline risk factors. PFS was defined as the time from the start of treatment to PSA progression, radiographic progression, or death from any cause. PSA

progression was defined using the Prostate Cancer Clinical Trials Working Group 3 criteria [9]. PSA response was defined as a ≥ 90% PSA decline (PSA90) or a PSA level ≤ 0.2 ng/mL. PSA response was assessed at 3 and 6 months, as well as at the nadir. The PSA nadir was defined as the lowest PSA level recorded during first-line treatment. Landmark analyses for survival were also performed at 3 and 6 months. In these landmark analyses, only patients who were alive and progression-free at each landmark time point were included, and survival was measured from the respective landmark time point. For the survival analysis, we dichotomized all continuous variables at the median values (e.g., LDH of 221 U/L, Hb of 12 g/dL, ALP of 381 U/L, and PSA of 442 ng/mL). Cutoffs were defined by cohort medians for internal consistency. As cohort-specific, median-based cutoffs limit external generalizability, these results should be interpreted with caution, and clinically established thresholds may be preferable for external validation.

Statistical analysis

Continuous variables across groups were compared using the Kruskal–Wallis test and are summarized as medians with ranges. Categorical variables were compared using Fisher's exact test. Survival curves were estimated using the Kaplan–Meier method and were compared using log-rank tests, including pairwise comparisons. Univariable Cox regression analysis was first performed for each factor, and variables with $p < 0.1$ were subsequently included in a multivariable Cox model. Effect sizes were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). We also stratified patients by the number of independent OS-related factors (EOD score ≥ 3, Hb ≤ 12 g/dL, Gleason Grade Group 5, and ECOG PS ≥ 2), and a Cox model was subsequently fitted using this factor count as a categorical variable. Using the cohort with 0–1 factors as the reference group, we estimated HRs for the cohorts with 2 and 3–4 factors. Treatment comparisons and baseline factor analyses were performed as the primary analyses. All tests were two-sided, with $p < 0.05$ considered significant. Statistical analyses were performed using EZR version 2.8-0 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is based on R version 4.4.4 [10].

Ethics

This study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Jichi Medical University Hospital (approval number A22-023). Written informed consent was obtained from all patients. Given the retrospective study design, additional trial registration was not required.

RESULTS

Study population

A total of 114 eligible patients were analyzed, including 75 treated with CAB, 23 treated with upfront DTX, and 16 treated with DAR + DTX. The median follow-up was 36.9 months for the overall cohort and 41.4,

63.1, and 15.4 months for the CAB, upfront DTX, and DAR + DTX groups, respectively. Table 1 shows the baseline characteristics of each group. Age, ECOG PS, BMI, PSA level, Gleason grade, metastatic stage, EOD score, and the presence of visceral, liver, or lung metastases did not differ significantly between the groups. In contrast, significant differences were observed in baseline Hb ($p = 0.017$), Alb ($p < 0.01$), LDH ($p = 0.040$), ALP ($p = 0.014$), NLR ($p = 0.036$), and PNI ($p = 0.036$), as well as pain at presentation ($p = 0.018$). The ADT type, initial DTX dose, and the rate of dose reduction also differed significantly (all $p < 0.001$). Notably, most patients in the DAR + DTX group (14/16, 88%) received full-dose DTX (75 mg/m²), whereas 92% of the upfront DTX group received a reduced dose (60 mg/m²). This systematic difference in DTX dose intensity represents a potential confounder.

Table 1
Baseline patient characteristics and treatment details

Characteristic	CAB (n = 75) n (%) or [range]	Upfront DTX (n = 23) n (%) or [range]	DAR + DTX (n = 16) n (%) or [range]	p value
Age, years	70 [49–86]	69 [53–76]	72 [51–77]	0.489
ECOG performance status				
0	49 (65)	14 (61)	7 (44)	0.141
1	15 (20)	9 (39)	9 (56)	
≥ 2	11 (15)	—	—	
Body mass index, kg/m²	21.9 [14.4–31.0]	24.4 [18.3–33.1]	23.4 [16–34.4]	0.331
Comorbidities				0.898
Cardiovascular disease	10 (13)	2 (8)	4 (25)	
Hypertension	31 (41)	6 (26)	7 (43)	
Diabetes mellitus	13 (17)	4 (17)	2 (12)	
Dementia	1 (1)	—	—	
History of other malignancies	4 (5)	—	—	
PSA, ng/mL	436 [8.0–10946]	344 [5.6–3569]	818.5 [8.1–5059]	0.848
Hb, g/dL	12.5 [7.6–17.5]	13.4 [8.7–17]	13.1 [10.9–15.7]	0.017
Alb, g/dL	3.9 [2.5–4.9]	4.2 [3.2–5.0]	4.2 [2.8–4.6]	< 0.01
LDH, U/L	226 [121–1456]	184 [149–450]	219.5 [171–281]	0.04
ALP, U/L	558 [166–11888]	176 [68–736]	139 [69–532]	0.014
NLR	2.8 [0.89–49]	3.4 [1.3–11.1]	2.1 [1.23–14]	0.036

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; Alb, albumin; BSA, body surface area; CAB, combined androgen blockade; DAR, darolutamide; DTX, docetaxel; ECOG, Eastern Cooperative Oncology Group; EOD, extent of disease; GnRH, gonadotropin-releasing hormone; Hb, hemoglobin; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PMI, psoas muscle index; PNI, prognostic nutritional index; PSA, prostate-specific antigen.

Characteristic	CAB (n = 75) n (%) or [range]	Upfront DTX (n = 23) n (%) or [range]	DAR + DTX (n = 16) n (%) or [range]	p value
PNI	45.7 [34–57.5]	48.5 [38–59]	50.2 [38.5–58.5]	0.036
PMI	5.2 [2.1–9.1]	5.5[3.5–10.3]	6.2 [3.2–10.2]	0.143
Gleason Grade Group				0.892
1	1 (1)	—	—	
2	1 (1)	—	—	
3	5 (7)	—	—	
4	27 (36)	8 (35)	7 (44)	
5	41 (55)	15 (65)	9 (56)	
Metastatic stage				1
M1b	57 (76)	18 (73)	12 (75)	
M1c	18 (24)	5 (27)	4 (25)	
EOD score				0.425
0	1 (1)	—	1 (6)	
1	11 (15)	7 (30)	1 (6)	
2	33 (44)	10 (43)	9 (57)	
3	19 (25)	5 (22)	4 (25)	
4	11 (15)	1 (5)	1 (6)	
Liver metastasis	3 (4)	2 (8)	—	0.414
Lung metastasis	15 (20)	3 (13)	3 (18)	0.755
LATITUDE high risk	69 (92)	18 (78)	16 (100)	0.056
Timing of metastatic disease				0.13
de novo	75 (100)	22 (95)	15 (93)	

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; Alb, albumin; BSA, body surface area; CAB, combined androgen blockade; DAR, darolutamide; DTX, docetaxel; ECOG, Eastern Cooperative Oncology Group; EOD, extent of disease; GnRH, gonadotropin-releasing hormone; Hb, hemoglobin; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PMI, psoas muscle index; PNI, prognostic nutritional index; PSA, prostate-specific antigen.

Characteristic	CAB (n = 75) n (%) or [range]	Upfront DTX (n = 23) n (%) or [range]	DAR + DTX (n = 16) n (%) or [range]	p value
metachronous recurrence	—	1 (5)	1 (7)	
Pain at initial presentation	45 (60)	9 (39)	4 (25)	0.018
ADT				< 0.001
Orchidectomy	1 (1)	2 (8)	6 (37)	
GnRH antagonist	19 (25)	10 (44)	8 (50)	
GnRH agonist	55 (74)	11 (48)	2 (13)	
Number of treatment cycles of docetaxel				0.222
6	—	18 (78)	8 (50)	
5	—	—	2 (12)	
4	—	3 (14)	2 (12)	
2	—	1 (4)	2 (12)	
1	—	1 (4)	2 (12)	
Initial dose of docetaxel				< 0.001
75 mg/m^2/BSA	—	2 (8)	14 (88)	
60 mg/m^2/BSA	—	21 (92)	2 (12)	
Dose reduction of docetaxel				< 0.001
without dose reduction	—	23 (100)	11 (69)	
70 mg/m^2/BSA	—	—	1 (6)	
60 mg/m^2/BSA	—	—	4 (25)	

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; Alb, albumin; BSA, body surface area; CAB, combined androgen blockade; DAR, darolutamide; DTX, docetaxel; ECOG, Eastern Cooperative Oncology Group; EOD, extent of disease; GnRH, gonadotropin-releasing hormone; Hb, hemoglobin; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PMI, psoas muscle index; PNI, prognostic nutritional index; PSA, prostate-specific antigen.

[Insert Table 1 here]

Overall survival

There were 55 deaths in the CAB group, 6 in the upfront DTX group, and zero in the DAR + DTX group, and OS differed significantly among the three groups (log-rank p = 0.012; Fig. 1). Because the DAR + DTX survival curve remained at 1.0 throughout the observation period (zero events), this overall test was driven almost entirely by the CAB-versus-upfront-DTX comparison. The median OS was 47.1 months in the CAB group and was not reached in the upfront DTX and DAR + DTX groups. In pairwise comparisons, OS was significantly longer in the upfront DTX group than in the CAB group (p = 0.043); however, no significant differences were observed between the CAB and DAR + DTX groups (p = 0.187) or between the upfront DTX and DAR + DTX groups (p = 0.213). Because no deaths occurred in the DAR + DTX group, the non-significant p-values involving this group (p = 0.187 and p = 0.213) reflect complete structural separation and severely limited follow-up rather than equivalent efficacy and have no inferential value.

Progression-free survival

PFS also differed significantly among the groups (log-rank, p < 0.001; Fig. 2). There were 65 progression events in the CAB group, 16 in the upfront DTX group, and zero in the DAR + DTX group. The median PFS was 10.0 months for the CAB group and 10.1 months for the upfront DTX group, whereas the median PFS was not reached in the DAR + DTX group. Furthermore, DAR + DTX showed significantly better PFS than both CAB (p < 0.001) and upfront DTX (p < 0.001), while CAB and upfront DTX did not differ significantly (p = 0.395).

Prostate-specific antigen response

The PSA response rates did not differ significantly between the groups (Table 2). At 3 months, the PSA90 rates were 76%, 78%, and 94% (p = 0.316), and the PSA nadir ≤ 0.2 ng/mL rates were 32%, 44%, and 56% (p = 0.185) in the CAB, upfront DTX, and DAR + DTX groups, respectively. The DAR + DTX group tended to have higher response rates, but the differences were not statistically significant.

Table 2
PSA response according to initial treatment group

Characteristic	CAB, n (%)	Upfront DTX, n (%)	DAR + DTX, n (%)	p value
PSA90 at 3 months	57 (76)	18 (78)	15 (94)	0.316
PSA ≤ 0.2 ng/mL at 3 months	6 (8)	3 (13)	4 (25)	0.142
PSA90 at 6 months	53 (88)	14 (78)	14 (100)	0.171
PSA ≤ 0.2 ng/mL at 6 months	16 (27)	4 (22)	6 (43)	0.411
PSA90 at PSA nadir	66 (88)	19 (83)	16 (100)	0.271
PSA nadir ≤ 0.2 ng/mL	24 (32)	7 (44)	9 (56)	0.185

CAB: combined androgen blockade, DAR: darolutamide, DTX: docetaxel, PSA: prostate-specific antigen, PSA90: ≥90% decline in PSA from baseline.

Univariable and multivariable analyses

Tables 3 and 4 show the Cox regression results. The multivariable OS model was based on 61 deaths, and HRs for the treatment-group comparisons were not estimable because the DAR + DTX group had zero events, producing complete separation in the standard Cox model (see footnotes to Tables 3 and 4). Four factors were independently associated with worse OS: an EOD score ≥ 3 (HR 1.87; 95% CI 1.10–3.19; p = 0.021), Hb ≤ 12 g/dL(HR 2.21; 95% CI 1.26–3.87; p = 0.006), Gleason Grade Group 5(HR 1.88; 95% CI 1.10–3.21; p = 0.021), and an ECOG PS ≥ 2(HR 2.40; 95% CI 1.17–4.91; p = 0.017). For PFS, an LDH level ≥ 221 U/L was independently associated with worse outcomes (HR 1.75; 95% CI 1.03–2.98; p = 0.038), whereas an EOD score ≥ 3 showed no such significant association (HR 1.74; 95% CI 0.99–3.06; p = 0.055). Initial treatment did not show any independent associated in either model. Although ALP showed a significant univariable association with OS (HR 2.31; p = 0.002), it was not retained in the multivariable model, possibly because its prognostic information overlapped with that of the retained measures of disease extent and tumor burden (EOD score and Gleason grade). This is noteworthy because ALP is a well-established surrogate for metastatic bone burden.

Table 3
Univariate and multivariable analyses of factors associated with overall survival

Characteristic	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age ≥ 75 (vs. < 75)	1.58 (0.89–2.80)	0.117		
PS ≥ 2 (vs. < 2)	2.65 (1.37–5.11)	0.003	2.40 (1.17–4.91)	0.017
PSA ≥ 442 (vs. < 442)	1.33 (0.80–2.20)	0.273		
Hb ≤ 12 (vs. > 12)	2.29 (1.36–3.84)	0.001	2.21 (1.26–3.87)	0.006
Alb < 4 (vs. ≥ 4)	1.22 (0.74–2.02)	0.436		
LDH ≥ 221 (vs. < 221)	1.51 (0.91–2.51)	0.11		
ALP ≥ 381 (vs. < 381)	2.31 (1.34–3.97)	0.002	1.20 (0.64–2.25)	0.578
NLR ≥ 2.75 (vs. < 2.75)	0.80 (0.45–1.40)	0.427		
PNI < 46.5 (vs. ≥ 46.5)	1.20 (0.69–2.11)	0.522		
PMI < 5.7 (vs. ≥ 5.7)	0.96 (0.55–1.68)	0.893		
Gleason Grade Group ≥ 5 (vs. < 5)	1.71 (1.01–2.88)	0.045	1.88 (1.10–3.21)	0.021
EOD ≥ 3 (vs. < 3)	1.88 (1.13–3.11)	0.014	1.87 (1.10–3.19)	0.021
Liver metastasis	1.98 (0.61–6.37)	0.253		
Visceral meta	0.95 (0.51–1.76)	0.869		
Metachronous recurrence vs. De novo	Not estimable†	0.996		
Pain at initial presentation	1.22 (0.73–2.02)	0.45		
CAB vs. Upfront DTX	2.76 (1.18–6.42)	0.018	1.67 (0.65–4.31)	0.287
CAB vs. DAR + DTX	Not estimable†	0.995	Not estimable†	
Upfront DTX vs. DAR + DTX	Not estimable†	0.998	Not estimable†	

†HR not estimable due to zero events in one of the compared groups, resulting in complete separation in the Cox proportional hazards model.

ALP, alkaline phosphatase; Alb, albumin; CAB, combined androgen blockade; CI, confidence interval; DAR, darolutamide; DTX, docetaxel; EOD, extent of disease; Hb, hemoglobin; HR, hazard ratio; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PMI, psoas muscle index; PNI, prognostic nutritional index; PS, performance status; PSA, prostate-specific antigen.

Table 4
Univariate and multivariable analyses of factors associated with progression-free survival

Characteristic	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age ≥ 75 (vs. < 75)	1.18 (0.71–1.95)	0.533		
PS ≥ 2 (vs. < 2)	1.69 (0.87–3.30)	0.121		
PSA ≥ 442 (vs. < 442)	1.02 (0.66–1.58)	0.929		
Hb ≤ 12 (vs. > 12)	1.46 (0.92–2.32)	0.111		
Alb < 4 (vs. ≥ 4)	1.13 (0.73–1.74)	0.595		
LDH ≥ 221 (vs. < 221)	1.75 (1.13–2.72)	0.012	1.75 (1.03–2.98)	0.038
ALP ≥ 381 (vs. < 381)	2.02 (1.28–3.16)	0.002	1.23 (0.71–2.14)	0.359
NLR ≥ 2.75 (vs. < 2.75)	1.39 (0.85–2.27)	0.185		
PNI < 46.5 (vs. ≥ 46.5)	1.73 (1.06–2.81)	0.027	0.82 (0.49–1.38)	0.451
PMI < 5.7 (vs. ≥ 5.7)	1.06 (0.65–1.72)	0.815		
Gleason Grade Group ≥ 5 (vs. < 5)	1.31 (0.83–2.05)	0.242		
EOD ≥ 3 (vs. < 3)	1.80 (1.15–2.80)	0.009	1.74 (0.99–3.06)	0.055
Liver metastasis	1.35 (0.49–3.72)	0.556		
Visceral meta	0.71 (0.41–1.21)	0.207		
Metachronous recurrence vs. De novo	Not estimable†	0.995		
Pain at initial presentation	1.70 (1.09–2.66)	0.019	1.15 (0.71–1.85)	0.818
CAB vs. Upfront DTX	1.27 (0.73–2.20)	0.397		
CAB vs. DAR + DTX	Not estimable†	0.996		

†HR not estimable due to zero events in one of the compared groups, resulting in complete separation in the Cox proportional hazards model.

ALP, alkaline phosphatase; Alb, albumin; CAB, combined androgen blockade; CI, confidence interval; DAR, darolutamide; DTX, docetaxel; EOD, extent of disease; Hb, hemoglobin; HR, hazard ratio; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PMI, psoas muscle index; PNI, prognostic nutritional index; PS, performance status; PSA, prostate-specific antigen.

Characteristic	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Upfront DTX vs. DAR + DTX	Not estimable†	0.998		
†HR not estimable due to zero events in one of the compared groups, resulting in complete separation in the Cox proportional hazards model.				
ALP, alkaline phosphatase; Alb, albumin; CAB, combined androgen blockade; CI, confidence interval; DAR, darolutamide; DTX, docetaxel; EOD, extent of disease; Hb, hemoglobin; HR, hazard ratio; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PMI, psoas muscle index; PNI, prognostic nutritional index; PS, performance status; PSA, prostate-specific antigen.				

[Insert Table 3 and 4 here]

Stratification by number of overall survival-related factors

We stratified patients according to the number of these OS-related factors (Fig. 3). The median OS was 95.4 months for the cohort with 0–1 factors (n = 65; 95% CI 72.5–not reached), decreasing to 38.7 months for those with 2 factors (n = 38; 95% CI 33.5–68.3), and further decreasing to 18.0 months for those with 3–4 factors (n = 11; 95% CI 10.1–29.8). Thus, OS decreased progressively as risk factors accumulated ($p < 0.001$). Multivariable Cox regression analysis confirmed this risk gradient (Table 5): using the 0–1 factor cohort as the reference, the HR was 2.72 for the 2-factor cohort (95% CI 1.57–4.73; $p < 0.001$) and increased to 9.94 for the 3–4-factor cohort (95% CI 4.31–22.96; $p < 0.001$).

Table 5
Cox regression analysis of overall survival according to risk group

Risk group	HR	95%CI	p value
0–1 factor	Reference	—	—
2 factors	2.72	1.57–4.73	< 0.001
3–4 factors	9.94	4.31–22.96	< 0.001

CI: confidence interval, HR: hazard ratio.

DISCUSSION

We compared initial treatments and assessed baseline factors in patients with high-volume mHSPC. An EOD score ≥ 3, low Hb, Gleason Grade Group 5, and poor PS were independently associated with worse OS, while high LDH levels were independently associated with worse PFS. A simple count of these OS-related factors clearly stratified the prognostic groups. In the Cox regression analysis, patients with 3–4 factors had a nearly tenfold higher hazard of death than those with 0–1 factors. Therefore, baseline risk assessment may aid in prognostication beyond treatment choice. This pattern raises an important interpretive point: because baseline factors were independently associated with OS, whereas initial

treatment was not, patients with adverse baseline biology appeared to fare poorly regardless of the regimen received. This may indicate that baseline disease biology dominated outcomes in this cohort; equally, however, it may reflect insufficient statistical power and the structural limitations described below rather than a true absence of treatment effect.

Our findings are consistent with prior evidence demonstrating that tumor burden and host fitness are associated with clinical outcomes. For instance, LDH reflects both tumor burden and tissue turnover, and a prior meta-analysis reported that high LDH levels were associated with worse OS and PFS in metastatic prostate cancer [11]. Similarly, low Hb levels have been shown to predict worse OS, including in patients with high-volume disease [12]. Bone burden is also an important prognostic factor in mHSPC; indeed, the CHAARTED high-volume definition explicitly stratifies risk by bone and visceral spread [1]. Furthermore, a multicenter study linked PNI to prognosis in mHSPC [8]. Reflecting these established patterns, our factor-count stratification is conceptually similar to the LATITUDE high-risk model, which similarly combines several clinical factors to predict survival outcomes [3]. Unlike validated prognostic tools such as the CHAARTED volume-based stratification and the MSKCC and GLASS nomograms, however, our factor count has not been benchmarked against these instruments; a head-to-head comparison of discrimination would be required to establish whether it adds value beyond existing validated models. Finally, the numerically better PSA response and PFS observed with DAR + DTX are consistent with prior data. The ARASENS analysis linked the deep, durable PSA decline achieved with triplet therapy to better outcomes [13], underscoring how PSA kinetics are associated with OS and radiographic PFS in castration-sensitive disease [14].

Some of our findings differ from those of previous studies. Initial treatment was not independently associated with OS in our cohort, whereas several phase 3 trials have demonstrated that treatment intensification improves OS. For instance, the ARASENS trial showed that triplet therapy improved OS compared with ADT plus DTX [4]. Importantly, the ARASENS population was enriched for patients fit enough to receive full-dose DTX (75 mg/m²), as in our DAR + DTX group but contrasting with the reduced-dose DTX administered to most of our upfront DTX patients. This difference in dose intensity is a critical potential confounder, and the apparent PFS advantage of DAR + DTX may partly reflect the higher DTX dose intensity rather than the addition of DAR. Similarly, the CHAARTED long-term analysis and the STAMPEDE trial both showed clear survival benefits with DTX in high-volume disease [2, 5]. These results suggest that treatment intensification can influence prognosis, contrasting with our lack of a statistically significant association. This discrepancy may be related to the small size and short follow-up of our DAR + DTX group, which had no events and therefore limited our ability to detect treatment effects. The significant difference in OS among the three treatment groups was driven almost entirely by the CAB-versus-upfront-DTX comparison and should not be interpreted as evidence that DAR + DTX is superior. Importantly, the benefits of DTX are not universal. In the GETUG-AFU 15 trial, the addition of DTX did not significantly improve OS [15]. By contrast, the long-term CHAARTED analysis demonstrated a sustained OS benefit of DTX specifically in high-volume disease [5], supporting its use in this population. Furthermore, while PSA nadir and response are strong independent prognostic markers in other literature [6, 7], our study deliberately focused on baseline factors. These discrepancies likely

reflect our retrospective design, small sample size, and different endpoints. Beyond the small size and zero events of the DAR + DTX group, the non-significant treatment effect may also have been influenced by confounding from the 20-year study period and differences in the use of subsequent life-prolonging therapies (abiraterone, enzalutamide, and cabazitaxel), which may have affected OS. Sarcopenia, captured here by the PMI, is increasingly recognized as an independent predictor of DTX toxicity and treatment completion in mHSPC. The higher PMI in the DAR + DTX group (6.2 vs. 5.2 in the CAB group) may have facilitated higher DTX dose intensity in that arm, potentially reflecting differences in host fitness rather than intrinsic disease biology [16].

Our study has some limitations. First, this single-center, retrospective design introduces potential selection bias and unmeasured confounding. We did not apply propensity score matching, and baseline imbalances in Hb, Alb, LDH, and ALP were present among the groups. Second, the sample size was small, and the newly introduced DAR + DTX group experienced no deaths or disease progression during the study period. Consequently, median OS and PFS could not be estimated. Furthermore, treatment effects were not estimable in the multivariable models, and overfitting remains a possibility. The highest-risk group (with 3–4 factors) included only 11 patients, which likely widened the CIs and reduced the precision of the risk estimates. Third, the follow-up period differed between groups. The newer DAR + DTX group had a shorter follow-up, limiting assessment of long-term survival. Fourth, the long enrollment window (2006–2026) spanned major changes in imaging, staging, and subsequent therapies. Such era effects and differences in subsequent treatments may have affected outcomes. Notably, we did not adjust for subsequent treatments for castration-resistant prostate cancer, which may have influenced OS. Fifth, risk factor cutoffs were set based on cohort medians without external validation, limiting generalizability. Sixth, imaging and PSA assessments were not standardized; therefore, progression ascertainment may have varied. Seventh, ISUP grading was not standardized by central pathology review across the 20-year period and multiple pathologists, which may affect the reproducibility of Gleason Grade Group 5 as a risk factor. Finally, DTX-induced bone-scan flare could have been misclassified as early radiographic progression in the DTX-treated arms, potentially inflating early PFS events in those groups. Taken together, these limitations indicate that our findings should be considered hypothesis-generating and require external validation.

CONCLUSIONS

Baseline clinical factors were independently associated with the prognosis of patients with high-volume mHSPC. OS was related to the EOD score, Hb level, Gleason grade, and PS, whereas PFS was related to the LDH level. A simple count of four OS-related factors provided a potentially useful prognostic gradient. Because this score was derived from a single-center cohort with only 61 events and has not been externally validated, it should be regarded as hypothesis-generating and requires prospective external validation before clinical implementation. No conclusion regarding the comparative efficacy of DAR + DTX can be drawn from these data. The DAR + DTX group requires longer follow-up to assess long-term outcomes, and larger prospective studies are needed to validate these findings.

ABBREVIATIONS

ADT
Androgen deprivation therapy
ALP
alkaline phosphatase
Alb
albumin
BMI
body mass index
CAB
combined androgen
CI
confidence intervals
CT
computed tomography
DAR
darolutamide
DTX
docetaxel
ECOG PS
Eastern Cooperative Oncology Group performance status
EOD
extent of disease
Hb
hemoglobin
HR
hazard ratios (HRs)
ISUP
International Society of Urological Pathology
LDH
lactate dehydrogenase
mHSPC
metastatic hormone-sensitive prostate cancer
NLR
neutrophil-to-lymphocyte ratio
OS
overall survival
PFS
progression-free survival

PMI
psoas muscle index
PNI
prognostic nutritional index
PSA
prostate-specific antigen
PSA90
≥90% PSA decline
ROI
region of interest

DECLARATIONS

Ethics approval and consent to participate:

This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients. This study was approved by the Ethics Committee of Jichi Medical University (approval number: A22-023).

Clinical trial number

Not applicable.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Author Contribution

Hirotaka Yokoyama: Investigation, writing—original draft, writing—review and editing; Toru Sugihara: writing—original draft, writing—review and editing; Masaki Ito: Writing—review and editing; Ryota Kawashima: Writing—review and editing; Tomonori Sato: Writing—review and editing; Kaho Takami:

Writing—review and editing; Yukinori Hamada: Writing—review and editing; Risa Imamura: Writing—review and editing; Hayato Sato: Writing—review and editing; Atsushi Yanase: Writing—review and editing; Masayuki Kurokawa: Writing—review and editing; Hayato Hoshina: Writing—review and editing; Ei-ichiro Takaoka: Writing—review and editing; Tetsuya Fujimura: Writing—review and editing, conceptualization, and supervision. All the authors have read and approved the final manuscript.

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Data availability statement:

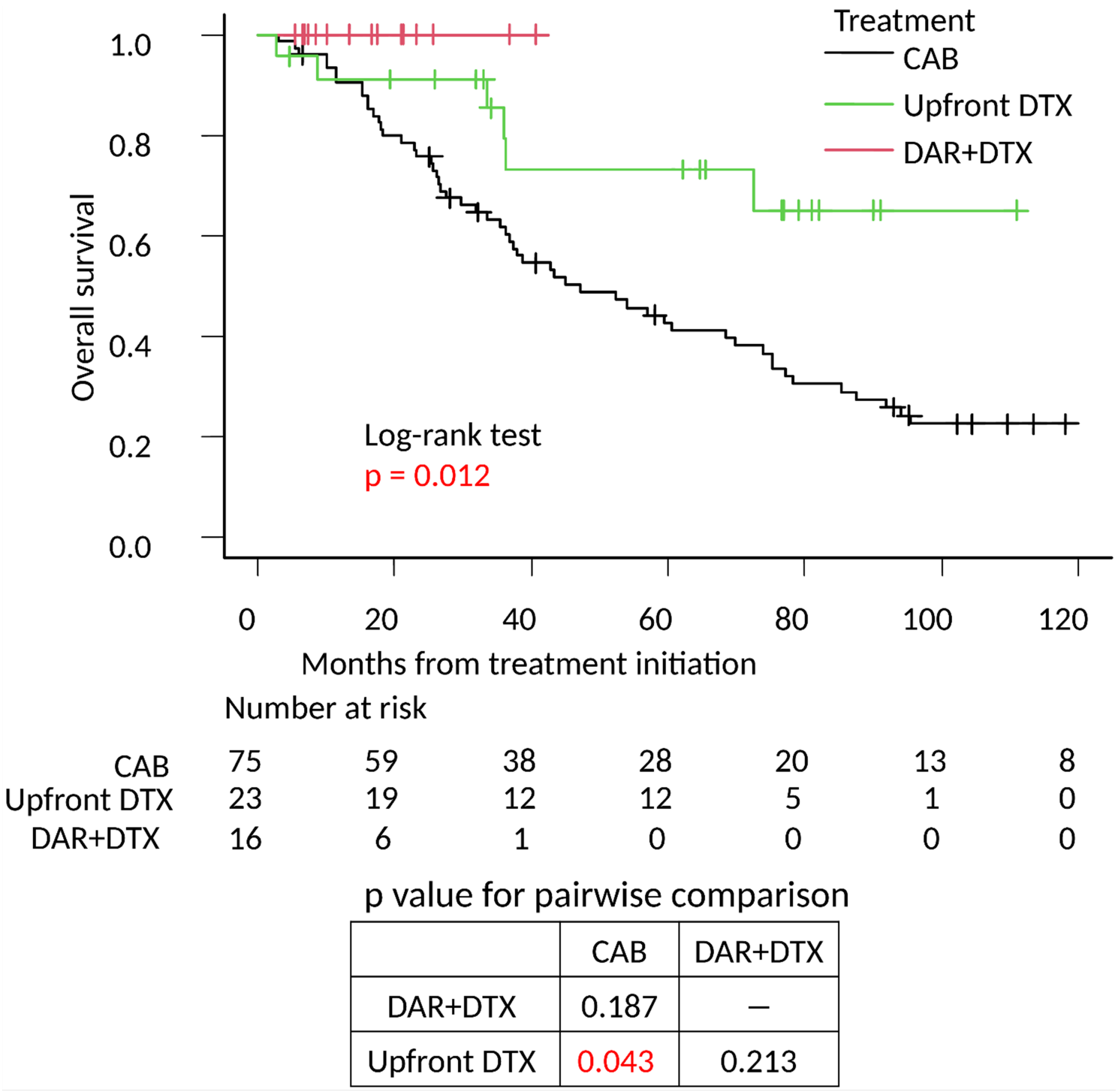
All data generated or analyzed in this study are included in this article. Further inquiries can be directed to the corresponding authors. All datasets on which the conclusions of the paper are based are available to the editors, reviewers, and readers without unnecessary restrictions, wherever possible.

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Figures



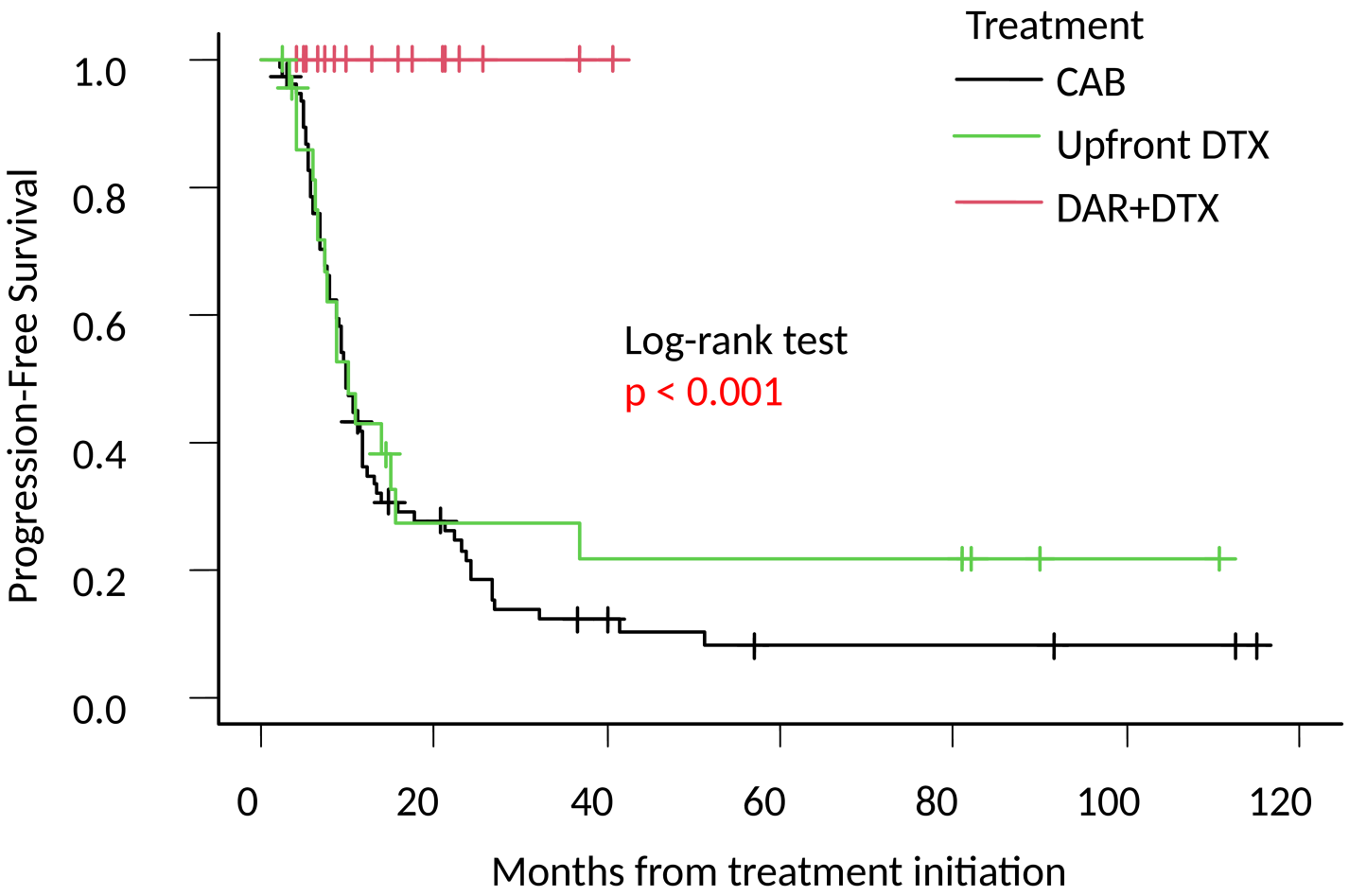
p value for pairwise comparison

	CAB	DAR+DTX
DAR+DTX	0.187	—
Upfront DTX	0.043	0.213

Figure 1

Kaplan–Meier curves for overall survival according to initial treatment group (CAB, upfront DTX, DAR + DTX). Log-rank p = 0.012.

CAB, combined androgen blockade; DAR, darolutamide; DTX, docetaxel.



Number at risk

CAB	75	19	7	3	3	2	0
Upfront DTX	23	5	4	4	4	1	0
DAR+DTX	16	6	1	0	0	0	0

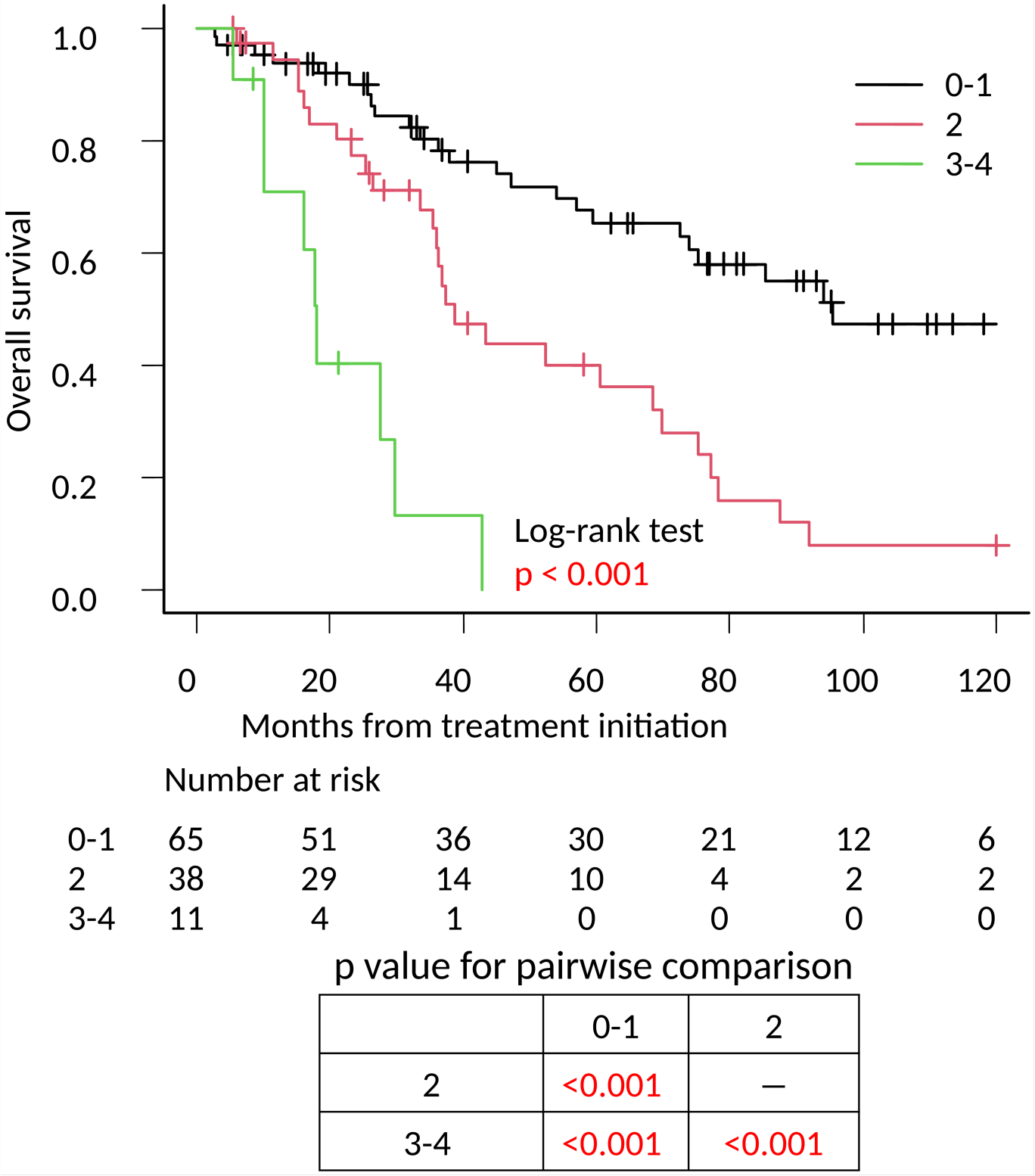
p value for pairwise comparison

	CAB	DAR+DTX
DAR+DTX	<0.001	—
Upfront DTX	0.395	<0.001

Figure 2

Kaplan–Meier curves for progression-free survival according to initial treatment group. Log-rank p < 0.001.

CAB, combined androgen blockade; DAR, darolutamide; DTX, docetaxel.



	0-1	2
2	<0.001	—
3-4	<0.001	<0.001

Figure 3

Kaplan–Meier curves for overall survival according to the number of overall survival-related risk factors (EOD score ≥ 3, Hb ≤ 12 g/dL, Gleason Grade Group 5, ECOG PS ≥ 2). Log-rank p < 0.001.