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Real-world Treatment Selection and Shared Decision-making in *De Novo* Metastatic Castration-sensitive Prostate Cancer in Japan

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Abstract

Background/Aim: This study aimed to describe the selection of first-line treatment and early outcomes in patients with *de novo* metastatic castration-sensitive prostate cancer (mCSPC) after the introduction of triplet therapy in Japan.

Patients and Methods: We retrospectively investigated 46 patients with *de novo* mCSPC treated at a specialist Japanese cancer center between March 2023 and August 2025. The patients were grouped according to whether they received androgen deprivation therapy (ADT) alone (the monotherapy group), doublet therapy consisting of ADT and an androgen receptor signaling inhibitor (the doublet group), or triplet therapy consisting of ADT with docetaxel 70 mg/m^2 and darolutamide (the triplet group).

Results: The median patient age was 73 years, and most patients had LATITUDE high-risk disease and CHAARTED high-volume disease. Patients in the monotherapy group were significantly older than those in the doublet group and triplet group (80 *vs*. 74 and 69 years, respectively, $p<0.001$). A prostate-specific antigen level of <0.2 ng/ml was detected in 27% of patients in the monotherapy group, 67% of those in the doublet group, and 63% of those in the triplet group, with ≥90% declines in 80%, 92% and 100%, respectively. In the triplet group, febrile neutropenia occurred in 5.3% of patients, interstitial pneumonitis in 5.3%, and peripheral neuropathy in 10.5%.

Conclusion: In Japan, treatment intensity in patients with *de novo* mCSPC is determined mainly by age rather than by metastatic burden.

Keywords: Metastatic castration-sensitive prostate cancer, androgen deprivation therapy, doublet therapy, docetaxel, triplet therapy, shared decision-making, Japan.

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Introduction

The treatment landscape for metastatic castration-sensitive prostate cancer (mCSPC) has changed dramatically over the past decade. Historically, androgen deprivation therapy (ADT) alone was the standard of care. However, the CHAARTED and STAMPEDE trials showed that adding docetaxel to ADT significantly improved overall survival (OS) in men with metastatic hormone-sensitive disease, particularly those with high-volume or *de novo* metastases (1, 2). Subsequently, the LATITUDE and STAMPEDE studies demonstrated that combining ADT with the androgen receptor signaling inhibitor (ARSI) abiraterone plus prednisone also prolonged survival in men with *de novo* mCSPC (3, 4). More recently, the ENZAMET and TITAN trials showed that enzalutamide and apalutamide, respectively, in combination with ADT improved OS and radiographic progression-free survival in mCSPC (5, 6). Triplet systemic regimens have further intensified first-line treatment. In the ARASENS study, OS was better in patients who received ADT plus docetaxel with addition of darolutamide than in those who received ADT plus docetaxel alone, with a similar overall adverse event profile (7). In PEACE-1, addition of abiraterone to ADT plus docetaxel prolonged OS and radiographic progression-free survival in men with *de novo* high-volume mCSPC (8). Network meta-analyses and comparative reviews also suggest that treatment intensification with an ARSI and/or docetaxel is superior to ADT alone and that triplet therapy is more effective than ADT plus docetaxel, particularly in patients with high-volume disease and a poor prognosis (9-11).

Based on these data, the major clinical practice guidelines now recommend intensification of systemic treatment rather than ADT as monotherapy for most patients with mCSPC. The National Comprehensive Cancer Network and the American Urological Association, American Society for Radiation Oncology, and Society of Urologic Oncology guidelines prioritize ARSI-based doublet therapy (ADT plus an ARSI) as the standard of care and also support the use of triplet therapy with ADT, docetaxel, and an ARSI in suitably fit patients, particularly those with high-volume disease (9, 12). Similarly, the European Association of Urology guideline recommends ADT plus an ARSI as the preferred option for men with *de novo* metastatic hormone-sensitive disease and acknowledges triplet therapy as an option in patients with high-volume disease (13). Importantly, the European Association of Urology guideline also cautions that its treatment flowcharts "… present a generalized approach only, and cannot take the management of individual patients into account, nor the availability of resources" (13). This statement highlights the fact that, despite strong evidence and the recommendations for treatment intensification in the guidelines, the choice among ADT monotherapy, ARSI-based doublet, and triplet regimens remains preference-sensitive and must be individualized.

In parallel with therapeutic advances, there is growing recognition that shared decision-making (SDM) is essential in prostate cancer care. A recent best–worst scaling study from Japan found that both physicians and their patients with metastatic castration-sensitive or castration-resistant prostate cancer prioritize treatment efficacy but that patients place relatively greater weight on preventing progression of metastasis and elevation of prostate-specific antigen (PSA) levels as well as on safety and out-of-pocket costs (14). A nationwide survey in Japan showed that nearly 90% of men with prostate cancer preferred active or shared involvement in treatment decisions, approximately 30% of physicians underestimated patients' desire for participation, and patients with worse health-related quality of life had a stronger preference for SDM (15). These findings suggest that first-line treatment for mCSPC is determined not only by tumor-related factors but also by patient values and context. Furthermore, recent Japanese data from the ULTRA-Japan Consortium indicated that a Gleason score of ≥9, an extent of disease score of ≥2 on bone scintigraphy, and the presence of liver metastasis were independent predictors of a shorter time to castration resistance in patients receiving ARSI-based doublet therapy, suggesting that such patients may be candidates

for alternative strategies such as triplet therapy (16). However, it is unclear how these risk factors influence treatment selection in routine practice.

The aims of this study were to 1) describe real-world patterns of first-line treatment selection for *de novo* mCSPC, 2) identify clinical factors associated with treatment intensity, focusing on age and metastatic burden, 3) evaluate early oncologic outcomes according to treatment strategy, and 4) explore the safety of docetaxel in patients receiving triplet therapy. We also interpreted our findings in the context of SDM and patient preferences.

Patients and Methods

Study design and population. This retrospective, single-center cohort study was performed at Kyushu Cancer Center, a specialized oncology hospital in Japan. We reviewed consecutive patients who were newly diagnosed with *de novo* mCSPC and received initial systemic therapy at our institution between March 2023 and August 2025. Triplet therapy with ADT, docetaxel and darolutamide (the only ARSI approved for use in triplet regimens in Japan during the study period) was approved in Japan in February 2023. Therefore, we limited our analysis to patients starting first-line systemic therapy after this approval to allow contemporary comparison among ADT monotherapy, doublet, and triplet regimens.

The inclusion criteria were as follows: histologically confirmed adenocarcinoma of the prostate; radiographically proven distant metastases at diagnosis; castration-sensitive status at commencement of systemic therapy; and availability of clinical data on baseline characteristics, treatment course, PSA kinetics, and survival. Patients who were enrolled in interventional clinical trials and receiving protocol-defined study treatments were excluded to avoid confounding by non-standardized regimens. Patients who had received prior local therapy or systemic treatment for prostate cancer were also excluded.

Treatment strategies and groups. All patients underwent medical or surgical castration as the backbone of systemic therapy. According to the initial planned regimen, patients were categorized into three groups: a monotherapy group, which received ADT alone or androgen blockade combined with a first-generation antiandrogen; a doublet group, which received ADT plus an ARSI (abiraterone, enzalutamide, or apalutamide); and a triplet group, which received ADT plus docetaxel and darolutamide.

At our institution, patients with *de novo* mCSPC are routinely informed about the available treatment options, namely, ADT monotherapy, ARSI-based doublet therapy, triplet therapy and, in very frail or highly comorbid patients, best supportive care alone, regardless of age or disease status. The treatment is then chosen by SDM between the patient and the treating urologic oncologist, taking into account tumor characteristics, expected benefits and risks, and the patient's preferences and life circumstances. The choice of regimen, docetaxel dose and schedule, and selection of ARSI are at the discretion of the attending urologic oncologists based on tumor characteristics, age, comorbidities, performance status, cognitive function, social background, and patient preference after SDM. In the triplet group, our standard starting dose of docetaxel was 70 mg/m^2, administered every 3 to 4 weeks at the discretion of the treating physician for up to six cycles, with further dose or schedule modifications according to toxicity.

Data collection and definitions. Patient data, including age, Eastern Cooperative Oncology Group performance status, serum PSA, Gleason score, clinical T and N stages, extent of disease on bone scintigraphy, and the presence and sites of visceral metastases, were collected from the electronic medical records. In the triplet group, modifications of the docetaxel dose and treatment discontinuation because of toxicity were also recorded.

The metastatic burden and risk were classified according to the CHAARTED criteria (high volume *vs*. low volume) (1) and LATITUDE criteria (high risk *vs*. low risk) (3).

PSA responses were evaluated as the proportions of patients achieving (i) a PSA of <0.2 ng/ml at any time during follow-up and (ii) a ≥90% decline from baseline. OS

was defined as the interval between initiation of systemic therapy and death from any cause or last follow-up, whichever came first. Docetaxel-related adverse events in the triplet group, including febrile neutropenia, interstitial pneumonitis, and peripheral neuropathy, were extracted from the electronic records and graded according to the Common Terminology Criteria for Adverse Events version 5.0 (17).

Statistical analysis. Continuous variables are summarized as the median [interquartile range (IQR)] and were compared among groups using the Kruskal–Wallis test. Categorical variables are presented as the count and percentage and were compared between groups using the chi-squared test or Fisher's exact test as appropriate. PSA response rates were compared between groups using Fisher's exact test. OS was estimated using the Kaplan–Meier method and compared across groups using the log-rank test. The statistical analyses were performed using EZR version 1.40 (Easy R, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) (18). Two-sided *p*-values of <0.05 were considered statistically significant.

Ethics statement. The study protocol was approved by the Institutional Review Board of Kyushu Cancer Center (approval number 2014-99) and conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived in view of the retrospective design of the study. However, patients were given the opportunity to opt out *via* our institutional website.

Results

Patient characteristics. Fifty-five consecutive patients with *de novo* mCSPC initiated systemic therapy at our institution during the study period. After nine exclusions, 46 patients (monotherapy group, n=15; doublet group, n=12; triplet group, n=19) were included in the study. Baseline characteristics are summarized in Table I. The median age at initiation of treatment was 73 years (IQR=69-80). Patients receiving monotherapy were substantially older than those in the doublet and triplet groups (median 80 *vs*. 74 and 69 years, respectively; $p<0.001$). Median baseline PSA was high in all groups [overall 224 ng/ml (IQR=94-633)], with no significant intergroup differences. Most patients had high-grade tumors, with a Gleason score of ≥8 observed in 41 patients (89%). Eight patients (17%) had visceral metastases and two (4%) had liver metastases. Thirty patients (65%) had high-risk disease according to the LATITUDE criteria, and 32 (70%) met the CHAARTED criteria for high-volume disease. The frequencies of high-risk and high-volume disease were numerically highest in the triplet group (LATITUDE high-risk 79%; CHAARTED high-volume 84%) but did not differ significantly among the groups.

Cross-tabulation of the CHAARTED and LATITUDE criteria showed that 30 of the 32 patients who met the CHAARTED criteria for high-volume disease also met the LATITUDE criteria for high-risk disease (Table II). Among these 30 high-burden/high-risk patients, nine (30%) received monotherapy, six (20%) received doublet therapy, and 15 received (50%) triplet therapy.

PSA response and overall survival. The PSA responses are shown in Table III. A PSA of <0.2 ng/ml at any time was achieved in four of 15 patients (27%) in the monotherapy group, eight of 12 (67%) in the doublet group, and 12 of 19 (63%) in the triplet group ($p=0.057$). A PSA decline of ≥90% from baseline was documented in 12 patients (80%) in the monotherapy group, 11 (92%) in the doublet group, and 19 (100%) in the triplet group ($p=0.127$).

There were four non-treatment related deaths (monotherapy group, n=2; doublet group, n=2) during a median observation period of 11.7 months (range=0.5-31.1 months). Median OS was not reached (NR) in any group at the data cutoff point, with 95% confidence intervals of 9.6-not estimable (Mono), 18.8–not estimable (Doublet) and not estimable–not estimable (Triplet). Kaplan–Meier curves demonstrated

Table I. *Baseline clinical characteristics of the entire cohort of men with de novo mCSPC and according to whether initial systemic treatment was ADT alone (monotherapy), ADT with an ARSI (doublet therapy), or ADT with docetaxel and darolutamide (triplet therapy).*

Characteristics		All (n=46)	Mono (n=15)	Doublet (n=12)	Triplet (n=19)	*p*-Value
Age (years), median (IQR)		73 (69-80)	80 (77-84)	74 (72-78)	69 (63-73)	<0.001
PSA (ng/ml), median (IQR)		224 (94-633)	209 (77-468)	160 (100-235)	452 (100-2,321)	0.219
Gleason score sum, n (%)						0.165
	≤7	5 (11)	1 (7)	1 (8)	3 (16)	
	8	17 (37)	10 (67)	3 (25)	4 (21)	
	≥9	24 (52)	4 (26)	8 (67)	12 (63)	
Visceral metastasis, n (%)		8 (17)	1 (7)	2 (17)	5 (26)	0.331
	Liver	2 (4)	0	1 (8)	1 (5)	
LATITUDE criteria, n (%)	High-risk	30 (65)	9 (60)	6 (50)	15 (79)	0.232
CHAARTED criteria, n (%)	High-volume	32 (70)	10 (67)	6 (50)	16 (84)	0.131

ADT: Androgen deprivation therapy; ARSI: androgen receptor signaling inhibitor; IQR: interquartile range; mCSPC: metastatic castration-sensitive prostate cancer; PSA: prostate-specific antigen.

no significant differences in OS among the three groups (log-rank *p*=0.233; Figure 1).

Tolerability of docetaxel in the triplet group. Six cycles of docetaxel were completed in 73.7% of patients in the triplet group, with an additional patient still receiving triplet therapy at the data cutoff point. Overall, 73.7% of patients required at least one dose reduction or delay. Regarding safety, any-grade febrile neutropenia occurred in one patient (5.3%), interstitial pneumonitis in one (5.3%), and peripheral neuropathy in two (10.5%). There were no treatment-related deaths.

Discussion

This single-center real-world study from a Japanese cancer center examined how first-line systemic therapy is selected for patients with *de novo* mCSPC and how these choices relate to early outcomes and tolerability. Despite the high prevalence of adverse features, namely, a Gleason score of ≥8 in nearly 90% of patients and high-risk/high-volume disease by LATITUDE and CHAARTED criteria in approximately two-thirds, ADT-based monotherapy was still chosen in one-third of cases. This finding contrasts with evidence from randomized trials such as CHAARTED, STAMPEDE, LATITUDE, ENZAMET, TITAN, ARASENS and PEACE-1 and with major guidelines recommending treatment intensification with ARSI-based doublet and/or triplet therapy for most men with *de novo* mCSPC (1-9, 12, 13); however, it is consistent with population-based analyses showing that many real-world patients who are theoretically eligible for combination therapy continue to receive ADT alone (9-11).

Table II. *Selection of first-line treatment for men with de novo metastatic castration-sensitive prostate cancer (mCSPC) according to their CHAARTED disease volume and LATITUDE risk classifications.*

	High-risk (n=30)	Low-risk (n=16)
High-volume (n=32)	n=30 (T 15; D 6; M9)	n=2 (T 1; D 0; M 1)
Low-volume (n=14)	-	n=14 (T 3; D 6; M 5)

D: Doublet therapy; M: monotherapy; T: triplet therapy.

A key observation in this study is that treatment intensity was more strongly associated with age than with metastatic burden or formal risk classification. Patients in the monotherapy group were, on average, more than 10 years older than those receiving triplet therapy, whereas the distributions of visceral metastases and high-risk/high-volume status were similar across the groups. This finding suggests that experienced urologic oncologists weigh aging-related factors, including frailty,

Table III. *Changes in prostate-specific antigen levels at any time according to first-line treatment intensity.*

PSA response (any time)	Mono (n=15)	Doublet (n=12)	Triplet (n=19)	*p*-Value
PSA <0.2, n (%)	4 (27)	8 (67)	12 (63)	0.057
PSA decline ≥90%, n (%)	12 (80)	11 (92)	19 (100)	0.127

Mono: ADT monotherapy; Doublet: ADT plus an androgen receptor signaling inhibitor; Triplet: ADT plus docetaxel and darolutamide; ADT: androgen-deprivation therapy; PSA: prostate-specific antigen.

comorbidities, cognitive status, and social circumstances, at least as heavily as the tumor burden when deciding between doublet and triplet strategies. Our findings align with those of a study by the ULTRA-Japan Consortium, in which a Gleason score of ≥9, an extent of disease score of ≥2, and liver metastasis predicted a shorter time to castration resistance in patients receiving ARSI-based doublet therapy, and such patients were proposed as candidates for alternative approaches such as triplet therapy (16). In our cohort, many patients receiving triplet therapy had similarly adverse features, and clinicians appeared to reserve triplet therapy, a theoretically more intensive upfront strategy combining ADT, an ARSI and docetaxel based on complementary mechanisms and early debulking of chemosensitive and androgen-independent clones (1, 2, 7, 8, 10, 11, 19), for biologically aggressive disease, even though direct randomized comparisons between triplet therapy and ARSI-based doublet therapy are lacking.

However, the presence of poor prognostic features does not, automatically render ARSI-based doublet therapy inappropriate, nor does it ensure that triplet therapy can overcome the adverse biology. Doublet therapy may offer a more acceptable balance between benefit and burden in older or frail patients with severe comorbidities, cognitive impairment, or limited social support, particularly when chosen through a thorough SDM process. Conversely, our experience, as well as that of the ULTRA-Japan Consortium, suggests that outcomes may remain suboptimal at the individual level even when triplet therapy is selected for patients with a Gleason score of ≥9, an extent of disease score of ≥2, or liver metastasis (16). Therefore, triplet therapy should be viewed as a preferential option for fit patients with particularly high-risk disease rather than a universally mandated standard.

In terms of efficacy, triplet therapy achieved the highest rates of profound PSA decline in our cohort, whereas OS did not differ significantly among the three strategies during follow-up, which was relatively short. The broader body of evidence indicates that long-term outcomes are better in patients who receive an ARSI-based doublet or triplet regimen than in those who receive ADT alone and that triplet therapy is clearly superior to ADT plus docetaxel (1-4, 7-9, 11). In contrast, there are no randomized head-to-head trials directly comparing triplet therapy with ADT plus an ARSI. Recent network meta-analyses suggest that progression-free survival is longer on triplet therapy than on ARSI-based doublet therapy, particularly in patients with high-volume disease, whereas the OS advantage is modest and often not statistically significant (9-11, 19). Therefore, while triplet therapy is an important option for fit patients with a poor prognosis, its superiority over an ARSI-based doublet remains uncertain, and decisions must also consider increased treatment complexity, toxicity and cost.

Our data also provide information on the tolerability of triplet therapy that includes dose-adjusted docetaxel in older Japanese patients. Docetaxel administered at a dose of 70 mg/m^2 every 3 to 4 weeks was feasible in our triplet group, with nearly three-quarters of patients completing six cycles and a similar proportion requiring dose modifications.

The ARASENS study reported febrile neutropenia and peripheral sensory neuropathy, respectively, in 7.8% and 11.7% of the overall population (7) and in 14.3% and 32.0% in the subgroup of Japanese patients (20).

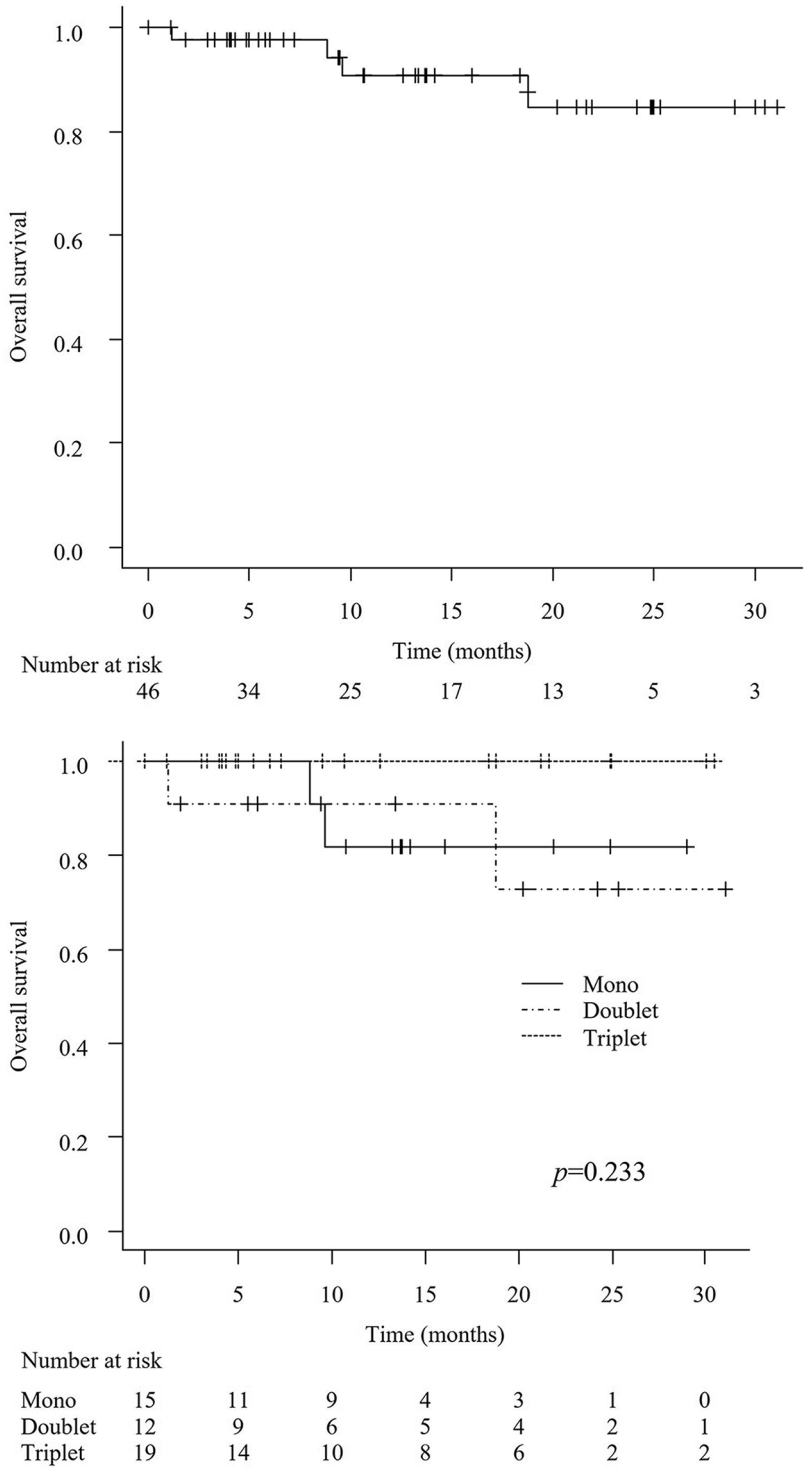

Figure 1. *Kaplan–Meier curves for overall survival in the entire cohort of men with de novo metastatic castration-sensitive prostate cancer; mono, monotherapy (mCSPC) and according to whether their initial systemic treatment was androgen deprivation therapy (ADT) alone (monotherapy), ADT with an androgen receptor signaling inhibitor (ARSI) (doublet therapy), or ADT with docetaxel and darolutamide (triplet therapy). OS: Overall survival.*

The rates of docetaxel-related toxicity in our cohort were comparable or numerically lower than in those in ARASENS, although interpretation is limited by our small sample size. The occurrence of interstitial pneumonitis in one patient underscores the need for vigilant monitoring and early multidisciplinary management when using docetaxel-containing regimens. Importantly, adding docetaxel exposes patients to chemotherapy-specific adverse events – such as myelosuppression, febrile neutropenia and drug-induced pneumonitis – that are seldom encountered with ARSI-based doublet therapy alone, and this incremental toxicity must be weighed carefully against potential gains in disease control.

The findings of this study are best interpreted within the framework of SDM. Preference studies from Japan have shown that physicians focus primarily on survival whereas patients with metastatic prostate cancer place substantial weight on not only efficacy but also prevention of the spread of metastasis and PSA elevation, avoiding adverse events and minimizing out-of-pocket costs (14, 21). Nearly all patients in these studies preferred active or shared involvement in treatment decisions (14, 21). Moreover, a nationwide survey found that approximately 90% of Japanese men with prostate cancer desired active or shared roles, while roughly one-third of physicians underestimated this preference; patients with worse quality of life were particularly likely to favor SDM (15).

Overall, these data support the notion that first-line treatment for mCSPC is inherently preference-sensitive; multiple reasonable options exist, and the optimal choice depends on both tumor-related characteristics and patient values. Our institutional practice reflects this perspective. Regardless of age or disease status, patients with *de novo* mCSPC at our cancer center are routinely informed about the full range of first-line options, including ADT monotherapy, ARSI-based doublet therapy, and triplet therapy, as well as best supportive care alone for very frail or highly comorbid patients. The treatment strategy is then chosen through SDM. Although we did not systematically collect data on the specific reasons why each patient selected a given regimen, the findings in our cohort, in which ADT monotherapy remained common even among high-risk/high-volume patients, highlight the fact that first-line management of mCSPC in the real world is preference-sensitive. Decision aids that present the absolute benefits and risks of each option may help align treatment choices more closely with both evidence and patient preferences.

The wording of the European Association of Urology prostate cancer guideline is also relevant. As mentioned earlier, the guideline explicitly notes that its flowcharts "… present a generalized approach only and cannot take the management of individual patients into account, nor the availability of resources" (13). Our real-world data exemplify this disclaimer: even among patients who meet high-risk and high-volume criteria derived from clinical trials, age, frailty, cognitive status, family support, and economic factors frequently lead physicians and patients to choose less intensive regimens. Therefore, decisions about whether to use ADT monotherapy, an ARSI-based doublet, or triplet therapy should not be based on expected efficacy alone and should also account for the risk and reversibility of adverse events, the patient's physical and cognitive reserve, caregiver availability, and the anticipated financial burden. Guideline recommendations provide an essential framework, but individualized care in mCSPC requires careful SDM that acknowledges clinical complexity and resource limitations.

Study limitations. First, it was a retrospective analysis performed at a single cancer center with a relatively small sample size, which limited its statistical power, the ability to conduct robust multivariable analyses, and generalizability to other settings. Second, the follow-up duration was short, and the OS data remained immature. Longer observation is needed to clarify the long-term impact of treatment intensity on survival and quality of life. Third, ARSI-related adverse events were not systematically recorded, so our safety assessment was focused on docetaxel-related toxicities in the triplet group. Fourth, we did not directly measure SDM processes, such

as patient-reported involvement, decision conflict, and satisfaction. Therefore, our discussion of SDM should be regarded as exploratory and hypothesis-generating rather than definitive. However, despite these limitations, this study provides clinically relevant insights into how a urologic oncology team at a specialist cancer center navigates the selection of first-line treatment for *de novo* mCSPC in an aging society.

Conclusion

In this single-center real-world cohort of patients with *de novo* mCSPC, the intensity of first-line treatment was influenced more by age and patient context than by metastatic burden or the formal risk classification. Despite the high prevalence of high-risk/high-volume disease, ADT monotherapy remained common among older and more vulnerable patients, whereas ARSI-based doublet and triplet regimens were mainly used in younger and fitter patients. Triplet therapy with dose-adjusted docetaxel was feasible with acceptable toxicity in routine practice. These findings support the view that first-line management of mCSPC is preference-sensitive and should be individualized by SDM that integrates tumor biology and patient-related factors.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, N.F., M.N., and T.N.; methodology, N.F. and T.N.; formal analysis, N.F. and T.N.; investigation, N.F., J.T., A.T., Y.S., M.N., and N.T.; resources, M.N. and T.N.; data curation, N.F.; writing – original draft preparation, N.F., M.N., and T.N.; writing – review and editing, all authors; visualization, N.F.; supervision, M.N. and T.N. All Authors have read and approved the final version of the manuscript.

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