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Case Report

Clinical Variables in the Diagnosis and Treatment of Advanced Hormone Sensitive Prostate Cancer

Zonana Farca E [1], Ramírez Pérez E.A [2*]

Urologist at Hospital Angeles Mocel and Hospital Angeles Lomas. Emeritus Professor of the Military Medical School.

***Correspondence Author:** Elías Zonana Farca. 29-107 STREET: Gelati, San Miguel Chapultepec, Miguel Hidalgo, ZIP code. 11850, Mexico

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Abstract

In recent years, novel imaging studies have emerged to increase the sensitivity in early metastatic disease detection and the recognition of biological subgroups of men with newly diagnosed advanced prostate cancer for the management of the primary tumor to improve overall survival in these patients considered fatal in the short or medium term with systemic disease managed just with androgenic hormonal suppression.

Keywords: advanced hormone sensitive prostate cancer; cn1 disease; oligometastatic disease in prostate cancer

Introduction

Prostate cancer is surprisingly heterogeneous with respect to its diagnosis, response to treatment, progression and development of resistance. Due to this heterogeneity, there is no specific and unanimous definition in the various clinical studies of metastatic prostate cancer, where different terms are applied, such as high volume of disease, high burden, high risk and low volume, low burden, low risk.The classification system developed by the American Joint Committee on Cancer (AJCC TNM) [1], taking into account various clinical factors from the analysis of studies of patients with prostate cancer based on the location of metastasis, has considered the following known subgroups: Nx not evaluated; N0 no regional lymph node metastases demonstrated; N1 regional lymph node metastases; M0 no distant metastasis; M1 distant metastasis; M1a non-regional lymph node metastasis, M1b bone metastasis, and M1c metastasis to other sites.

Cn1 Disease: Pelvic retroperitoneal lymph nodes such as sacral, obturator, hypogastric and iliac lymph nodes constitute one of the significant sites of prostate cancer dissemination, historically representing a population with systemic disease recommending only long-term androgen suppression therapy (AST) as treatment.In 2018 [2], it was reported that 12 to 13% of men with prostate cancer (CaP) had only nodal involvement (cN1) at the time of their clinical diagnosis, and it is expected that this subgroup will increase over the years with the use of new molecular imaging modalities, since conventional studies such as abdominal computed tomography (CT) and magnetic resonance imaging (MRI) have very low sensitivity for detecting lymph node Briganti and Colbs [3] demonstrated, through anatomopathological surgical mapping, that patients with metastatic retroperitoneal lymph nodes always had pelvic lymph nodes with malignancy. Oligometastatic prostate cancer (M1 disease): Despite numerous publications and consensus, there is no consistent or standard definition for defining oligometastatic CaP. Factors such as the number, location, and volume of metastatic lesions and whether they appear synchronously or metachronously at the time of cancer diagnosis using new imaging modalities are considered.In 1995, Hellman and Colbs [4] applied the term oligometastatic CaP to describe an intermediate tumoral state between localized lesions and widespread metastases. In the STAMPEDE [5] and HORRAD [6] clinical studies, metastatic load was used to define oligometastatic CaP, and the criteria from the CHAARTED [7] clinical study were applied to guide the treatment and prognosis of these patients. High-load patients were identified as those with four or more bone metastases, one or more outside the pelvis, or visceral metastases, and all others were considered low-load.In the LATITUDE [8] clinical trial, patients with newly diagnosed high-risk metastatic CaP were determined to have at least two of three risk factors: an aggressive prostate tumor (Gleason 8 or higher), three or more bone lesions, or three or more lesions in other organs.At the third Consensus Conference in December 2019, APCCC [9], 48% of panelists voted for three or fewer metastases, and 46% voted for five or fewer lesions to consider the disease oligometastatic. There was no general consensus, and reaching a consensus requires a 75% vote. It is important to note that these discussions among a significant number of experts providing guidance in controversial areas of advanced CaP with a low level of evidence are not definitive guidelines. Diagnosis and treatment decisions must be individualized based on economic possibilities and access to diagnostic and treatment procedures.

Image Studies.

Even today, in most clinical studies, conventional imaging techniques for staging advanced prostate cancer (PCa) have been cross-sectional cuts of abdominal computed tomography (CT) and magnetic resonance imaging (MRI) and bone scans. CT and MRI detect lymph node lesions based on size and morphology with 8mm resolution; their sensitivity is very low, and their positive predictive value ranges between 31 and 33% [10] [11].Multiparametric magnetic resonance imaging with increased contrast resolution for T2 morphological sequences and functional diffusion and perfusion sequences can report the existence of extracapsular extension, seminal vesicle invasion, and regional lymph node disease; currently, it is considered the technique of choice for planning a biopsy in the diagnosis of PCa.In recent years, studies have integrated new molecular imaging tracers: PET/CT 11C Choline, PET/CT 18F Choline, and PET/CT Gallium 68 PSMA (prostate-specific membrane antigen). The latter has shown to be more sensitive and specific and have a positive predictive value in staging patients with advanced and recurrent PCa with a lower metastatic burden, particularly with single lymph node involvement. Useful for more accurate staging in patients with localized PCa in the intermediate and high-risk groups (T2b-T2c, PSA (prostate-specific antigen) 10-20 ng. /Ml, Gleason 7/T3a, PSA + 20 ng. /Ml, Gleason 8-10, +3 positive biopsy fragments [12] [13]; as well as in patients with oligometastatic cancer with a low tumor burden, in whom targeted therapy for metastasis is planned.

These techniques are still far from being widely used in the clinic due to their availability and economic viability.

Treatment of advanced PCa: cN1 Disease.

Clinical guidelines suggest the use of radical prostatectomy (RP) and/or local radiotherapy (RT) in selected patients in this clinical subgroup. It is important to note again that the diagnosis of lymph node involvement must be accurate to consider local treatment and systemic therapy. The justification for local treatment of the disease is based on reducing tumor volume and local control, inhibiting the initiation of systemic disease and the progression of existing metastases. In this context, literature reports show the execution of radical prostatectomy and extensive lymph node dissection to achieve these goals, and specifically to achieve more precise staging for the subsequent multimodal treatment of the disease [14] [15]. As is well known, extensive lymphadenectomy is a laborious procedure that includes all regional nodes and is not without perioperative and postoperative complications. Its therapeutic benefit is still questionable.In a retrospective clinical study of 1,338 patients with pN1 after RP and pelvic lymph node dissection with undetectable PSA, adjuvant RT plus androgen suppression therapy (AST), compared to observation or AST alone, had a significant impact on overall survival (OS) [16]. In another analysis of over 8,000 patients from the National Cancer Data Base (NCDB) [17], an improvement in overall survival was observed with adjuvant RT plus AST, in patients with adverse pathological characteristics, pT3b, Gleason 8-10, and 3 or more positive nodes.The value of RT in cN1 patients has been demonstrated. Ventimiglia et al. in 2019 [18] reported a very rigorous meta-analysis of non-randomized comparative retrospective clinical studies from 1995 to 2018 in over 4,500 men with clinical cN1 disease to assess combined treatment of AST and local prostate treatment, either RT or RP versus AST alone. Only when using local radiotherapy in patients with cN1, the National Comprehensive Cancer Network (NCCN) and the European Association of Urology recommend combining it with androgen suppression hormonal therapy based on the results observed in frequently mentioned retrospective clinical studies (20) (21), from the radiation oncology group (RTGO 86-10, 9202, 85-31) and the European Organization for Research on Cancer (EORTG 2283), where RT plus TSA vs. Only RT or TSA was used in patients with locally advanced or high-risk CaP, showing an improvement in overall survival and progression-free survival with combined treatment. It should be noted that the radiation dose in most patients ranged from 60-64 Gy with conventional linear accelerators and only targeted the prostate; currently, with new intensity-modulated accelerators, treatment for the primary tumor uses doses of 78 Gy in high-risk patients and includes regional lymph nodes. At the 2019 Consensus Conference, for patients with cN1M0 disease, 98% of panelists voted for local regional treatment with or without systemic therapy; regarding regional therapy, 39% voted for radiotherapy, 12% for surgery, and 49% had no preference. As for the duration of androgen suppression therapy in cN1M0 patients undergoing local regional radiotherapy, 53% voted for 24-36 months, 41% for 12-24 months, and 4% for 4-12 months; none for life. The results support the use of local regional radiotherapy and long-term androgen suppression therapy (24-36 months) in patients with cN1M0 and do not include other medications in systemic therapy.

Metastatic prostate cancer M1

In recent years, new evidence has emerged regarding the treatment of primary tumors and the metastatic burden in newly diagnosed patients. Two randomized comparative clinical trials were conducted to evaluate prostate radiotherapy combined with androgen suppression therapy (AST) vs. AST alone in patients with metastatic prostate cancer (CaP). In the HORRAD randomized study (6), 432 patients with CaP with bone metastases and a PSA > 20 ng/ml received androgen suppression therapy with or without radiotherapy to the prostate (57 and/or 70 Gy fractionated); no improvement in overall survival was observed in unselected patients for either group, but a benefit was observed in a subgroup of patients with fewer than 5 bone metastases.In STAMPEDE M1/RT clinical trial (5), arms A and H were compared in 2061 patients with metastatic CaP and were randomly assigned to receive AST with or without radiotherapy in two variants (55.5 Gy in 20 fractions or 36 Gy in 6 weekly fractions of 6 Gy). No improvement in overall survival (OS) was observed in the entire general group of unselected patients, but a benefit was observed in the analysis of pre-specified subgroups with low metastatic disease burden. Some characteristics of this multicentric comparative randomized phase 3 clinical trial conducted in 117 hospitals in the United Kingdom and Switzerland in patients with a recent diagnosis of metastatic CaP are mentioned. Patients were randomly assigned in a 1:1 ratio to standard treatment with androgen suppression (control group) and external radiotherapy to the prostate and AST. From January 2013 to September 2016, 2061 patients were recruited, of which 1029 with TSA and 1032 wit RT and TSA. In addition, 367 patients (18%) received docetaxel, 184 in the control group and 183 in the RT and TSA group. The average age of the patients was 68 years old (63-73); PSA 97 ng/ml (33-315); 1630 patients (79%) with Gleason 8-10 and 1836 (89%) with bone metastases; 819 patients (40%) with low metastatic burden and 1120 (54%) with high burden, and in 122 (6%) it was unknown. Metastatic disease was confirmed by CT scan and bone scan. The primary endpoint was overall survival (time from treatment initiation to death from any cause), and secondary endpoints were progression-free survival. Radiotherapy improved progression-free survival, but not in the overall unselected patients. In the pre-specified subgroup analysis, in patients with low metastatic burden, overall survival improved in the radiotherapy group with a 3-year average of 81% vs. 73% in the control group; in patients with high metastatic burden, no treatment effect was observed. No evidence was found that adding docetaxel to prostate RT was more effective aside from known toxicity. A total of 761 deaths were

reported, 643 due to prostate cancer (84%), 329 in the control group and 314 in the RT group. In a recent analysis of the clinical subgroups of this study, a favorable effect on progression-free survival and overall survival was found in men with positive non-regional lymph nodes M1a (22). In the meta-analysis of the STOPCAP study (23), only 7% with more than 4 bone metastases had an improvement in overall survival at 3 years. It is necessary to underline that in the HORRAD and STAMPEDE studies, radiotherapy was directed only at the prostate. There is no phase III randomized clinical trial reporting on surgery for treating the primary tumor with metastatic disease. A pilot study, TROMBONE, is assessing the effect of surgery in 51 patients with up to 3 metastases or lymph node invasion (Study ISRCTN15704862), and a phase 3 study, SWOG 1802 (NTC03678025), plans to recruit 1200 patients with metastatic PCa to receive systematic treatment with or without radical prostatectomy or radiation to the primary tumor (mentioned in the 2019 Consensus Conference).There is some debate on the optimal approach in men with oligometastatic disease in relation to focal ablation therapy or initial systemic therapy combined with androgen suppression therapy, using docetaxel, abiraterone, enzalutamide, or apalutamide. The standard treatment for oligometastatic disease remains androgen suppression therapy as a starting pointFocal ablation therapy targeting metastases using stereotactic body radiotherapy (SABR) has generated significant interest, and although it is not included in formal guidelines as a treatment for oligometastatic disease, it is used by many experts. In multiple retrospective clinical studies, local ablation has shown an improvement in overall survival (OS) and progression-free survival, as well as adequate cytoreduction and symptomatic improvement in patients. Stereotactic body radiotherapy can deliver very high doses of radiation (50 to 80 Gy) divided into small fractions over several days, using modern intensity-modulated linear accelerators with integrated imaging systems (CT and/or PET) to locate mobile lesions during each treatment session without damaging adjacent structures. In various retrospective clinical studies on this topic, metastatic burden has been reported as 3 bone lesions or 5 lesions, where progression-free survival, OS improvement, and delaying androgen suppression therapy for up to 2 years (24) (25) (26) have been achieved; some of these studies have included patients with recurrences after primary radical treatment. In recent years, there have been reports from 3 randomized phase III clinical trials evaluating the effect of the initial combined treatment of adding docetaxel to androgen suppression therapy (AST) versus AST alone in patients with hormone-sensitive prostate cancer.The first multicenter GETUG AFU-15 study (27) included 385 randomized patients, with 192 receiving treatment with docetaxel and androgen suppression therapy (AST) and 193 receiving only AST for metastatic prostate cancer. The evaluation of the metastatic load was carried out using conventional imaging studies, bone scans, computed tomography, and/or magnetic resonance imaging. With a median follow-up of 50 months, the median overall survival was 58.9 months for the docetaxel group and 54.2 months for the AST-only group. Seventy-two serious events were reported in the docetaxel group (neutropenia) and 4 treatment-related deaths. Based on these results, the authors indicate that docetaxel should not be part of the first line of treatment for patients with metastatic hormone-sensitive cancer. The second CHAARTED clinical trial (7) focused on tumor volume in patients with metastatic prostate cancer and randomized participants to receive either docetaxel (6 cycles) and androgen suppression therapy or hormone therapy alone. The primary objective was to assess overall survival, and the secondary objective was to evaluate the treatment effect on patients with high and low tumor volume according to their classification mentioned earlier in this review. At a median follow-up of 53.7 months, the median overall survival was 57.6 months in the combined therapy group, versus 47.2 months in the hormone therapy alone group. For patients with a high volume of disease (543 patients), the median overall survival was 51.2 months with combined therapy versus 34.4 months with hormone therapy alone. In patients with low disease volume, no overall survival benefit was observed. The conclusions of this study were that the benefit of chemotherapy in extending overall survival was for patients with a high volume of disease, without evidence of benefit for those with a low volume.A recent meta-analysis of patient subgroups with high and low metastatic burden randomized to docetaxel and hormonal therapy versus hormonal therapy alone in these two studies (GETUG AFU 15 and CHAARTED) found no benefit for patients with low metastatic burden (according to CHAARTED criteria) compared to TSA alone. In both clinical trials, the early administration of docetaxel to hormonal therapy had a consistent effect on improving overall survival in patients with high burden, who, due to the disease itself, have a poor prognosis, and the toxicity of docetaxel could outweigh its benefit (28); many of these patients are of advanced age, with associated comorbidities and poor health performance. These results caused uncertainty since a high percentage, around 40% of patients with newly diagnosed oligometastatic prostate cancer are low burden and would not be eligible to receive combined treatment of docetaxel and hormonal therapy. In a recent analysis of the STAMPEDE study (29), the addition of docetaxel to hormonal therapy in patients with advanced prostate cancer with high and low metastatic burden was evaluated to assess long-term survival. A total of 1086 patients were included, randomized 2:1 to receive: 724 long-term androgen suppression therapy alone and 362 docetaxel (6 cycles) and hormonal therapy; clinical characteristics in both groups were well balanced; metastatic burden based on conventional imaging studies was recorded in 76% of patients (830/1086); of these 830, 362 patients (44%) had low metastatic burden and 468 (56%) had high burden (according to the CHAARTED criteria): In terms of tumor burden, out of 362 patients with low burden, 238 received hormone therapy alone, and 124 received treatment with docetaxel; out of the 468 with high burden, 320 received hormone therapy alone, and 148 received combined therapy. With a median follow-up of 78.2 months, 719 deaths were reported; 494 (68%) out of the 724 patients who received hormone therapy alone and 225 deaths (62%) out of the 362 patients who received docetaxel.

In the group of patients with hormone therapy alone, the median overall survival was 43.1 months, and the five-year estimate was 37%, while in patients who received docetaxel, the median overall survival was 59.1 months, and the five-year estimate was 49%. There was considered to be strong evidence of survival benefits in patients who received docetaxel. In the subgroup of patients with low metastatic burden (362), the median survival for the hormone therapy alone group was 76.7 months, with an estimated five-year survival of 57%, compared to a median of 93.2 months and an estimated five-year survival of 72% in the docetaxel group.In patients with high metastatic burden (468), the median survival in the control group was 35.2 months, and the five-year estimate was 24%, compared to 39.9 months and a five-year estimate of 34% in the docetaxel group. In conclusion, the authors believe that there was evidence of benefit in overall survival (OS) in patients who received docetaxel and androgen suppression therapy compared to those who only received hormone therapy. There was evidence of the benefit of docetaxel over only hormoal therapy by itself in the survival free of failure. Free of progression in the subgroups of metastasic burden.Based on these reports of docetaxel, new options for combined systemic treatment as a first-line therapy have expanded to include androgen deprivation therapy (ADT) with androgen receptor blockers (abiraterone,

enzalutamide, apalutamide) in the treatment of patients with hormone-sensitive oligometastatic prostate cancer. In an initial report from the multicenter, controlled LATITUDE (30) clinical trial, 1,199 patients were randomized 1:1 to receive androgen suppression therapy plus abiraterone acetate (1,000 mg in a single dose) plus 5 mg of prednisone (597 patients) versus androgen suppression therapy plus placebo (602 patients). All patients had high-risk metastatic hormone-sensitive prostate cancer, documented with conventional imaging studies, and were classified as having 2 of 3 risk factors: Gleason 8 or higher, at least 3 or more bone lesions, and the presence of measurable visceral metastases (LATITUDE criteria). The first interim analysis was performed after 406 deaths and with a median follow-up of 30.4 months; of the deaths, 169 occurred in the abiraterone group and 237 in the placebo group. The overall 3-year survival rate was 66% in the abiraterone group and 44% in the placebo group; the median progression-free survival was 33 months in the abiraterone group and 14.8 months in the placebo group; the relative risk of radiographic progression or death was 38% lower in the abiraterone group. The treatment effect of this drug was consistently favorable in almost all pre-specified subgroups (pain control, prostate-specific antigen, skeletal events).The higher frequency of adverse effects (high blood pressure, hypokalemia) was greater in this study than in previous clinical studies in patients with castration-resistant prostate cancer who were treated with 10 mg of prednisone and shorter exposure to abiraterone (31). The addition of abiraterone acetate and prednisone to androgen deprivation therapy significantly increases overall survival and radiographic progression-free survival in men with newly diagnosed hormone-sensitive metastatic prostate cancer.

According to the results of this LATITUDE study, the observed benefits were only in patients with a high metastatic burden. After this information, the STAMPEDE clinical study analyzed risk subgroups stratified according to the CHAARTED criterion in patients receiving abiraterone plus prednisone and androgen suppression therapy versus hormonal therapy alone (32). A total of 901 patients were selected, 428 with a low burden and 473 with a high burden. With the administration of combined systemic therapy from the beginning, a benefit was found in disease control and prolonging overall survival in all men with metastatic disease. No heterogeneous status effect was observed between the high and low metastatic burden subgroups for failure-free survival and overall survival.Two other randomized phase 3 clinical studies evaluated the effect of adrenergic receptor blockers combined with androgen suppression therapy versus placebo and androgen suppression therapy alone In patients with metastatic hormone-sensitive prostate cancer (mHSPC), the ENZAMET study (33) evaluates the effect of enzalutamide, and the TITAN clinical trial (34) assesses the effect of apalutamide. In both studies, some patients were receiving docetaxel or TSA, and in the TITAN study, some had undergone radical primary treatment with PR or RT (10%); in both studies, subgroups of tumoral volume were stratified. Benefits were observed in failure-free survival and overall survival in the combined therapy group versus placebo and androgen suppression therapy alone. In the ENZAMET study, the estimated 3-year overall survival was 80% in the patient group receiving enzalutamide compared to 72% in the placebo and hormonal therapy group. In the TITAN study, with a median follow-up of 24 months, the percentage of patients free of radiographic progression was 62.2% in the apalutamide group and 47.5% in the placebo group; overall survival was 82.4% versus 73.5%. Numerous clinical studies in the literature examine these three adrenergic receptor blockers in the treatment of patients with advanced hormone-sensitive and castration-resistant prostate cancer, showing their benefits in overall survival. Phase III clinical trials are currently underway to evaluate the benefit of a 3-regimen therapy combination. However, there is no high level of evidence to support the triple combination of androgen suppression therapy, an androgen receptor blocker, and primary treatment.It is interesting to know the opinion of the 2019 Consensus Conference (APCCC) experts regarding the management of oligometastatic hormone-sensitive prostate cancer with new diagnosis.79% indicated that conventional imaging studies are not sufficient to define oligometastatic disease for treatment planning.

To consider when prostate cancer is oligometastatic, 48% voted for a cutoff of 3 or fewer metastases, 41% for 5 or fewer, and 11% for any number that can be treated with an ablative attempt.For patients with oligometastatic prostate cancer who have not received primary treatment, detected with conventional imaging studies or next-generation molecular studies, 53% of experts voted for TSA, primary treatment, and focal treatment of lesions; 42% for TSA and primary treatment only.92% considered it important for treatment planning to distinguish disease that only affects the lymph nodes (M1a) from metastatic disease in other sites.

98% agreed that local primary treatment in patients with low volume or tumor burden has a benefit in overall survival. 84% considered radiotherapy as the local treatment, and 16% for prostatectomy; 75% believed that regional pelvic nodes with cN1 disease should also be included in the radiation field.Based on the results with radiotherapy in patients with low tumor burden, 88% of panelists voted that it is not appropriate to extrapolate this result to radical prostatectomy. If the benefit of radiotherapy is mediated by the eradication of the primary tumor, it is expected that surgery would be at least equally effective; however, radiotherapy appears to be more effective through a mechanism of immune system modulation, which would not occur with surgery; the role of surgery remains undemonstrated.Regarding which treatment to add to androgen deprivation therapy (ADT) in patients with low volume or low metastatic burden, without symptoms of the primary tumor, 54% voted for a receptor antagonist (RA) blocker, plus treatment of the primary tumor; 13% for docetaxel plus local treatment of the primary tumor. Regarding which treatment to add to ADT in newly diagnosed patients with low volume or low metastatic burden who have relapsed after radical treatment of the primary tumor, 59% voted for an RA blocker, 4% for docetaxel as the only therapy, 7% for ADT only, and 30% for any of these drugs.In patients with oligometastatic disease with high volume or high tumor burden, without symptoms of the primary tumor, in addition to ADT, 56% agreed to add docetaxel or an RA blocker, 24% for an RA blocker, 16% for docetaxel, and none for ADT only.In patients with high volume or high tumor burden oligometastatic disease who have relapsed after radical treatment of the primary tumor, the vote was to add to ADT 58% for docetaxel or an RA blocker, 26% for an RA blocker, and 8% for docetaxel.Regarding the use of the combination of docetaxel and an RA blocker, in addition to ADT, 81% voted against this combination, 8% agreed, and 11% voted for their sequential use.Regarding which RA blocker they would recommend adding to ADT for most newly diagnosed patients with M1 disease, 37% voted for abiraterone, 11% for either enzalutamide or apalutamide, and 52% had no preference.

Conclusions:

Although there is no general consensus in all of these assessments, there is majority approval in some concepts based on the reports of randomized clinical trials and others already mentioned, which can be summarized:In men with newly diagnosed, hormone-sensitive advanced and high-risk CaP (prostate cancer), new imaging techniques should be performed, depending on availability and possibility, to stage and detect the disease at an early stage

when only lymph node involvement (cN1) or low burden oligometastatic disease is present.In patients with cN1 disease, primary treatment in favor of extended radiation therapy to regional lymph nodes, concomitantly with long-term androgen suppression therapy (24 months), is the most appropriate therapy.

Radical prostatectomy with extensive lymphadenectomy, for local disease control and more accurate staging, is controversial.

In men with low-burden oligometastatic CaP (3 or fewer lesions), the most recommended treatment is locoregional radiation therapy and lesion-targeted therapy, combined with long-term hormonal therapy.Radical prostatectomy should not be considered as a first step in the multimodal treatment of this disease.In men with high-burden oligometastatic CaP, first-line therapy would be combined systemic treatment, with androgen suppression therapy and one of the androgen receptor blockers, relegating docetaxel to subsequent support if the patient's general condition allows.Finally, it is important to note that as the treatment of advanced CaP continues to evolve rapidly, urologists should stay up-to-date on the diagnostic and treatment options for these patients; and, if possible, use advanced technology to detect the disease at an earlier stage, that may allow for more effective management.

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