Chapter 05 / Capítulo 05

Advanced Prostate Adenocarcinoma and Androgen Deprivation Therapy. Clinical Outcomes, Risk Stratification, and Therapeutic Results
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Study results

Age distribution and risk classification

The distribution of patients by age group clearly showed a pattern of concentration in older age groups. The largest proportion of the cohort was in the over70 years of age group, which was the most represented age segment in the analyzed group.

When the risk classification was examined simultaneously, this age predominance remained consistent both in patients categorized as high risk and in those classified within the very high-risk group. In both cases, individuals over 70 years of age represented more than half of the patients included in each category.

The younger age groups showed considerably lower participation. The 50–59 years age group accounted for a small fraction of the total cases, whereas patients between 60 and 70 years of age were moderately represented, although not to the same extent as the older age group.

From a clinical perspective, this distribution is consistent with the epidemiological behavior of prostate adenocarcinoma, whose incidence increases progressively with age. The accumulation of cases in advanced stages of life can be linked both to the natural history of the disease and to diagnostic detection patterns.

Similarly, the high proportion of high- and very high-risk patients in the older age groups suggests a possible association between age at diagnosis and clinical aggressiveness. This finding reinforces the importance of timely detection strategies, systematic follow-up, and adequate risk stratification in aging populations.

Table 5.1. Distribution of patients according to age group and risk classification

Age	High		Very High		Total
	No	%	No	%	
50 to 54 years old	1	3	1	3	2
55 to 59 years old	3	9	4	9	7
60 to 65 years old	5	15	5	12	10
66 to 70 years old	4	12	7	18	11
>70 years old	20	61	23	58	43
Total	33	100	40	100	73

Adherence to treatment throughout the observation period

The analysis of therapeutic adherence showed variations throughout the different time points considered within the observation period. In general, most patients adhered to the indicated treatment, suggesting sustained acceptance of the total androgen deprivation strategy within the analyzed cohort.

However, when the distribution according to the different time points of follow-up was examined, relevant differences emerged. The late intermediate phase had the highest frequency of nonadherent cases, representing the interval in which this condition reached its highest expression. This behavior contrasted with that observed at the beginning of the period and in the early intermediate phase, stages in which adherence was the clearly predominant pattern.

During the beginning of the period, episodes of interruption or noncompliance with therapy were recorded in a reduced proportion, reflecting relative stability in treatment continuity. Similarly, in the early intermediate phase, adherence remained predominant, suggesting initial consolidation of the therapeutic regimen within the healthcare dynamic.

In the late intermediate phase, however, there was a noticeable increase in nonadherence. This variation could be linked to multiple clinical and contextual factors, including the cumulative onset of adverse effects, changes in the subjective perception of therapeutic benefit, difficulties in accessing medication, or changes in patients' personal and social circumstances.

Toward the end of the period, although cases of nonadherence persisted, their magnitude was lower than that recorded in the late intermediate phase. This behavior suggests a partial reduction in the variability observed previously, although without fully returning to the levels of adherence predominant in the initial stages.

From a clinical perspective, these fluctuations underscore the dynamic nature of therapeutic adherence in prolonged hormone treatments. The continuity of total androgen blockade does not depend exclusively on medical indications but also on individual tolerance, the subjective experience of treatment, and sustained interaction between the patient and the healthcare system.

Likewise, the identification of a phase with a higher frequency of nonadherence invites consideration of the possible influence of organizational, care, or psychosocial factors that may have affected this behavior. Adherence, especially in the context of chronic oncological diseases, is an essential component not only of therapeutic effectiveness but also of patient evolutionary stability.

Finally, nonadherence should not be interpreted solely as isolated individual behavior. It often reflects complex interactions between treatment characteristics, clinical conditions, perceptions of side effects, institutional support, and patients' life circumstances.

Therapeutic adherence according to time during the observation period

The distribution of treatment adherence varied among the different time points considered within the observation period. In general, adherence remained the predominant pattern at all stages of follow-up, although there were noticeable differences in the magnitude of nonadherence.

Table 5.2. Distribution of patients according to treatment adherence

Time of the period	Adherence	Nonadherence	Total
Start of period	16	1	17
Early intermediate stage	19	2	21
Late intermediate stage	14	7	21
End of period	10	4	14

During the beginning of the period, cases of nonadherence were rare, suggesting initial stability in treatment continuity. In the early intermediate phase, this behavior continued, with only a small proportion of patients interrupting or not adequately complying with the therapeutic regimen.

The late intermediate phase had the highest frequency of nonadherence, representing the moment of greatest variability within the series analyzed. At this stage, the highest number of patients who did not maintain therapeutic continuity was observed, suggesting the possible influence of clinical, pharmacological, or contextual factors that could have affected adherence.

Toward the end of the period, although episodes of nonadherence persisted, their frequency was lower than that recorded in the late intermediate phase. This behavior indicates a partial reduction in the variability observed previously, without fully reaching the levels of stability present in the initial stages.

From a clinical perspective, these fluctuations reinforce the dynamic nature of adherence to prolonged hormone treatments. The continuity of total androgen blockade may be influenced by the appearance of adverse effects, the subjective perception of benefit, individual tolerance to treatment, and conditions of access and follow-up care.

Clinical evolution according to initial risk classification

Analysis of the evolution of patients toward high-risk categories allowed us to identify relevant differences on the basis of initial stratification. The observed distribution revealed that progression toward more clinically aggressive states did not occur uniformly across the different risk groups.

Patients initially classified in the unfavorable intermediate-risk group constituted the segment with the highest proportion of progression to high risk. This pattern suggests that, within this category, the disease showed a greater tendency to present signs of progression or clinical restratification during follow-up.

Similarly, although to a lesser extent, individuals belonging to the favorable intermediate-risk group also showed a significant proportion of progression to higher-risk categories. This finding is of particular clinical interest, as it highlights that even within classifications considered relatively more stable, less favorable evolutionary trajectories can be recorded.

In contrast, patients in the low- and very low-risk groups presented the lowest frequencies of progression to high risk. This behavior suggests greater clinical stability within these categories, which is consistent with the prognostic profile generally associated with these classifications.

From an analytical perspective, the difference observed between the favorable and unfavorable intermediate groups reinforces the relevance of substratification within intermediate risk. This group, which is far from constituting a uniform category, brings together patients with potentially divergent trajectories, underscoring the need for differentiated clinical surveillance.

The progression to high risk not only implies a change in prognostic categorization but also may translate into modifications in therapeutic strategy, follow-up intensity, and the evaluation of progression markers. In this context, the identification of transition patterns has both clinical and organizational value.

Furthermore, these results invite reflection on the biological dynamics of advanced prostate adenocarcinoma. Disease progression may involve multiple mechanisms, including variations in hormonal sensitivity, tumor heterogeneity, the emergence of resistant clones, and individual host factors.

Finally, the lower proportion of progression observed in the low- and very low-risk groups does not exclude the possibility of progression but suggests more stable trajectories within the period analyzed. This finding reaffirms the importance of initial risk classification as a fundamental tool in predicting progression and planning clinical management.

Table 5.3. Distribution of patients according to progression to high risk by risk classification

Risk	No	High risk	%
Very low	57	10	13,7
Low	31	9	12,3
Favorable intermediate	33	12	16,4
Unfavorable intermediate	40	22	30,1
Subtotal	161	53	72,6
Total High Risk		73	

Clinical progression and time of onset of manifestations

Analysis of the relationship between treatment time and clinical signs associated with disease progression revealed distinct patterns in the presentation of complications.

Table 5.4. Correlation between signs of progression and time of onset

Treatment time	Bone metastases		Lymphadenopathy		Renal failure		Total
	No	%	No	%	No	%	
1 year	9	39,1	4	17,4	0	0,0	23
2 years	8	40,0	3	15,0	2	10,0	20
3 years	19	76,0	3	12,0	0	0,0	25
Total	36	49,3	10	13,7	2	2,7	73

Bone metastases were the most frequent manifestation of clinical progression within the evaluated cohort. Approximately half of the patients developed bone involvement during follow-up, confirming the predominant role of the skeleton as a common site of progression in advanced prostate adenocarcinoma.

When the time of onset was examined, the highest proportion of bone metastases was recorded in patients with longer treatment times. This behavior suggests a progressive accumulation of the risk of bone dissemination as the clinical course of the disease under total androgen deprivation is prolonged.

Lymphadenopathy, although present in a relatively small proportion of patients, represents another relevant form of progression. Its distribution was relatively stable between the different treatment intervals, without evidence of a pattern of concentration as marked as that observed in bone metastases.

Renal failure occurred in a small number of patients. This low frequency suggests that, within the group analyzed, renal involvement associated with tumor progression was a less common event. However, its clinical relevance is significant because of its potential impact on prognosis, quality of life, and the complexity of therapeutic management.

From a clinical perspective, these findings reflect the heterogeneity in the evolutionary

trajectories of advanced prostate adenocarcinoma. Progression does not manifest uniformly but rather takes on diverse clinical expressions that are influenced by biological factors, tumor characteristics, response to hormonal treatment, and individual patient conditions.

The predominance of bone metastases as the main sign of progression reaffirms the importance of systematic monitoring of skeletal involvement during follow-up. Timely detection of this manifestation is essential for adjusting therapeutic strategies, preventing related skeletal events, and optimizing symptom control.

Likewise, the appearance of adenopathy and, to a lesser extent, renal failure underscore the need for a comprehensive evaluation that considers both locoregional progression and possible systemic complications.

Time of onset of hormone resistance

Analysis of the timing of hormone resistance revealed different patterns depending on the duration of treatment and the biochemical markers evaluated. The transition to hormone escape states was not uniform but showed significant variations between the different follow-up intervals.

In the earliest phases of treatment, particularly during the first few months, the identification of signs compatible with hormone resistance was limited. Elevated prostate-specific antigen (PSA) levels were detected in a small number of patients, whereas no significant increases in testosterone levels were detected.

As the treatment time increased, a progressive increase in the frequency of biochemical alterations was observed. During the first year of follow-up, elevated PSA emerged as the predominant finding, suggesting residual tumor activity or disease reactivation in a considerable group of patients.

At later intervals, the distribution of the markers substantially changed. Elevated testosterone became more relevant in patients with longer treatment durations, reaching its maximum expression in those with longer treatment durations. This behavior suggests an association between the duration of androgen blockade and the appearance of hormonal escape mechanisms.

The predominance of elevated testosterone in later stages reinforces its role as a critical parameter in identifying hormone resistance. The recovery or increase in serum testosterone levels may reflect a loss of effective androgen suppression, a phenomenon closely linked to the biological progression of the tumor.

PSA elevation, which is observed more frequently in intermediate phases of treatment, is an early indicator of possible tumor reactivation. Its dynamic behavior during follow-up allows changes in disease activity to be detected before the onset of obvious clinical manifestations.

From a clinical perspective, these findings underscore the importance of joint monitoring of PSA and testosterone in patients undergoing total androgen deprivation. The integrated interpretation of both markers allows for a more accurate assessment of therapeutic response and detection of hormonal escape states.

Likewise, the variability in the timing of hormone resistance onset reflects the biological complexity of advanced prostate adenocarcinoma. Intrinsic tumor factors, cellular heterogeneity, clonal adaptation, and differential sensitivity to hormone suppression may contribute to explaining these evolutionary trajectories.

Table 5.5. Distribution of patients according to the timing of hormone resistance onset

Treatment time	PSA elevation		Elevation of testosterone		Total
	No	%	No	%	
6 months	5	10,0	0	0,0	5
1 year	10	52,6	9	47,4	19
2 years	7	46,7	8	53,3	15
3 years	3	13,6	19	86,4	22
Total	25	41,0	36	59,0	61

Behavior of the metastatic lesions

Analysis of the behavior of the metastatic lesions allowed us to characterize the clinical evolution of patients who presented with bone involvement during follow-up. Within this group, a significant proportion of patients received treatment with zoledronic acid as part of the therapeutic strategy aimed at controlling skeletal complications.

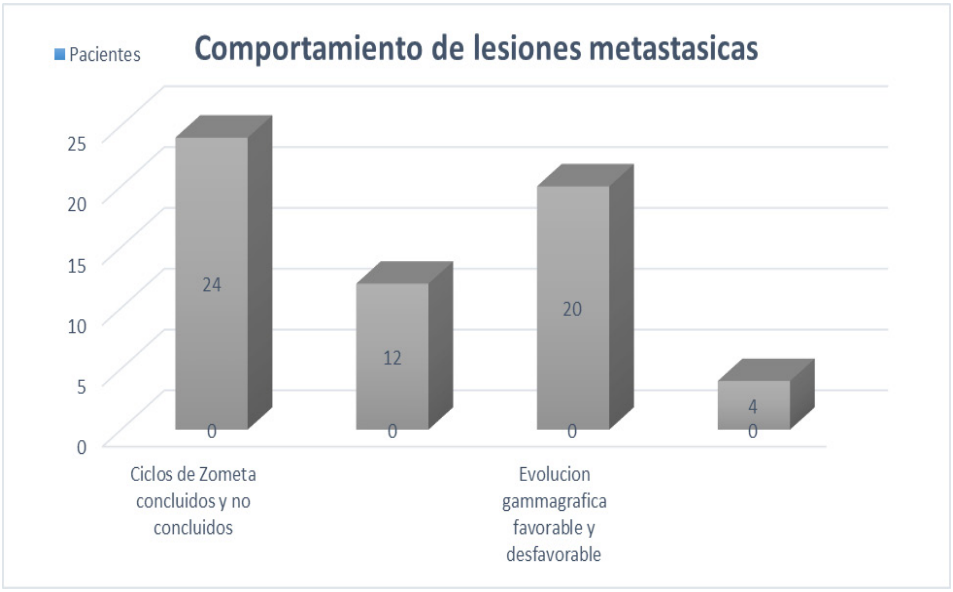

Figure 5.1. Distribution of patients according to metastatic lesions

The distribution revealed that most patients who started treatment with zoledronic acid were able to complete it, suggesting adequate tolerability and therapeutic continuity in a considerable number of cases. This finding is relevant in the context of the management of advanced prostate adenocarcinoma, where adherence to complementary therapies is crucial for the prevention of related bone events.

Scintigraphic follow-up allowed for the evaluation of the structural response of the metastatic lesions. In a significant proportion of patients, improvements in previously identified alterations were observed, suggesting a favorable effect of the therapeutic approach on skeletal disease activity.

However, the evolution was not uniform in all the cases. The coexistence of favorable and unfavorable trajectories reflects the biological complexity of metastatic disease, as well as the influence of individual factors, tumor burden, hormonal response, and the characteristics of systemic treatment.

From a clinical perspective, the scintigraphic improvement observed in a group of patients supports the relevance of using antiresorptive agents in the comprehensive management of advanced prostate cancer with bone involvement. Stabilization or reduction of metastatic activity can translate into functional benefits, pain reduction, and better control of skeletal complications.

Likewise, the need to complete therapeutic cycles highlights the importance of systematic follow-up, evaluation of adverse effects, and adherence to treatment as central components of clinical effectiveness.

Impact of androgen deprivation on health status

The evaluation of the clinical impact associated with androgen deprivation revealed a variety of manifestations perceived by patients during treatment. The distribution of the events described showed that alterations in sexual function were the most frequent expression within the cohort analyzed.

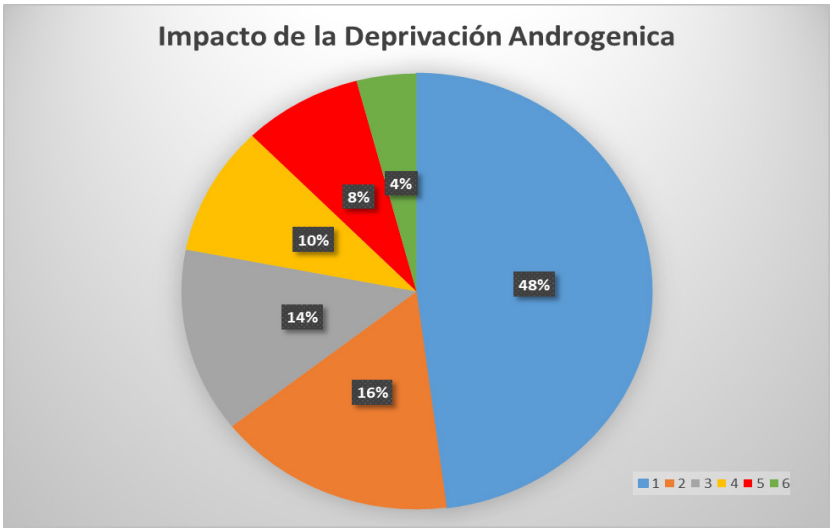

Figure 5.2. Impact of androgen deprivation on health status
Note: 1. Sexual dysfunction 2. Gynecomastia 3. Mastodynia; 4. flashes 5. Bone pain; 6. Hepatotoxicity

Sexual dysfunction emerged as the predominant adverse effect, accounting for the highest proportion of responses. This finding is consistent with the mechanism of action of androgen blockade, whose interference with testosterone production and activity directly affects erectile

function, libido, and the overall sexual response.

To a lesser extent, patients reported vasomotor symptoms, particularly hot flashes, a widely recognized manifestation in the context of hormonal suppression. Although their frequency was lower than that of sexual dysfunction, their subjective impact can be significant because of their recurrent nature and potential interference with daily well-being.

Other events, such as gynecomastia and mastodynia, have also been reported, reflecting alterations related to the hormonal imbalance induced by therapy. These manifestations, even when they occur in a smaller proportion of patients, can cause physical discomfort and psychological repercussions in certain patients.

Bone pain was reported in a small fraction of the sample. This symptom may be linked to both the systemic effects of treatment and the natural progression of the disease, particularly in patients with skeletal metastatic involvement.

Hepatotoxicity, identified in a limited number of cases, was the least frequent manifestation. Despite its low relative incidence, its clinical relevance is considerable, as it may require therapeutic adjustments, modifications to the pharmacological regimen, or specialized follow-up interventions.

From a comprehensive clinical perspective, these findings underscore that androgen deprivation, although essential in the control of advanced prostate adenocarcinoma, is associated with adverse effects that transcend the strictly oncological dimension. The patient's therapeutic experience involves physical, functional, and psychosocial components that require systematic evaluation.

Similarly, the high frequency of sexual dysfunction highlights the need to incorporate clinical support strategies, therapeutic guidance, and an interdisciplinary approach focused on quality of life.

Partial conclusions of the chapter

The findings presented in this chapter allow us to perform a comprehensive characterization of the clinical and evolutionary behavior of patients diagnosed with advanced prostate adenocarcinoma who are undergoing total androgen deprivation.

The age distribution clearly revealed a predominance of older patients, a pattern consistent with the known epidemiology of the disease. This concentration in older age groups not only reflects demographic trends but also introduces relevant clinical considerations in terms of comorbidities, therapeutic tolerance, and functional vulnerability.

Analysis of therapeutic adherence revealed that although treatment continuity remained the predominant behavior, there were fluctuations between different points in the observation period. The identification of a phase with increased nonadherence underscores the dynamic nature of this phenomenon and its possible link to clinical factors, adverse effects, the subjective perception of treatment, and contextual conditions.

In relation to clinical progression, bone metastases have emerged as the most frequent manifestation of disease progression. This finding reaffirms the central role of skeletal

involvement in the natural history of advanced prostate adenocarcinoma and highlights the importance of therapeutic strategies aimed at its control and monitoring.

The evaluation of the timing of hormone resistance revealed different patterns among the biochemical markers analyzed. Elevated PSA was more frequently observed in the intermediate stages of follow-up, whereas elevated testosterone became more prominent in the later stages of treatment. This behavior reflects the biological complexity of hormonal escape and the need for integrated monitoring of both indicators.

The clinical impact associated with androgen deprivation revealed that sexual dysfunction was the most frequently reported manifestation among patients. This result highlights that, along with oncological control, the therapeutic experience involves functional and psychosocial dimensions that directly affect quality of life.

Taken together, the findings described here reveal that the evolution of advanced prostate adenocarcinoma under total androgen blockade is a heterogeneous process influenced by complex interactions between clinical, biochemical, and therapeutic variables. This heterogeneity requires individualized follow-up approaches, systematic evaluation of progression markers, and clinical care that integrates both the biological dimension of the disease and the patient's experience.

The analysis developed in this chapter thus lays the groundwork for the critical interpretation of the results, addressed in subsequent chapters, which delve into the clinical, therapeutic, and healthcare implications derived from these findings.