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EDITORIAL

Castrate resistant prostate cancer. Consensus recommendations of the Spanish Association of Urology☆

Cáncer de próstata resistente a la castración. Recomendaciones de consenso de la Asociación Española de Urología

Prostate cancer is the most prevalent cancer in men and the second leading cause of oncologic death, despite the opportunistic screening conducted and an increasingly frequent diagnosis in the early stages of the disease.

Patients with advanced prostate carcinoma mostly undergo androgenic suppression. With this hormonal treatment, temporary remissions are achieved with a mean response of 2–3 years, depending on the tumor burden and the biological profile of the tumor.

When the treatment ceases to be effective, it reaches the so-called castration-resistant phase (CRPC). Because there are many controversies and unanswered questions, members of the Spanish Association of Urology with experience in this field have met to create a document regarding the definition of castration-resistant patients to approximate some treatment and follow-up recommendations depending on the characteristics of the disease and creating patient profiles for it.

This document has also been embodied in a computer application that enables updates when they occur.

Scientific evidence from different clinical practice guidelines (National Comprehensive Cancer Network,[1] European Association of Urology[2] and American Urological Association[3]), as well as the most relevant publications on the diagnosis, treatment and follow-up of these patients, has been reviewed.

Definition

Testosterone levels below 50 ng/dl or 17 nmol/l and also: three consecutive PSA elevations, separated by at least one week, with two increments of 50% on the PSA nadir, and provided that it is greater than 2 ng/ml, or progression of bone lesions $\geq$2 in bone scan or progression of soft tissue lesions according to the criteria of response assessment in solid tumors (RECIST).

The exclusive symptomatic progression is not enough at present to label the patient as resistant to castration.

Initial evaluation recommendations in castration-resistant prostate cancer

We must consider two different scenarios, the patient without metastasis (M0) and the patient who at this stage of the disease has metastasis (M1) (Fig. 1).

Patients without objective metastatic disease

There is no consensus to define the moment of performing the initial imaging study, or the optimal method of choice, or follow-up recommendations.

Bone scan (BS) is still considered the diagnostic standard for the detection of bone metastases, although axial or whole-body MRI provides greater sensitivity and specificity, and choline PET/CT the highest diagnostic specificity in early stages of the disease.[4]

Neither are specific recommendations for the detection of lymph node or visceral metastases made. Baseline PSA, PSA velocity, and PSA doubling time (PSADT) are

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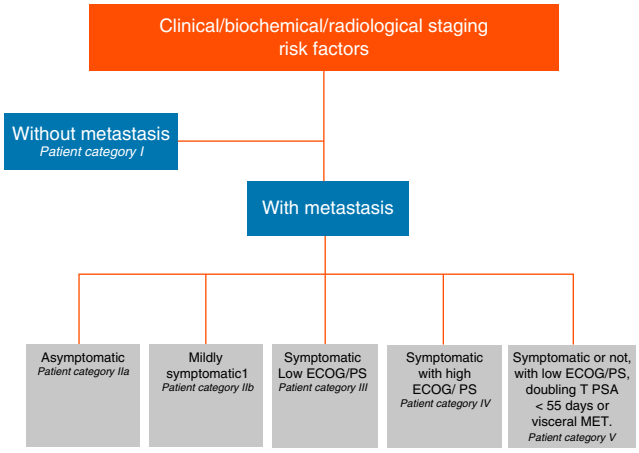

Figure 1 Patient profiles. Patient categories are defined based on stage and risk factors. ECOG: scale of the *Eastern Cooperative Oncology Group*; MET: metastasis; PS: Karnofsky Index; PSA: prostate-specific antigen. [1]It does not require opioid drugs.

Source: Based on patient categories. Modified from AUA Guideline.[3]

significantly correlated with the time to the first metastasis and metastasis-free survival. Several studies (Enthuse[5] and IMAAGEN[6]) show a percentage of bone involvement not demonstrated in the conventional study higher than 30% in theoretical M0 patients. Additionally, 33% of M0 patients will develop metastases within the next 2 years. Baseline PSA > 8 ng/ml and a PSADT < 10 m have been set as the two main predictors of bone metastasis development.

Our recommendation is to perform extension study with abdominopelvic CT scan and BS at initial diagnosis of CRPC, in order to define the baseline situation of the disease.

Patients with metastatic disease

In M1 patients, further evaluations will depend on the patient's symptoms that may condition targeted extension studies.

Follow-up recommendations

Metastases may have three defined patterns with significantly different prognosis and management:

- Exclusive lymph node involvement.
- Bone involvement, with or without simultaneous lymph node involvement.
- Visceral involvement, regardless of any of the above.

There is no consensus on the optimal follow-up scheme. This will depend on factors such as the treatment applied, the patient's symptomatology, his health status, tumor extension, predominant involvement, and PSA kinetics.

According to the recommendations of the prostate cancer working group 2[7] and 3[8] for patients in a clinical trial, the PSA determination and imaging studies should be performed every 12 weeks. In usual clinical practice, the factors mentioned can condition the periodicity and the type of follow-up. Anamnesis and physical examination, biomarkers, and imaging tests are the axis of the follow-up at this stage of the disease.

Clinical signs and symptoms

All the changes in symptoms, including the determination of signs such as blood pressure, weight, presence of edema, or any other that shows the occurrence of characteristic side effects of the disease or the treatment used should be recorded.

Specific questionnaires should be used to assess the presence and characteristics of pain, as it should be considered an independent progression criterion; that is, an increase in pain attributed to the 3-point tumor is a sign of progression, regardless of the radiological findings. In addition, its prognostic influence is known. The best known are the Brief Pain Inventory,[9] the Visual Analog Scale, or quantifying the pain based on the analgesics needed.

It is also essential to take into account the general health/activity status of the patient, using the scale of the Eastern Cooperative Oncology Group or the Karnofsky Index.

Biomarkers

Each review should include a complete analysis with biochemistry and blood count. PSA control and its kinetics, as a prognostic and progression marker. In addition, determination of testosterone, LDH, calcium, renal profile with electrolytes, liver profile, and bone markers such as alkaline phosphatase is mandatory.[10]

It will serve to evaluate the therapeutic response, adverse effects of the treatments, or progression of the disease.

Imaging tests

In M0 patients, as mentioned, the PSADT is the main predictor of the occurrence of bone metastases.[11] In patients with a PSADT < 6 months, given the risk of progression, it is recommended to perform BS every 3–6 months. In patients with PSADT > 6 months, the BS can be performed every 6–12 months.

In patients with M1 disease, restaging with imaging tests is recommended to be performed every 12 weeks for disease evaluation and control of the therapeutic response. Additional imaging scans will be performed based on the patient's symptoms.

Other imaging modalities, such as directed simple Rx, bone CT, MRI and PET/CT may be useful to clarify equivocal lesions in BS (Fig. 2).

Assessment of progression

The progression criteria are:

- Increased pain related to the tumor according to the Brief Questionnaire of Pain (>3 points), on the Visual Analog