Treatment of metastatic prostate cancer

Stage $T_{2-4} \, N_+ \, (N_1, \, M_{1a})$

- $T_{2-4} \, M_{1a}$
  - $T_4N_1$
  - Hormonal therapy

- $T_{2-3} \, N_1$
  - Radical prostatectomy + lymph node dissection (selected cases)
  - RT (3D or IMRT with IGRT*) + HT** (24-36 months)

Stage $T_{2-4} \, N_xM_{1b,c}$

- Hormonal therapy

* IGRT: image-guided radiation therapy for doses >78 Gy
** HT: neoadjuvant, concomitant, and adjuvant hormonal therapy
Radiotherapy
External radiation therapy (RT) is an option with few indications in the treatment of metastatic prostate cancer.

- **Indications:**
  - *Bone metastases: local palliative RT for pain control.* Doses of 800 cGy in one fraction are as effective as 3000 cGy in 10 fractions, except in vertebral metastases.

- **Results:** the biochemical relapse-free survival rate (stage pN<sub>1</sub>M<sub>0</sub>) at 5 years is 54%; after 9 years of follow-up it is 10%.

Hormone therapy (HT)
- **Basis of hormone therapy:** prostate cells depend on androgens for growth, function, and proliferation. The two main sources are the testes (90-95% of circulating androgens) and the adrenal gland (5-10%). If prostate cells are deprived of this stimulus, apoptosis occurs.
- **Castration levels:** the standard level of castration has typically been 50 ng/dL. Currently, <20 ng/dL is considered to be a more appropriate level, given that the average testosterone level after castration is 15 ng/mL.
- **Types of hormonal suppression:** androgen deprivation can be achieved in two ways:
  - *Suppression of testicular androgen:* surgically or through drugs.
  - *Inhibition of the activity of circulating androgens:* at the receptor level in prostatic cells (antiandrogens).
- **Indications for castration (subalbugineal orchiectomy or LHRH analogs):**
  - *Symptomatic metastases (M<sub>1</sub>):* treatment of symptoms and reduction of the likelihood of disease-related events (spinal cord compression, pathological fractures, ureteral obstruction, extraskeletal metastasis).
  - *Asymptomatic metastases (M<sub>1</sub>):* early initiation of HT delays the progression of metastasis to the symptomatic phase and prevents complications related to disease progression.
  - *Lymph node metastasis (N<sub>1</sub>) after radical surgery:* use of HT in these cases extends biochemical progression-free and overall survival. Its indication in cases of micrometastases after extensive lymphadenectomy is more questionable.
  - *High-risk localized tumors:* indicated in combination with long-term RT (24-36 months).
  - *Intermediate-risk localized tumors:* indicated in cases treated with short-term (6 months) low-dose RT (<75 Gy). For higher RT doses (>75 Gy), adjuvant HT is questionable.
  - *Locally advanced tumors:* indicated in combination with long-term RT (24-36 months).
- **Indications for antiandrogen treatment:**
  - *Short-term administration:* indicated in combination with LHRH analogs to reduce flare ups.
  - *Monotherapy:* as an alternative to castration in patients with locally advanced tumors (T<sub>3-4</sub>, N<sub>any</sub>, M<sub>any</sub>). Not indicated in localized disease, in combination with RT, nor as an adjuvant to surgical treatment.
- **Types of hormone therapy:**
  - *Bilateral subalbugineal orchiectomy:* suppresses the testicular source of testosterone. It is the fastest method of hormonal suppression (12 h). Causes loss of libido, impotence, hot flashes, and fatigue. Among its long-term effects, the most notable are its psychological effects, osteoporosis, anemia, and even cognitive impairment. Does not allow for intermittent treatment.
  - *Estrogens: diethylstilbene diphosphate or fosfestrol disodium (HONVAN®) and polyestradiol phosphate (PEP):* estrogen treatment reduces the secretion of LHRH by the hypothalamus through negative feedback, inactivates androgens, directly suppresses Leydig cell function, and produces direct toxicity to the prostatic epithelium. Its cardiovascular and thromboembolic morbidity are both noteworthy. It is contraindicated in
cases of heart or liver failure. It is used less due to its severe side-effects (cardiotoxicity) and is currently not available in Spain.

- **LHRH antagonists**: these act directly and in competitive fashion with LHRH receptors, inhibiting their action. They induce a more rapid decrease of LH, FSH, and testosterone levels than LHRH agonists without causing flare ups. However, they are associated with severe secondary effects mediated by histamine. More studies are needed to demonstrate their long-term efficacy.
  - **Abarelix**: approved by the FDA for the treatment of metastatic and symptomatic PC in which no other treatment option is feasible.
  - **Degarelix**: drug with monthly, subcutaneous administration, with initial doses of 250 mg and then monthly doses of 80 mg. Its efficacy is similar to that of analogs at 3 months and after 1 year of follow-up in phase II trials. Its main side-effect is pain at the site of injection (40% of cases).

- **LHRH agonists**: synthetic analogs of LHRH released in depot preparations (1, 2, 3, or 6 months). Their initial effect is to stimulate the LHRH receptors in the pituitary gland, producing a transient increase in the release of FSH and LH. This results in an initial increase in testosterone levels (the flare up phenomenon) 2-3 days after the first injection and lasting for about the first week of treatment. Concomitant administration of antiandrogens reduces the likelihood of flare ups if administered one week prior to the initiation of treatment and maintained for 2 weeks. Chronic exposure to agonists causes a dysregulation of LHRH receptors, suppressing the production of LH, FSH, and testosterone. Target castration effects are reached after 2-4 weeks. All agonists are equally effective regardless of composition.
  - **Leuprolide acetate** (PROCRIN DEPOT®): monthly administration of 3.75 mg in a single intramuscular injection. Also available: leuprolide acetate administered every 3 months in 11.25 mg doses (PROCRIN®) or every 6 months in 30 mg doses (PROCRIN®).
  - **Triptorelin** (DECAPEPTYL DEPOT®): monthly intramuscular administration (DECAPEPTYL® 3.75 mg). Also available: triptorelin administered every 3 (DECAPEPTYL DEPOT® 11.25 mg) or 6 months (DECAPEPTYL DEPOT® 22.5 mg).
  - **Goserelin acetate** (ZOLADEX IMPLANT® 3.6): subcutaneous monthly administration. Also available: Goserelin acetate administered every 3 months (ZOLADEX IMPLANT® 10.8 mg).
  - **Buserelin acetate**: subcutaneous administration every 2 (SUPREFACT DEPOT® 6.3 mg) or 3-month administration (SUPREFACT DEPOT® 9.45 mg).
  - **Leuprolide acetate**: 1-month depot (ELIGARD® 7.5 mg). Subcutaneous administration. Also available: Leuprolide acetate 3-month depot (ELIGARD® 22.5 mg) or 6-month depot (ELIGARD® 45 mg).

- **Antiandrogens**: these act on androgen receptors to block the effects of androgens. They can be used alone or as a component of a maximum androgen blockade. There are 2 types:
  - **Steroidal drugs**: Cyproterone acetate (CIPROTERONE ACETATE GENERICS 50 mg®): one 50 mg tablet twice a day. When a satisfactory result has been achieved, the therapeutic effect can be maintained with lower doses (50 or 25 mg/day for various weeks). They have a progestogenic effect and also suppress the secretion of LH and the production of testosterone. Associated with the loss of libido and erectile dysfunction as well as hepatic and cardiac toxicity.
  - **Non-steroidal drugs**: these are pure antiandrogens that do not suppress the synthesis of testosterone, thus preserving potential interest in sexual activity and bone mineral density. Can cause gynecomastia and breast pain. These side-effects can be treated with antiestrogens (Tamoxifen), prophylactic breast RT, or mastectomy. Used alone, they tend to increase testosterone levels, but maintain them at physiological levels, providing a better quality of life than castration. Because they can cause hepatic toxicity, periodic control of transaminases is necessary. Non-steroidal drugs include Flutamide and Bicalutamide.
- **Flutamide** (FLUTAMIDE GENERICS 250 mg ®): 250 mg pills. Recommended dose: 250 mg / 8 h oa.

- **Bicalutamide** (BICALUTAMIDE ASTRAZENECA 50mg®): 50 mg pills taken as a single daily dose (50 mg/day). Better tolerated than Flutamide or Nilutamide with respect to diarrhea, hepatotoxicity, alcohol intolerance, and adapting to changes in light. Taken alone (1st line hormonal therapy) or as adjuvant therapy, the daily dose is 150 mg/day in one dose.

- **Indications for Bicalutamide** (BICALUTAMIDE ASTRAZENECA 150 mg®) as monotherapy: in patients with locally advanced tumors without metastases as an alternative to castration or in highly selected, well-informed patients with metastasis, but low PSA values. Not indicated in patients with localized PC or in combination with RT (absence of clinical data).

- **Inhibitors of adrenal androgen synthesis (2nd step of HT):**
  - **Ketoconazole** (KETOCONAZOL TABLET®): 200 mg pill/day oa taken with meals. Dosage can be increased to 400 mg/day.
  - **Aminoglutethimide** (ORIMETEN®): in 250 mg pills. Requires hospitalization for accurate dose adjustment. The initial dose is 250 mg/day oa, increased by 250 mg/day per week, adjusting the dose according to tolerance and without exceeding 1000 mg/day. Requires supplementary glucocorticoid therapy to compensate for the suppression of production e.g. 20 mg of Hydrocortisone (ORALSONE®) twice a day.
  - **Prednisone** (PREDNISONE SANDOZ 20 mg ®): 30 mg in a day. Dose must be adjusted accordingly.

- **Hormone treatment modalities:**
  - **Complete androgen blockade (CAB):** although castration reduces testosterone levels by more than 95%, intraprostatic androgen stimulation is maintained by the conversion of circulating adrenal androgens to dihydrotestosterone (DHT). The use of antiandrogens blocks this stimulation, reaching a complete or maximum androgen blockade (CAB). In patients with metastasis, CAB has shown a benefit in overall survival of only 5% in 5-year trials comparing CAB to castration. It is also associated with higher costs, more side-effects, and a lower quality of life.
  - **Minimum androgen blockade:** the combined treatment of a 5α-reductase inhibitor (dutasteride or finasteride) and a non-steroidal antiandrogen. Their joint action prevents the conversion of testosterone to DHT, which, together with a blockade of DHT receptors on the part of the antiandrogen, maintains circulating testosterone levels. A good option in patients for whom quality of life is a primary objective. However, this treatment should be considered experimental until there is more long-term data.
  - **Intermittent analog therapy:** seems to delay the appearance of androgen-independent cell clones. Its main benefit is the reduction of side-effects (protects bones and cognitive function and has a protective effect against metabolic syndrome) in off periods with significant cost reduction. Indicated in patients with metastases, locally advanced tumors, or with a biochemical relapse who are candidates for HT. An induction period no shorter than 6-9 months is recommended, to be interrupted empirically when PSA levels <4 ng/mL in metastatic disease or 0.5 ng/mL in cases of biochemical relapse. The blockade is resumed when PSA reaches 10-15 ng/mL in patients with metastases or 4 ng/mL in non-metastatic patients or when symptoms related to disease progression appear.
  - **Immediate or delayed hormone therapy:** in patients with advanced PC who are candidates for HT, immediate initiation of treatment has been shown to reduce both disease progression and the rate of complications related to it in comparison to patients receiving delayed treatment, although with no improvement in cancer-specific survival rates.

- **Side-effects of hormone therapy:**
  - **Erectile dysfunction and loss of libido.**
  - **Hot flashes:** appear within 3 months after the start of treatment with a significant effect on quality of life. Addition of low doses of estrogen decreases their frequency and intensity, but increases cardiac toxicity. The use of progesteronic antiandrogens (Cyproterone...
acetate) or the combination of an antidepressant (Sertraline) has proven to be useful in reducing this side effect.

- **Non-metastatic pathological fractures**: secondary to the reduction of bone density caused by HT. Regular exercise and Calcium supplements are recommended.
- **Obesity**: the expected increase in body mass fat is 10% from early stages of treatment.
- **Blood lipid levels**: the increase in blood lipids occurs during the initial 3 months and is maintained throughout the treatment period. Physical exercise is recommended.
- **Metabolic syndrome**: the two most important factors in its appearance are the association of independent cardiovascular risk factors and peripheral resistance to insulin, both produced by HT. This syndrome includes a hip circumference >102 cm, blood levels of triglycerides >1.7 mmol/L, BP >130/80 mm Hg, HDL cholesterol <1mmol/L, and glycemia >6.1 mmol/L.
- **Cardiovascular disease**: androgen deprivation is associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction. The best prevention is weight loss, increased exercise, quitting smoking, and healthy dietary habits.

- **Cost-effectiveness of hormone treatment options:**
  - **Treatment with best cost-effectiveness ratio**: for patients who accept it, bilateral subalbugineal orchiectomy is the most cost-effective option; it also provides the best survival rates adjusted for quality of life.
  - **Treatment with worst cost-effectiveness ratio**: CAB is the costliest option for the lowest quality of life benefit.
  - **Treatments with an acceptable cost-effectiveness ratio**: intermittent therapy and hormone therapy in patients with metastases when they become symptomatic.
Hormonal therapy introduction scheme

Hormonal therapy indications

5-ARI inhibitor

Anti-androgens alone or 5 ARI + anti-androgens

LHRH analogs

Complete androgen blockade