Germ Cell Testicular Tumors

Ignacio Duran, MD PhD
Servicio de Oncología Medica
Hospital Universitario Virgen del Rocío
Sevilla
Outline

• Testis Anatomy-Pathogenesis
• Epidemiology
• Diagnosis & Natural History
• Approaching the patient (treatment decision)
• Treatment by stage
• Summary & Conclusions
• Appendix
Testis and Testis Cancer

Cell types in the testis:

• Macrophages

• Myoid Cells: Muscle cells

90% of tumors that develop from the testis arise from the Germ Cells. So Testicular Cancer equivalent to Germ Cell Tumor development. Germ Cells: Cells that are going to mature and become spermatogonia, spermatocytes
Pathogenesis: A special disease

- Aberrant Chromatid exchange in early meiosis
- Cyclin D2
- Iso- chromosome 12


Epidemiology: A rare disease but...quite unique

- GCTs represent 1% of all cancers
- ≈8,000 new cases/year (US) (≈ 700 in Spain*)
- It is the most frequent neoplasm in young adults (15-35 y/o)
- Arrival of cisplatin, better surgical techniques and multidisciplinary work: CURABLE NEOPLASM
Diagnosis: Symptoms/Signs

• Testicular lump (painless)

• Symptoms mimicking infection

• Symptoms related to advanced disease
  – Dyspnea /Cough/ Hemoptysis
  – Lower Back Pain
Diagnosis: The med-onc patient

• When the patient arrives to the medical oncologist there is already an orchidectomy and a histological diagnosis

• The orchidectomy must be performed via inguinal

• In exceptional cases the orchidectomy might be postponed and systemic treatment started up front
Diagnosis: Key Point

- **Seminomas**
  - Around 45%
  - On average appear 10 y later [40s]
  - Tend to be big masses
  - 15% of them produce HGC
  - **NONE** of them produce AFP
  - Typically rise LDH
  - More radio sensitive

**Subtypes:**
- Classic Seminoma
- Atypical Seminoma
- Spermatocytic Seminoma*

![Classic Seminoma](image)

![Spermatocytic Sem](image)
Diagnosis: Key Points

• **Non-Seminomas**
  
  – More frequent (≈55%)
  
  – Younger patients[30]
  
  – **Any marker** (HGC,AFP,LDH)
  
  – Less Radio sensitivity
  
  – Chemotherapy and surgery

4 Types:

• **EC** (the most frequent)

• **Yolk Sac Tumor** (AFP)

• **Choriocarcinoma** (HGC)

• **Teratoma**
Overview: Natural History

Natural history ranges from local growth to lymph node spread and visceral disease (Lung, Liver, Bone, Brain, etc …)
Staging

- CT Chest-Abd-Pelvis
- CT brain (if visceral mets/very high markers or neurological sympt)
- PET CT **should NOT** be used routinely
- **Tumor markers** (before & after orchidectomy)**
  - In advanced disease TM **pre-chemo** are the ones used to classify patients
  - Attention to **half lives** of TM (AFP: A7P; HGC: 3 Dias)
**Stage I:** Tumor confined to the testis
  - **Ia:** No vascular invasion. **Ib** Vascular Invasion

**Stage II:** Retroperitoneal Lymph Nodes
  - **IIa:** <2cm; **IIb:** 2-5cm; **IIc:** >5cm

**Stage III:** Visceral disease or Lymph Nodes above the diaphragm
Treatment Decision

**Histology:**
- Seminoma
- Non-Seminoma
- Mixed Histologies (non sem mandates)

**Staging:**
- Localized Disease (Stage I)
- Lymph Node Pelvic Disease (Stage II)
- Visceral Disease (Stage III) (Risk Group)
Stage I Disease

- Over 50% of GCTs are **clinical stage I** disease at presentation
- Curability **approaches** 100% in this setting
- **Multiple options** have been traditionally considered

Cure without long term sequelae of treatment is the goal of management in Stage I disease

- Normal Tumor markers after orchiectomy
- No evidence of metastatic disease on imaging studies

Clinical Stage I- Seminomas

- Common presentation (≈ 80% of SGCT)
- **Cure rates** ≈ 100% regardless treatment option
- **Different Treatment Strategies**
  - Adjuvant **Radiation** to retrop LN
  - Adjuvant **Chemotherapy** (Carboplatin)
  - **Active Surveillance**

- Risk adapted strategies?

- **Attention to toxicity profiles** (long survivors!!)

Chung P. Warde P. JNCI 2011

I.Duran. Escorial 2014
SIU/ICUD Consensus.
Seminomas

• “In stage I disease, the consensus conference recommended that patients should be informed of all treatment options (…)

• In patients willing and able to adhere to a surveillance program, this should be considered the management option of choice” [we are still defining the best surveillance schema]

Clinical Stage I NS-GCT

- Over 50% NS-GCT present with stage I
- Stage Ia-Ib (Lymphovascular invasion y/n)

**Treatment options after orchidectomy:**
- Primary **RPLND**
- Adjuvant **Chemotherapy (BEP x2)**
- Active **Surveillance**

**Equivalent outcomes**: 5-year OS~ 99%

**Objective**: Diminishing treatment related morbidity while keeping efficacy

SIU/ICUD Consensus 2009 Non Seminomas

• Patients should be made aware of all treatment options (surveillance, chemo, RPLND) and their potential side effects. For patients with low risk of occult metastasis surveillance is preferred. For those at high risk all 3 options can be considered”

Stephenson AJ et al. Urology 2011

I.Duran. Escorial 2014
Seminomas Stage Ila-IIb

Enfermedad retroperitoneal ≤ 5 cm (N1.N2)

- **Tratamiento estándar**: Radioterapia

- Ila 30 Gy
  - Ilb- 36 Gy

-Dosis y campos han sido comparados

**Campo de radiación “HOCKEY STICK FIELD”**

- RFS 6 años 95% y 86% en Ila y Ilb
- OS próxima al 100%

*Si contraindicación para radioterapia: BEP x 3


I. Duran. Escorial 2014
NSGCTs
STAGE IIa-IIb

Two strategies:

- LPRND-NS +/- ad.tt
  - Low volume disease
  - Negative markers

- CHEMOTHERAPY
  - BEP x 3
  - High volume tumors
  - Positive markers


I.Duran. Escorial 2014
Advanced Disease IIc-III

We will classify our patients in PROGNOSTIC GROUPS according to predefined criteria (IGCCCG)

- 5862 pts with advanced GCTs
- 1975-1990 (F/u of 5 years)
- Analysis of prognostic factors

**Non Seminomas:**
- Markers, Location (Pr & Mets)

**Seminomas:**
- Only location of Mets

---

**TABLE 3: International Germ-Cell Collaborative Group Consensus Conference criteria for good- and poor-risk testicular cancer patients treated with chemotherapy**

### NONSEMINOMA

- **Good prognosis**
  - All of the following:
    - AFP < 1,000 ng/mL, β-hCG < 5,000 IU/L, and LDH < 1.5 × upper limit of normal
    - Nonmediastinal primary
    - No nonpulmonary visceral metastasis

- **Intermediate prognosis**
  - All of the following:
    - AFP = 1,000-10,000 ng/mL, β-hCG = 5,000-50,000 IU/L, or LDH = 1.5-10 × normal
    - Nonmediastinal primary site
    - No nonpulmonary visceral metastasis

- **Poor prognosis**
  - Any of the following:
    - AFP > 10,000 ng/mL, β-hCG > 50,000 IU/L, or LDH > 10 × normal
    - Mediastinal primary site
    - Nonpulmonary visceral metastasis present

### SEMINOMA

- **Good prognosis**
  - No nonpulmonary visceral metastasis
- **Intermediate prognosis**
  - Nonpulmonary visceral metastasis present

---


AFP = alpha-fetoprotein; hCG = human chorionic gonadotropin; LDH = lactic dehydrogenase
GOOD PROGNOSIS PATIENTS

3 Cycles of BEP

4 EP is an alternative

INTERMEDIATE OR POOR PROGNOSIS

-Manage as one group:

-Standard of care is :

-BEP x 4

Recent studies at ASCO have tried to define a new standard for intermediate or poor prognosis however the results are not so solid as to change the standard

De Witt R. et al ASCO 2011: Fizazi K et al. ASCO 2013
RESIDUAL DISEASE

NON-SEMINOMA

>1 cm

45% Fibrosis/necrosis
-35% Teratoma
-20% Tumor

When there is a residual mass after chemotherapy greater than 1 cm in NSGCT we have no clear data to support what is behind.

RESIDUAL DISEASE

NON-SEMINOMA

*Any residual mass >1cm in NSGCT should be resected

I.Duran. Escorial 2014
RESIDUAL DISEASE

SEMINOMAS

≤ 3 cm → Surveillance

> 3 cm → PET 8 Weeks after + Surgery - Other opt

Salvage Therapy

- Patients who **relapse after first line** or those who **never respond** to primary treatment
- They should be **managed by expert teams** (look for help)
- Relapse after Surveillance; Treat adv disease
- Relapse after 1st line: **Stratification Systems**:

| Table 4. Prognostic Score for Patients With Nonseminoma and Seminoma |
|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Score Points    | 0               | 1               | 2               | 3               | Score           |
| Primary site     |                 | Gonadal         | Extragonadal    | —               | Mediastinal     | nonseminoma     |
| Prior response   | CR/PRm—PRm+SD | PD              |                 |                 |                 |                 |
| PFI, months      | ≥ 3             | ≤ 3             | —               | —               | —               | —               |
| AFP salvage      | Normal          | ≤ 1,000         | > 1,000         | —               | —               | —               |
| HCG salvage      | ≤ 1,000         | > 1,000         | —               | —               | —               | —               |
| LBB              | No              | Yes             | —               | —               | —               | —               |
| Score sum (values from 0 to 10) |                 |                 |                 |                 |                 |                 |
| Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3 |                 |                 |                 |                 |                 |                 |
| Add histology score points: pure seminoma = —1; nonseminoma or mixed tumors = 0 |                 |                 |                 |                 |                 |                 |
| Final prognostic score (1 = very low risk; 2 = low risk; 3 = intermediate risk; 4 = high risk; 5 = very high risk) |                 |                 |                 |                 |                 |                 |

- **Location** of primary
- **Prior response**
- **Progression Free Interval**
- **Markers** at the time of rescue
- **Liver, Bone or Brain mets**

Abbreviations: CR, complete remission; PRm—partial remission, negative markers; PRm+, partial remission, positive markers; SD, stable disease; PD, progressive disease; PFI, progression-free interval; AFP, alpha fetoprotein; HCG, human chorionic gonadotrophin; LBB, liver, bone, brain metastases.
Conclusions

- **Testicular cancer** is a rare but quite relevant tumor
- If well managed is a **curable disease** in most cases
- **Early stages** can be handled with less aggressive strategies with excellent outcomes
- **Advanced Disease** requires **stratification** into prognostic groups before treatment
- **Refractory disease** should ideally be treated in institutions with large experience
- Don’t forget the **long survivors & potential toxicity**
Tiempo para más?
Special Scenarios

• **HIV patients**: Identical management but HAART should be given concurrently +/- prophylaxis if CD4<200

• **Very high tumor burden**: “Cooling schemas”
  – Normal renal function:
    • 2 days of EP & on day +11. BEP or VIP
    • Mini BOP
  – Abnormal renal function:
    • Avoid Bleomycin. Carbo +/- etop & on day +11 BEP or VIP

• **Brain Metastases**:
  – Start with full chemotherapy +/- Rad/Surg
Special Situations

• **Marker Elevation with no clinical/radiological evidence of disease:**
  – Rule out disease in **Sanctuaries** (brain, testis)
  – High **BHGC:**
    • Rule out hypogonadism
    • Rule out drugs (Marihuana might increase BHGC)
  – High **AFP:**
    • Liver damage: 2ary to toxics, virus, anaesthetics

Late toxic effects

• Hypogonadism:
  – Testosterone < 8 nmol/L
  – 11-35%
  – Testost determination reccomended during fu

• Cardiovascular Toxicity:
  – 2-3 increased risk of CV toxicity: Raynaud Sdm

• Metabolic Syndrome:
  – 20-30% long term GCT survivors
  – Aprox 3-5 years after treatment

• Second Tumors: Double RR. GI/GU
  – Solid tumors > 10 years after
  – Leukemias 0.5%-2% (Etoposide dose <2<)
The near future


MUCHAS GRACIAS
Y FELIZ VERANO!!