XXVI Curso Avanzado de Oncología Médica

Germ Cell Testicular Tumors

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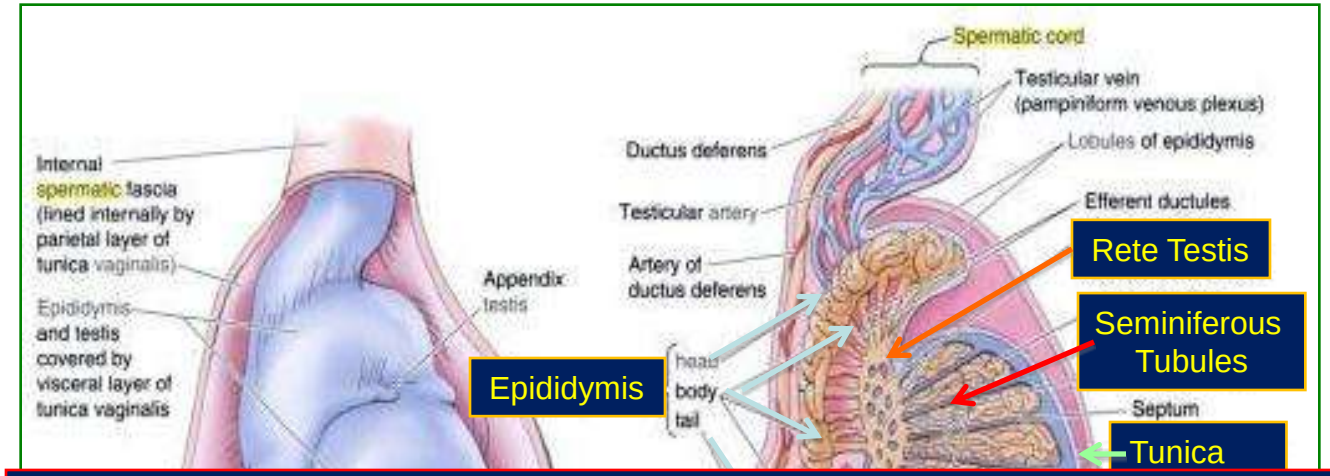
Outline

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

Testis and Testis Cancer



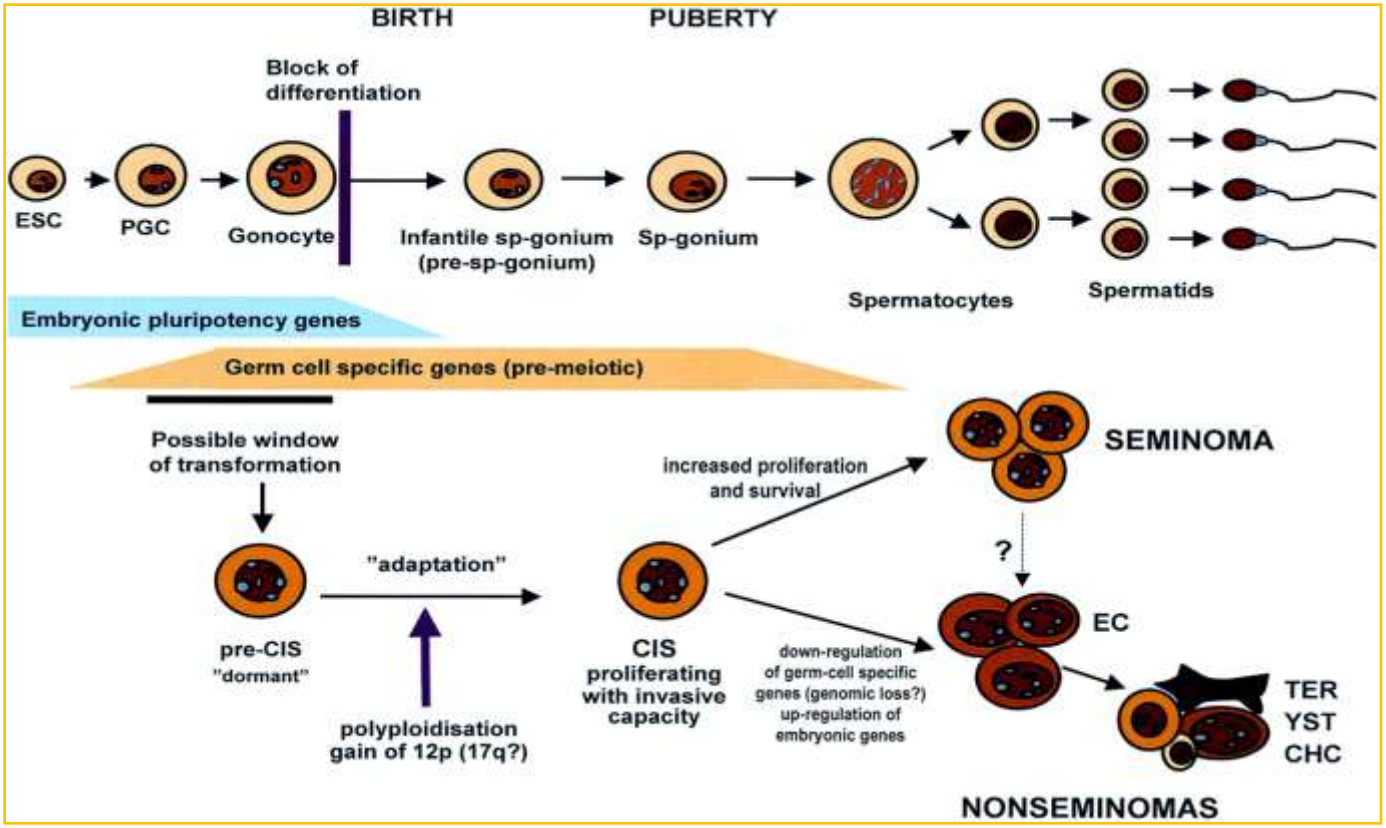
Cell types in the testis:

- **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

ESC: Embryonic Stem Cells; PGC: Primordial Germ Cells. CIS: Carcinoma in situ. EC: Embryonal Carcinoma. TER: Teratoma. YST: Yolk Sac tumor. CHC: Choriocarcinoma

Chaganti RS et al. Cancer Res. 2000 Mar 15;60(6):1475-82.

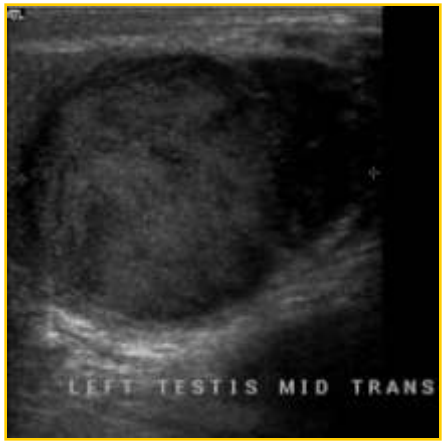
Epidemiology: A rare disease but…quite unique

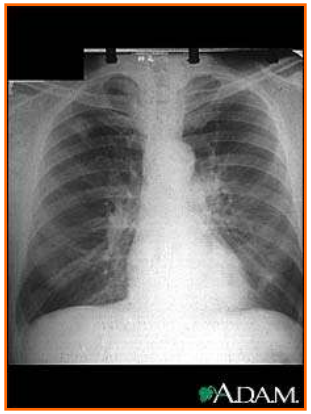
- GCTs represent **1%** of all cancers
- ≈8.000 new cases/year (US)
  (≈ 700 in Spain*)
- It is the most frequent neoplasm in **young** adults (15-35 y/o)
- Arrival of **cisplatin**, better **surgical techniques** and **multidisciplinary work: CURABLE NEOPLASM**

CA CANCER J CLIN 2013;63:11–30GLOBOCAN 2008

Diagnosis: Symptoms/Signs

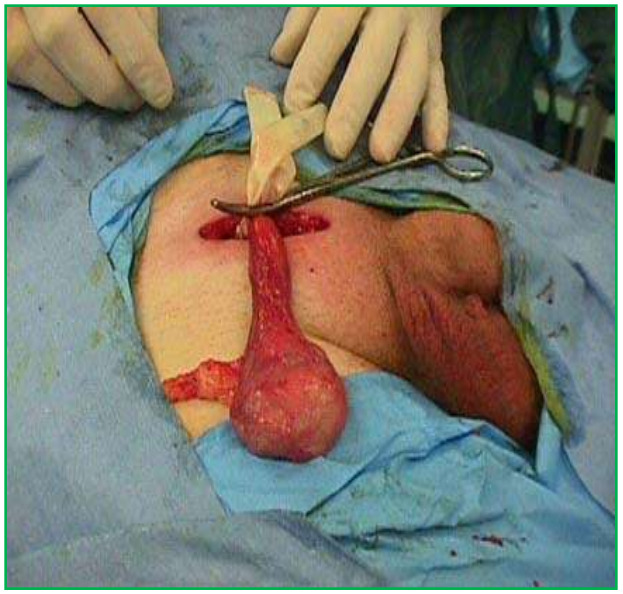
- Testicular lump (painless)
- Symptoms mimicking infection
- Symptoms related to advanced disease
  - Dyspnea /Cough/ Hemoptysis
  - Lower Back Pain





Diagnosis: The med-onc patient

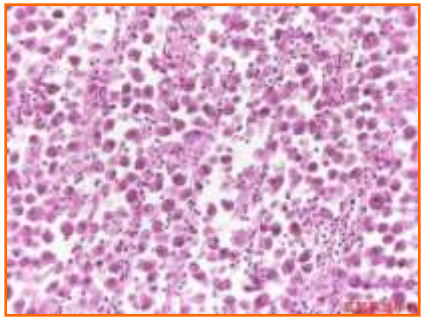
- When the patient arrives to the medical oncologist there is already an **orchidectomy** and a **histological diagnosis**



- The orchidectomy must be performed **via inguinal**
- In **exceptional cases** the orchidectomy might be postponed and systemic treatment started up front

Diagnosis: Key Point

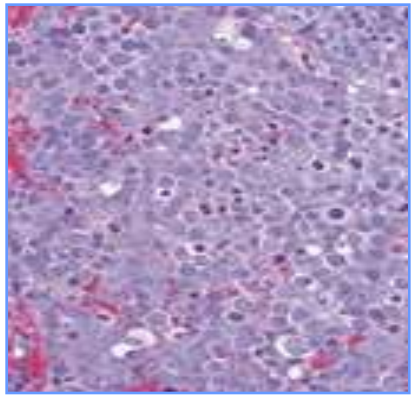
- **Seminomas**
  - Around 45%
  - On average appear 10 y later[40s]
  - Tend to be big masses
  - 15% of them produce HGC
  - **NONE of them produce AFP**
  - Typically rise LDH
  - More radio sensitive



Classic Seminoma

Subtypes:

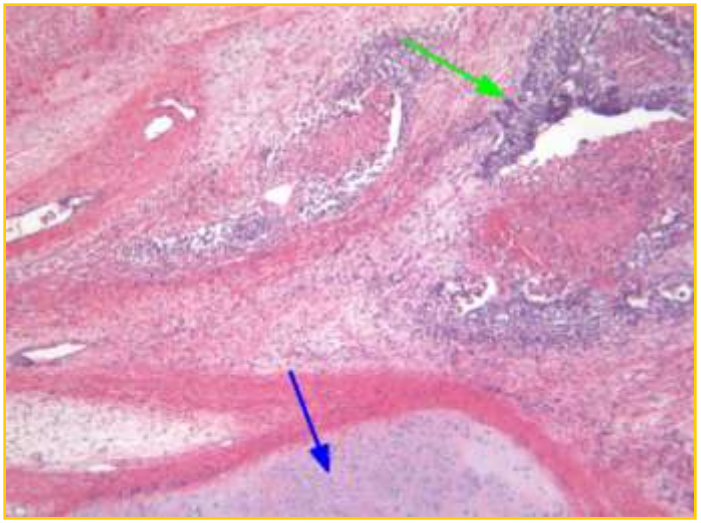
- Classic Seminoma
- Atypical Seminoma
- Spermatocytic Seminoma*



Spermatocytic Sem

Diagnosis: Key Points

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

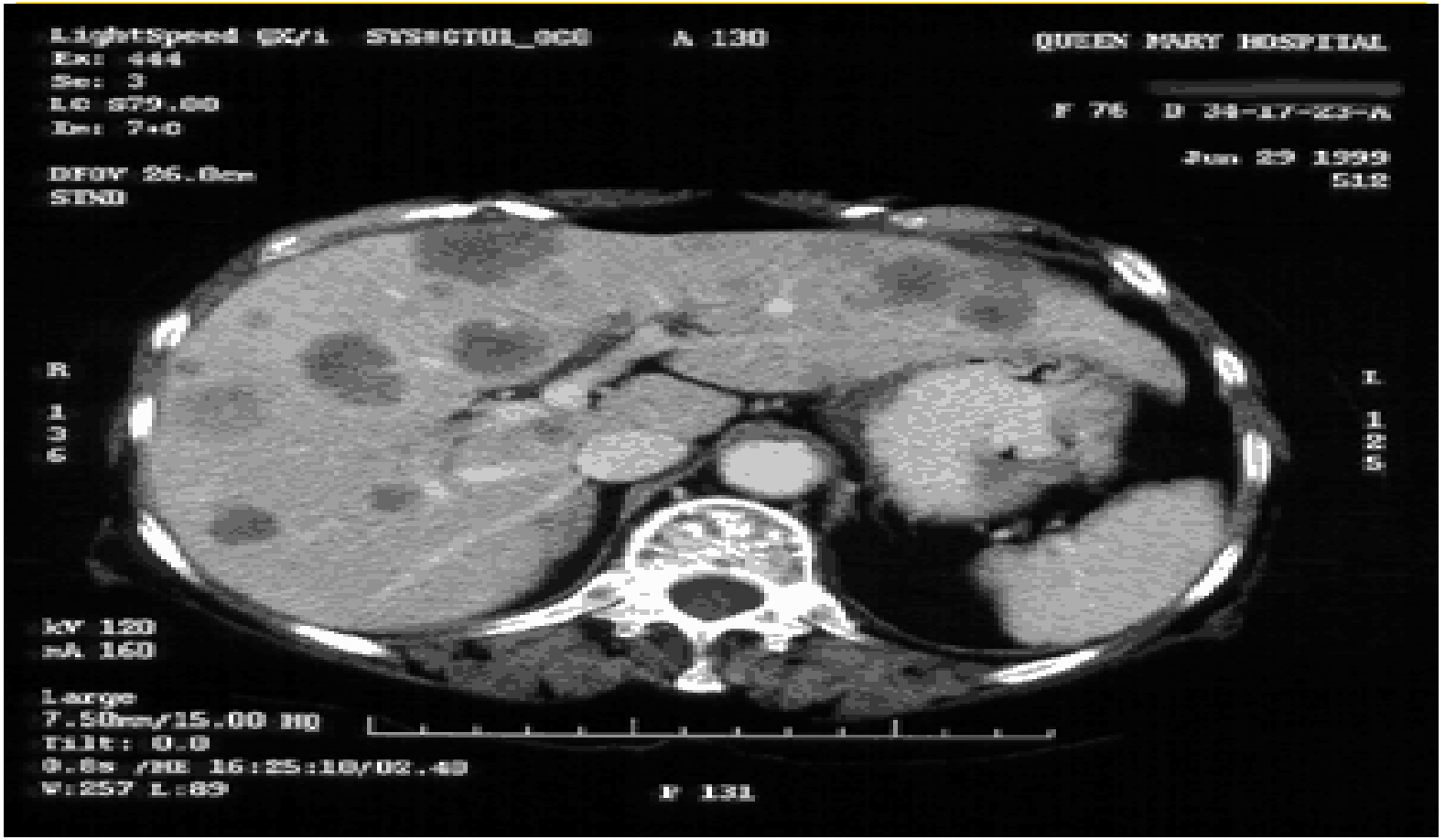


Non Seminomatous Tumor (Teratoma)

4 <u>Types:</u>

- **EC**(the most frequent)
- **Yolk Sac Tumor** (AFP)
- **Choriocarcinoma** (HGC)
- **Teratoma**

Overview: Natural History

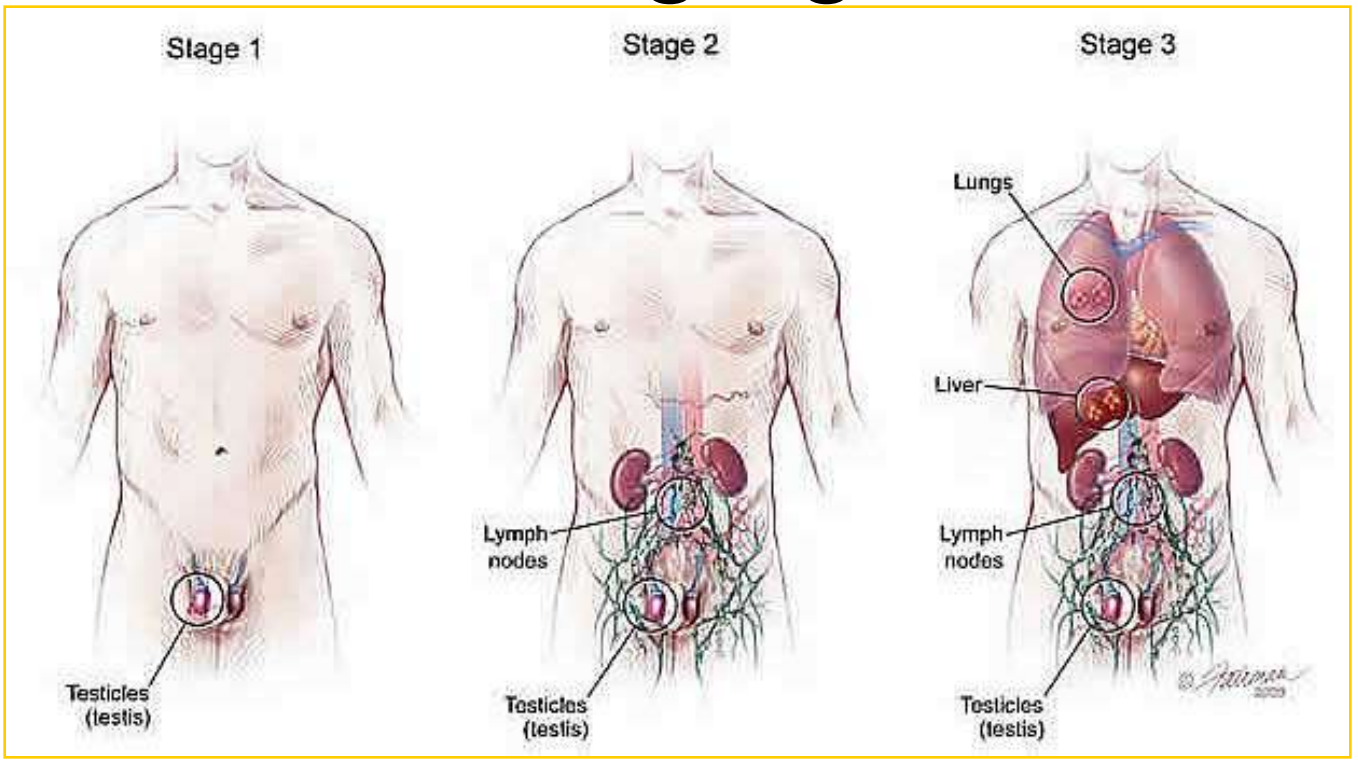


Natural history ranges from local growth to lymph node spread and visceral disease (Lung, Liver, Bone, Brain, etc …)

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: A**7**P; HGC: 3 Dias)

Staging



Stage I : Tumor confined to the testis

Ia No vascular invasion. **Ib** Vascular Invasion

Stage II: Retroperitoneal Lymph Nodes

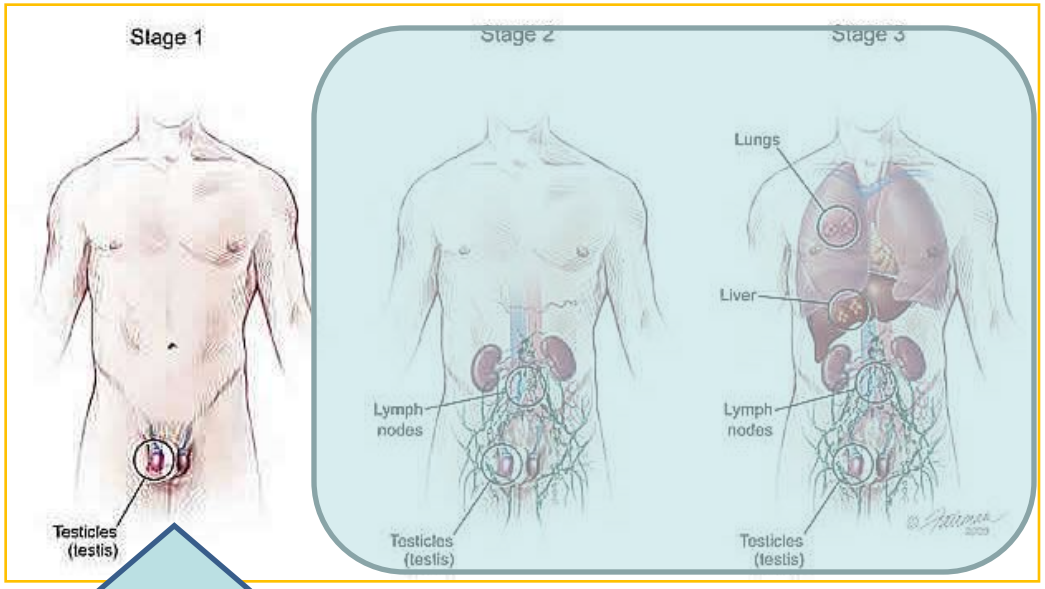
IIa [<2cm];**IIb** [2-5cm];**IIc** [>5cm]

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

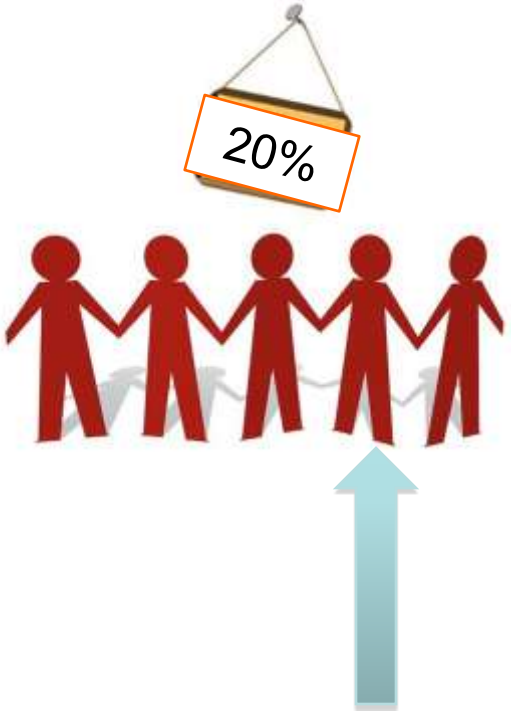
•Normal Tumor markers after orchydectomy
•No evidence of metastatic disease on imaging studies

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

Urol Clin North Am 1998. Warde P, Zuñiga A et al. BJU Int 2009

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

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]

Warde P et al. Urology 2011. Beyer J et al. Annals of Oncology 24: 878-888. 2013

Clinical Stage I NS-GCT

- Over 50% NS-GCT present with stage I
- Stage Ia-Ib (Lymphovascular invasion y/n)
- **<u>Treatment options after orchidectomy</u>**:
  - Primary **RPLND**
  - Adjuvant **Chemotherapy (BEP x2)**
  - <u>Active **Surveillance**</u>
- **Equivalent outcomes** : 5-year OS~ 99%
- **Objective**: Diminishing treatment related morbidity while keeping efficacy

Bhardwa JM et al. BJU Int 2005; de Wit R et al. J Clin Oncol 2006. Sturgeon et al. Eur Urology 2011

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

Seminomas Stage IIa-IIb

Enfermedad retroperitoneal ≤ 5 cm(N1.N2)

-**Tratamiento estándar**: Radioterapia

-IIa 30 Gy

IIb- 36 Gy

-Dosis y campos han sido comparados

Bamberg M et al. Int J Cancer 83,823-827.1999

-Campo de radiación "HOCKEY STICK FIELD"

-RFS 6 años 95% y 86% en IIa y IIb

-OS proxima al 100%

*Si contraindicación para radioterapia: BEP x 3

Classen J et al. JClin Oncol 21:1101-06. 2003;Paterson H et al.Radiother Oncol 59.5-11.2001

NSGCTs
STAGE IIa-IIb

-Two strategies:

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

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

Rabbani F, Sheinfeld J et al: Low volume nodal metastases detected at retroperitoneal lymphadenectomy for testicular cancer. J Clin Oncol 19.2020-2025.2001

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

J Clin Oncol 15: 594-603. 1997

GOOD PROGNOSIS PATIENTS

3 Cycles of BEP

4 EP is an alternative

BEP 500/5
Cisplatin 20mg/m2/day x 5 days
Etoposide 100mg/m2 day x 5days
Bleomicyne 30 U days 2,9 and 16

INTERMEDIATE OR POOR PROGNOSIS

-Manage as one group:

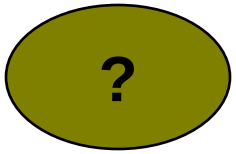
-Standard of care is : **-BEP x 4**

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

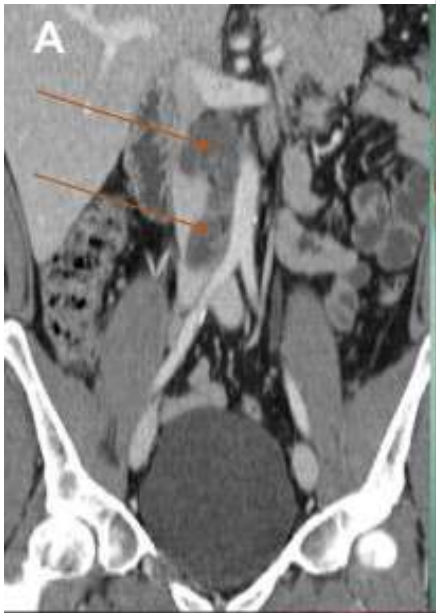
De Witt R. et al ASCO 2011: Fizazi K et al. ASCO 2013

RESIDUAL DISEASE

NON-SEMINOMA



>1 cm



45%Fibrosis/necrosis

-35% Teratoma

-20% Tumor

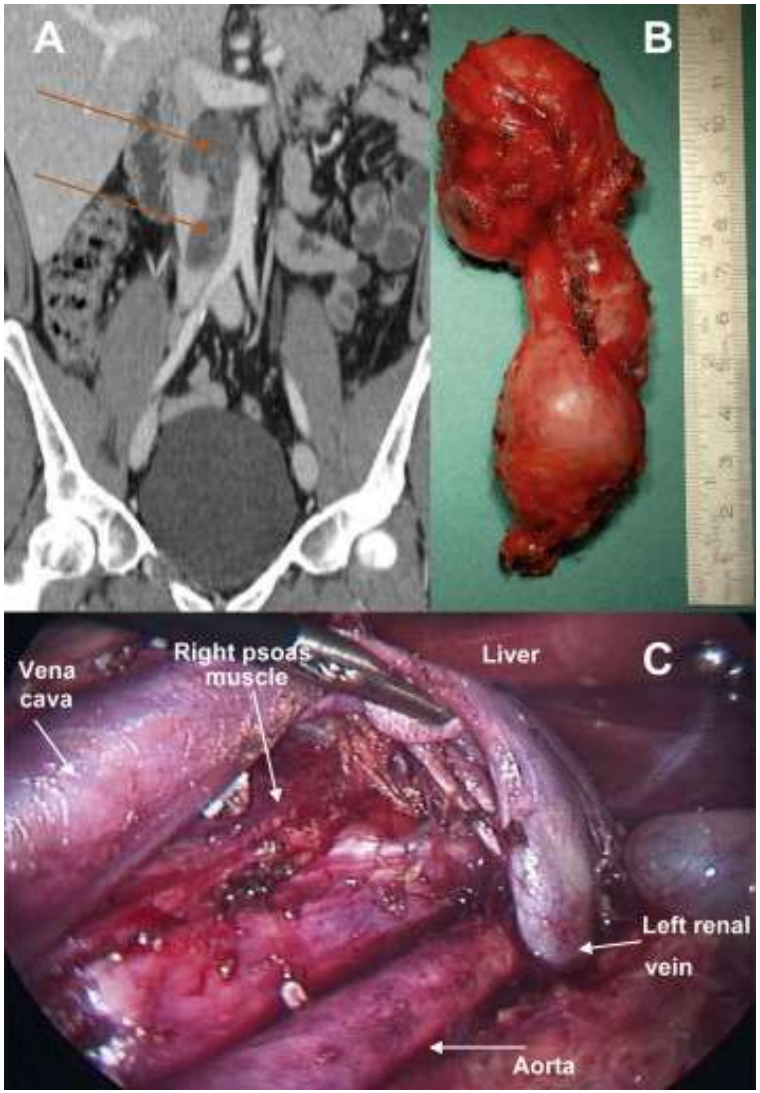
When there is a **residual mass after chemotherapy** greater than 1 cm in NSGCT we have **no clear data to support what is behind**

Bosl G NEJM 1997; Sheinfeld J. et al. J Urol 2003. 1159-1162:Fox EP et al: J Clin Oncol 11 1294-99. 1993; Riggs SB, Burgess EF, Gaston KE, Merwarth CA, Raghavan D Oncologist. 2014 Apr 9.

RESIDUAL DISEASE

NON-SEMINOMA

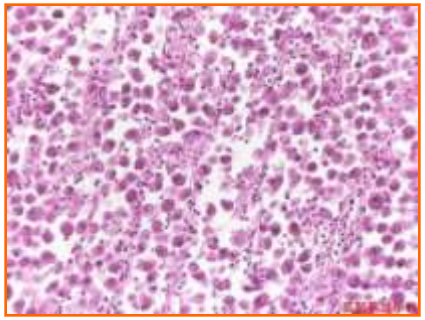
***Any residual mass >1cm in NSGCT should be resected**

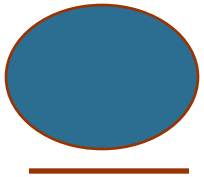


I.Duran. Escorial 2014

RESIDUAL DISEASE

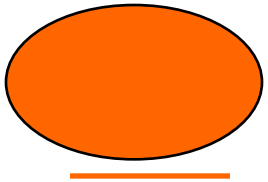
SEMINOMAS



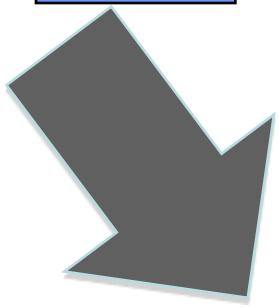


≤3 cm

Surveillance



> 3 cm



PET
8 Weeks
after

\+

Other opt

Surgery

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Surveillance

Bosl G NEJM 1997; Sheinfeld J. et al. J Urol 2003. 1159-1162:Fox EP et al: J Clin Oncol 11 1294-99. 1993; Riggs SB, Burgess EF, Gaston KE, Merwarth CA, Raghavan D Oncologist. 2014 Apr 9.

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:**

- 10 /Y
- 5 relap. Or poor

Table 4. Prognostic Score for Patients With Nonseminoma and Seminoma

Parameter	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; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)					

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.

-**Location** of primary

-**Prior response**

-**Progression Free Interval**

-**Markers** at the time of rescue

-**L**iver, **B**one or **B**rain mets

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**

IF YOU WANT TO LEARN MORE……

SIMPOSYUM SOGUG 2014

Tiempo para mas?

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[1]
    - Rule out drugs (Marihuana migh increase BHGC)
  - High **AFP**:
    - Liver damage: 2ary to toxics, virus, anaestetics[2]

Catalona WJ, Vaitukaitis JL, Fair WR.. J Urol. 1979 Jul;122(1):126-8 Germà JR, Llanos M, Tabernero JM, Mora J.. Cancer. 1993 Oct 15;72(8):2491-4.

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

- Korkola JE, Houldsworth J, Feldman et al. Identification and validation of a gene expression signature that predicts outcome in adult men with germ cell tumors. **J Clin Oncol.2009 Nov 1;27(31):5240-7**

- Cavallo F, Graziani G, Antinozzi et al Reduced proficiency in homologous recombination underlies the high sensitivity of embryonal carcinoma testicular germ cell tumors to Cisplatin and poly (adp-ribose) polymerase inhibition. **PLoS One. 2012;7**(12):e51563.

MUCHAS GRACIAS

Y FELIZ VERANO!!