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Germ Cell Testicular Tumors

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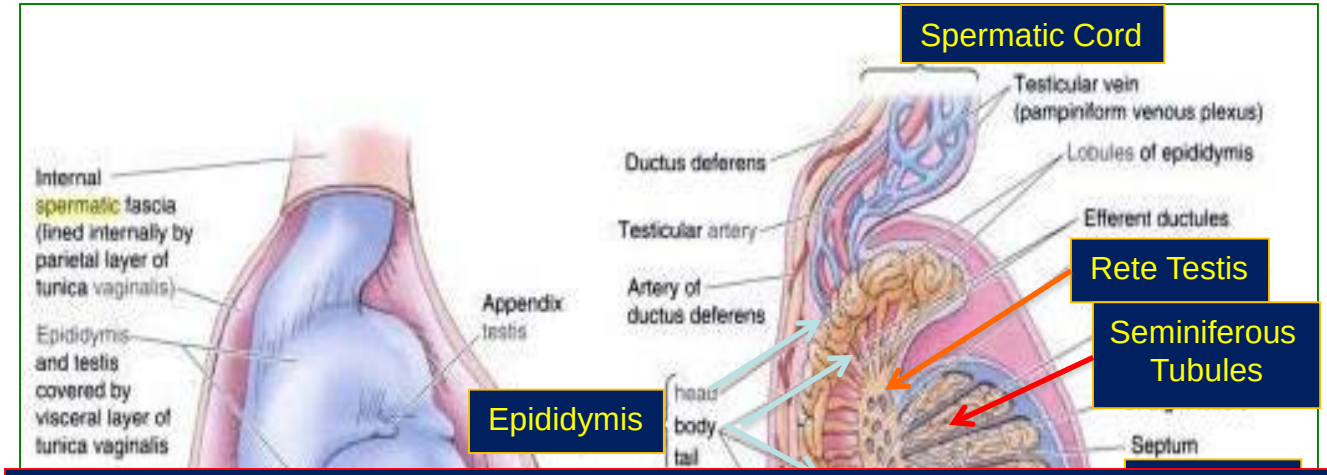
I+D+i Hospitales Universitarios Virgen Macarena - Virgen del Rocío

Outline

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

Why Germ Cell Cancer?



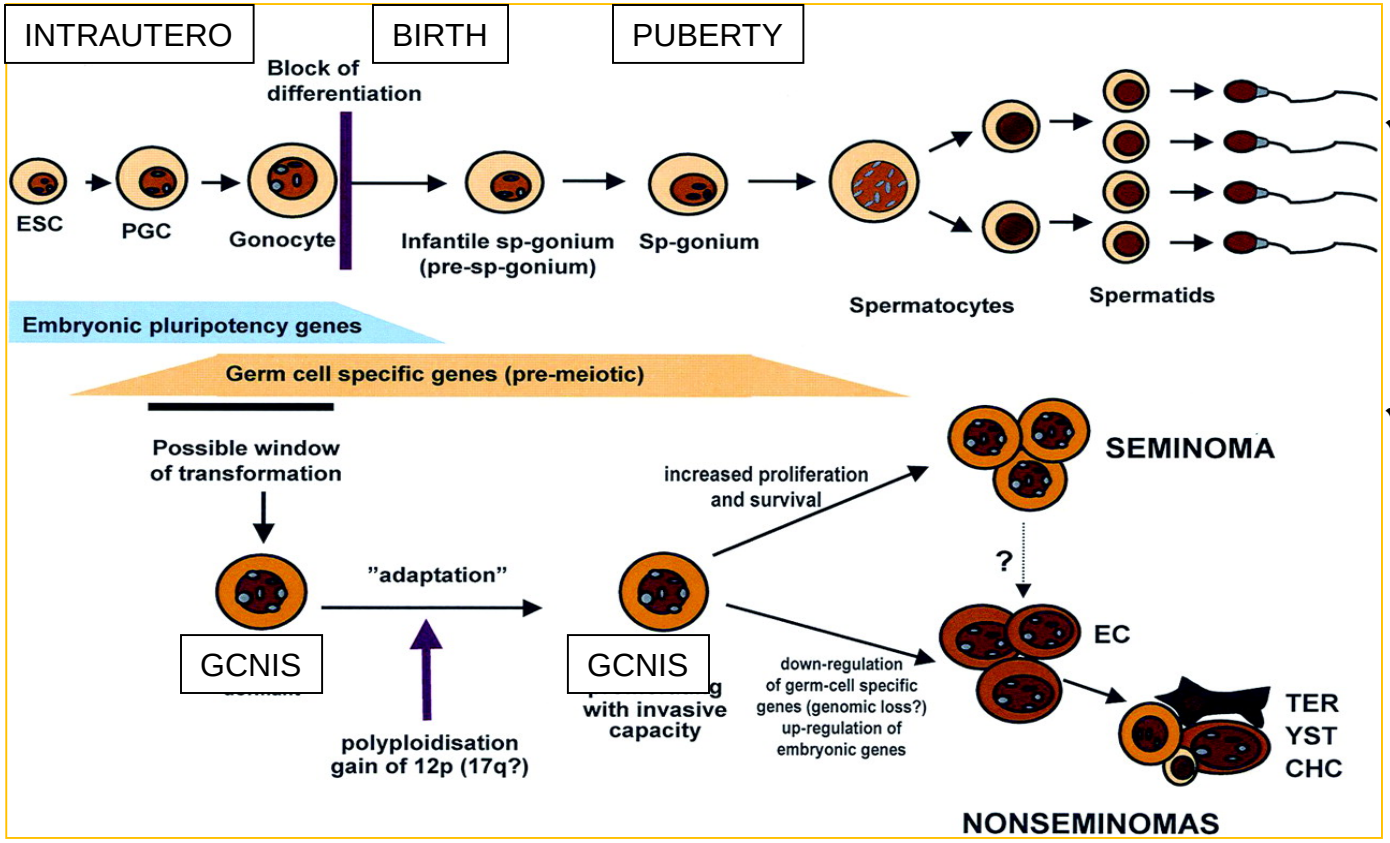
Cell types in the testis:

- **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

Within the sem. Tubule: **Sertoli Cells**: The “nurse”. Nourish the cells in development. **Germ Cells**: Cells that are going to mature and become spermatogonia, spermatocytes

Pathogenesis: A special disease



- ✓ Initiation of pathogenesis occur intrautero
- ✓ Primordial germ cells (PGC)would escape normal differentiation to become GCNI)

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

✓ GCNIS during puberty would gain invasive capacity

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

Epidemiology: A rare disease but…quite unique

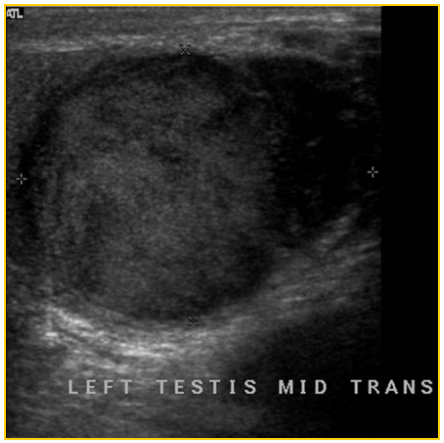
- In 2012, ≈ 55,000 new cases worldwide
- Incidence increasing; variable distribution
- ≈ 800 new cases/year in Spain; Intermediate ASR [3.5 cases per 10^5]
- 1.5% of all cancer diagnosis
- Most frequent neoplasm in young adults
- Arrival of cisplatin, better surgical techniques and multidisciplinary work: **The paradigm of curable neoplasm**

Ferlay J,, et al**. GLOBOCAN** 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Siegel RL et al. **CA CANCER J CLIN** 2017;67:7–30

Diagnosis: Symptoms/Signs

- Testicular lump (painless):

Testis ultra sound to confirm diagnosis and explore contralateral



- Physical exam, cxr, blood work & pre- and post-orchiecto**my** serum **tumor markers**

- **CT abd-pelvis** [chest (mandatory in non-seminoma)

SEOM clinical guidelines for the management of germ cell testicular cancer (2016) Aparicio J et al. Clin Transl Oncol (2016)

Diagnosis: The med-onc patient

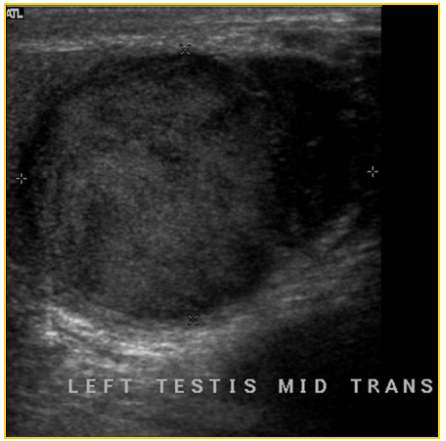
- When the patient arrives to the medical oncologist there is already an **orchidectomy** and a **histological diagnosis**

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

Diagnosis: Symptoms/Signs

- Testicular lump (painless):

Testis ultra sound to confirm diagnosis and explore contralateral



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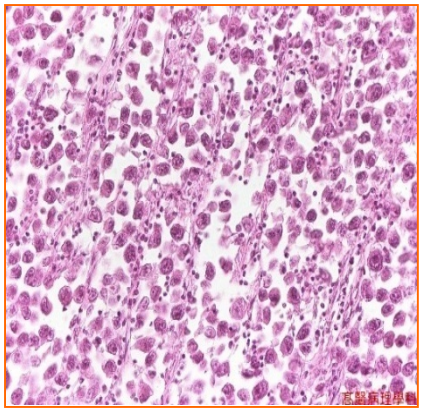
SEOM clinical guidelines for the management of germ cell testicular cancer (2016) Aparicio J et al. Clin Transl Oncol (2016) 18:1187–1196

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

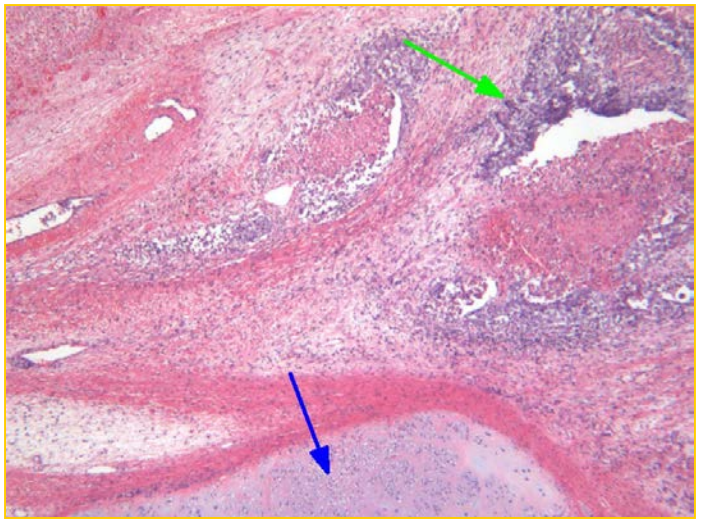
Subtypes:

- Seminoma
- Seminoma with syncytiotrophoblast cells
- Spermatocytic Seminoma* [spematocytic tumour]

Moch H, Humphrey PA, Ulbright TM, Reuter V. WHO Classification of Tumours of the Urinary System and Male Genital Organs. Lyon: International Agency for Research on Cancer; 2016.

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 Types:

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

Moch H, Humphrey PA, Ulbright TM, Reuter V. WHO Classification of Tumours of the Urinary System and Male Genital Organs. Lyon: International Agency for Research on Cancer; 2016.

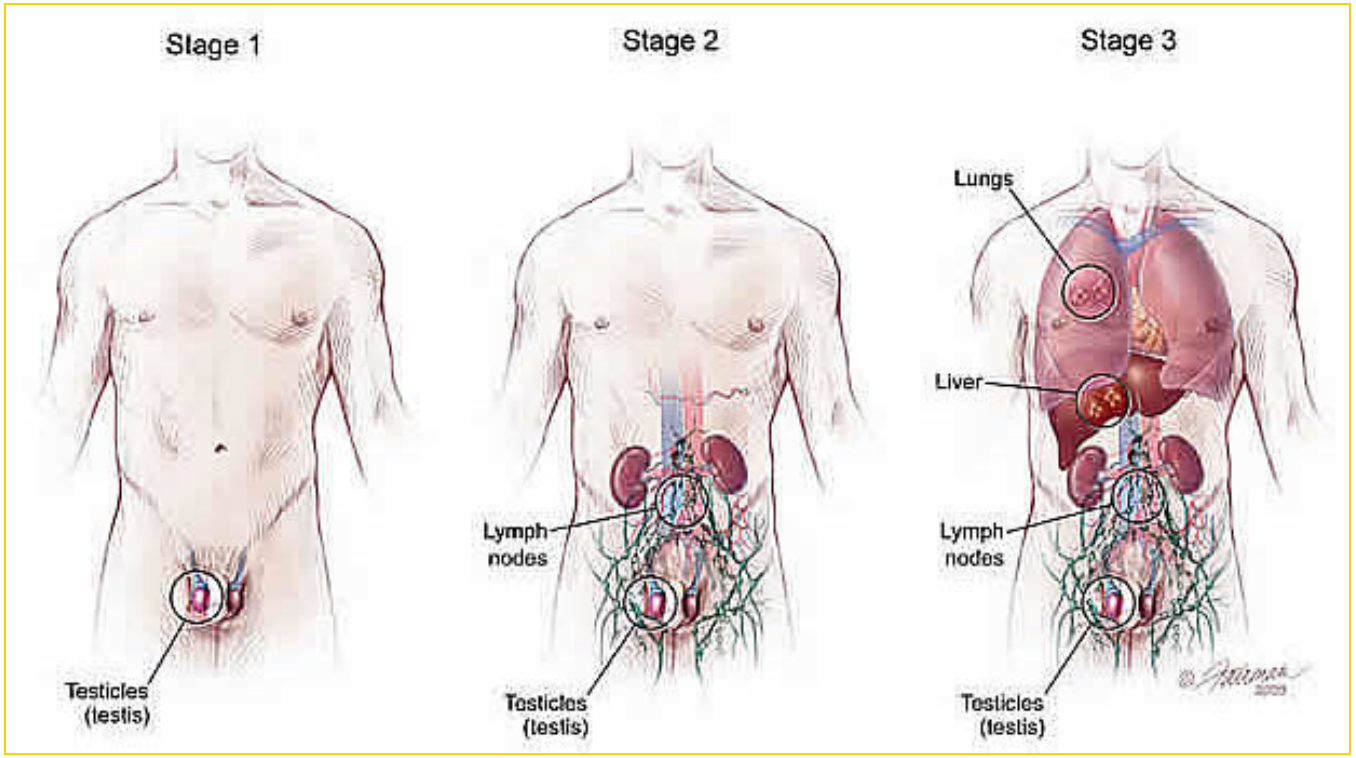
Overview: Natural History

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

Staging

- CT Chest-Abd-Pelvis
- CT /MRI CNS (if visceral mets/very high markers or neurological sympt)
- Bone Scan [only if symptoms suggesting bone mets]
- PET -FDGCT **should NOT** be used routinely
- **Tumor markers** (before & after orchiectomy)**
  - In advanced disease TM post-cx and **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

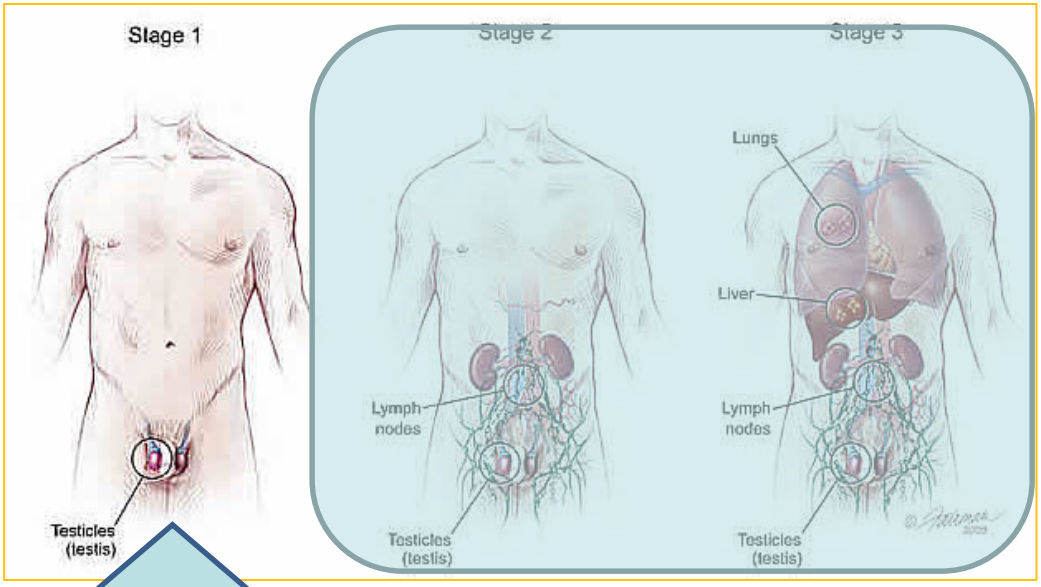
IIa [<2cm];**IIb** [2-5cm];**IIc** [>5cm]

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

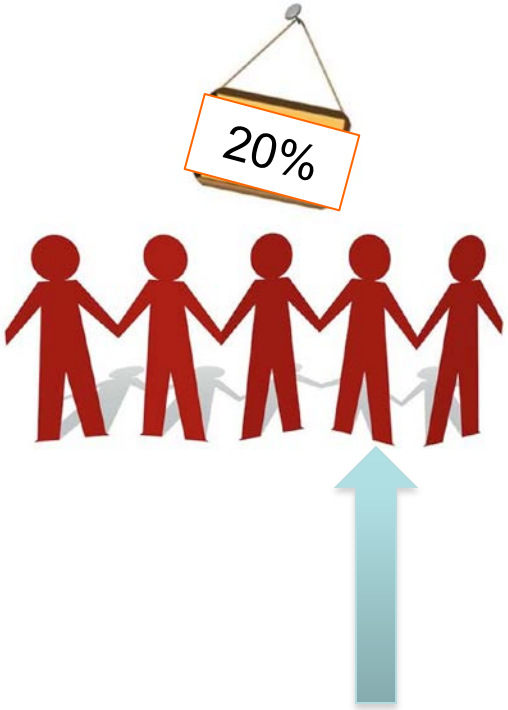
Cure without long term sequelae of treatment is the goal of management in Stage I disease

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 Strategies:**
  - Adjuvant **Radiation** to retrop LN
  - Adjuvant **Chemotherapy**

    (Carboplatin AUC7 x 1-2)
  - Active **Surveillance**



- Risk adapted strategies?
- Attention to toxicity profiles (long survivors!!)

Chung P. Warde P. JNCI 2011; Albers P,.. Eur Urol. 2015 Dec;68(6):1054-68

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

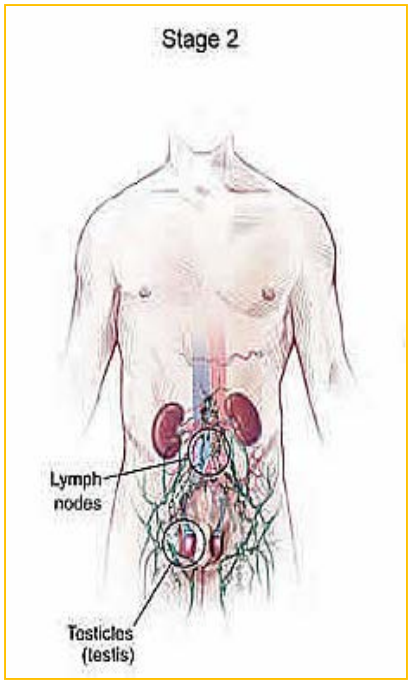
Bhardwa JM et al. BJU Int 2005; de Wit R et al. J Clin Oncol 2006. Sturgeon et al. Eur Urology 2011

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-b



Retroperitoneal Lymph nodes <5 cm

-Radiation to **para Ao and ipsilateral iliac LN** has been the standard treatment [Hockey stick radiation field] [30Gy]

-RFS 6 years 95%-86% in IIa-IIb

-OS close to 100%

-Recent studies justify as an alternative the use of **3 cycles of BEP/4 EP**

-Equivalent efficacy and less toxicity in the long term

Garcia-del-Muro X et al. Chemotherapy as an alternative to radiotherapy in the treatment of stage IIA and IIB testicular seminoma: a Spanish Germ Cell Cancer Group Study. J Clin Oncol. 2008;26:5416–21.; Tandstad T,, et al. Management of seminomatous testicular cancer: a binational prospective population-based study from the Swedish norwegian testicular cancer study group. J Clin Oncol. 2011;29:719–25. Classen J, et al. Radiotherapy for stages IIA/B testicular seminoma: final report of a prospective multicenter clinical trial. J Clin Oncol. 2003;21(6):1101–6.

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 by the French Group 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 GU 2017

ADVANCED DISEASE

CHEMOTHERAPY

COMPLETE RESPONSE
[neg. mms/no r.d]

F/U

PARTIAL RESPONSE
[neg mms/r.d.]

RESIDUAL MASS

PROGRESSIVE DISEASE
[NO neg mms/growing mass]

RESCUE TT.

Residual mass with negative mm [NS]

45%Fibrosis/necrosis

-35% Teratoma

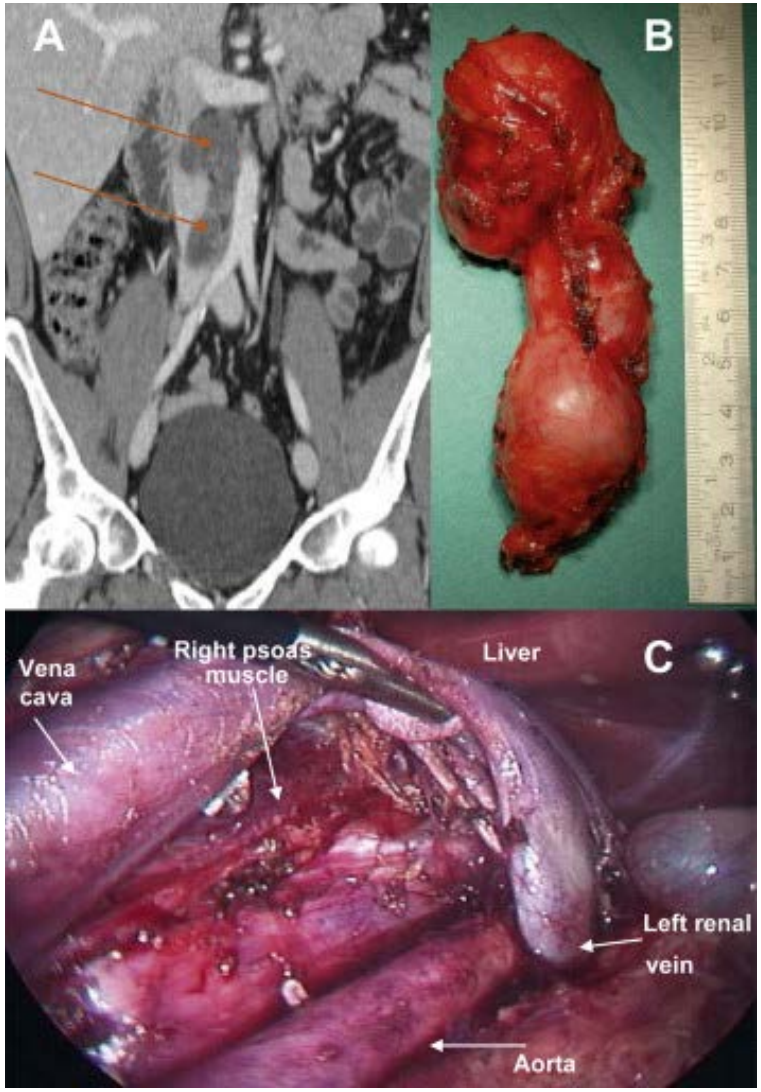
-20% Tumor

After chemotherapy we achieve a normalization of tumor markers with reduction of original tumor mass but still persistence of something > 1cm

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.

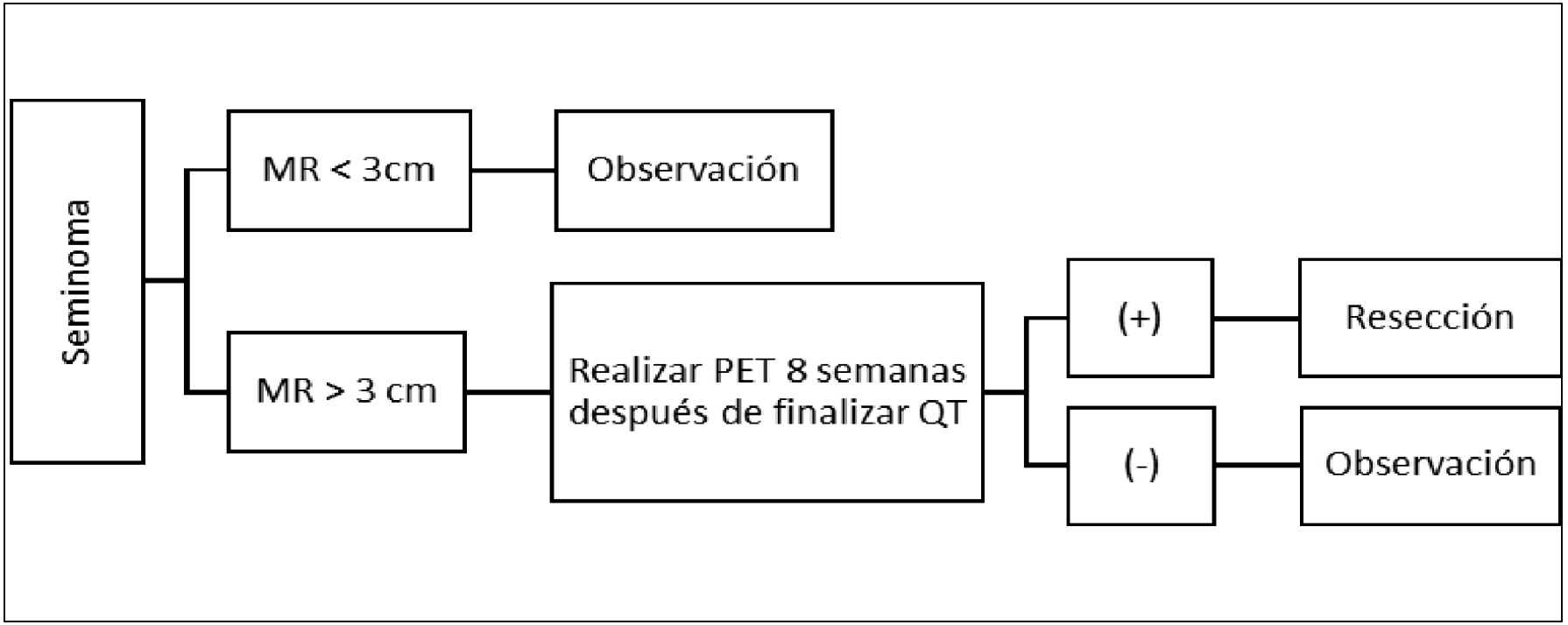
RESIDUAL DISEASE NON SEMINOMATOUS GCT



NON-SEMINOMA

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

Residual Masses in Seminomas



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)

- 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

  [Long survivors/potential toxicity]
- **Advanced Disease** requires **stratification** into prognostic groups before treatment
- **Refractory disease** should ideally be treated in **institutions with large experience**

Tiempo para mas?

Si no para esas noches de insomnio

Brain Metastases

- Brain metastases (BM) can be present at the initial diagnosis or at relapse, although is a poor prognosis population some of these patients can still be potentially cured
- Adverse risk factors for both groups are:
  - (1) The multiplicity of BM
  - (2) The presence of liver or bone metastases concurrently
- BM synchronous [better prognosis]
  - BEP X 4 +/- consolidation [attention to late tox]
- BM metachronous [worse prognosis]
  - HDCT +/- surgery or rads

Girones R, et al. Spanish Germ Cell Cancer Group (SGCCG). Synchronous versus metachronous brain metastasis from testicular germ cell tumors (TGCT): an analysis from the Spanish Germ Cell Cancer Group data base. Clin Transl Oncol. 2014;16:959–65.

Special Scenarios

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

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!!