Testicular cancer

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First publication on the treatment of testicular tumors

Dean AL Jr.

The treatment of teratoid tumors of the testes with radium and the x-ray. *J Urol*. 1925. 13:149-75.

Testicular tumor

- Basic epidemiology
- Pathology, spread & staging
- Work up & Primary treatment
- Overview of treatment principles
- Principles of chemotherapy
- Principles of Radiotherapy
- Rare tumors

Big concept

Testicular tumors are curable

10year survival > 90%

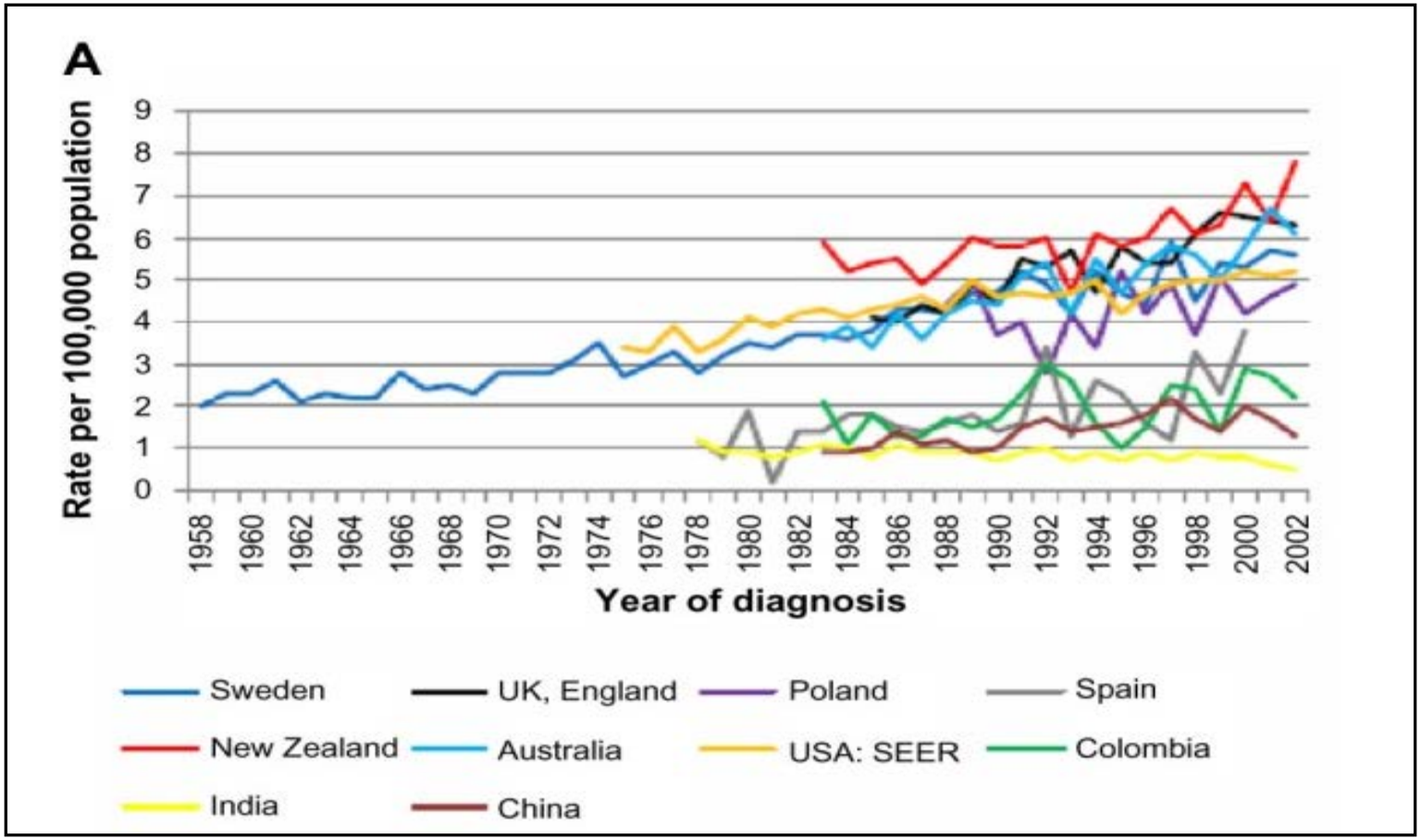
We are MORE concerned with treatment related late effects than outcome

- Most common malignant neoplasm of male 15-35yrs
- >95% Cancer specific survival rate
- >95% Germ cell tumor
- >95% GCT are testicular
- 1% of malignant tumor of male

Global stat :

Age adjusted annual incidence

Birth cohort phenomena in Nordic countries



Sunmugalingam T Clin Epidemiol. 2013; 5: 417–427

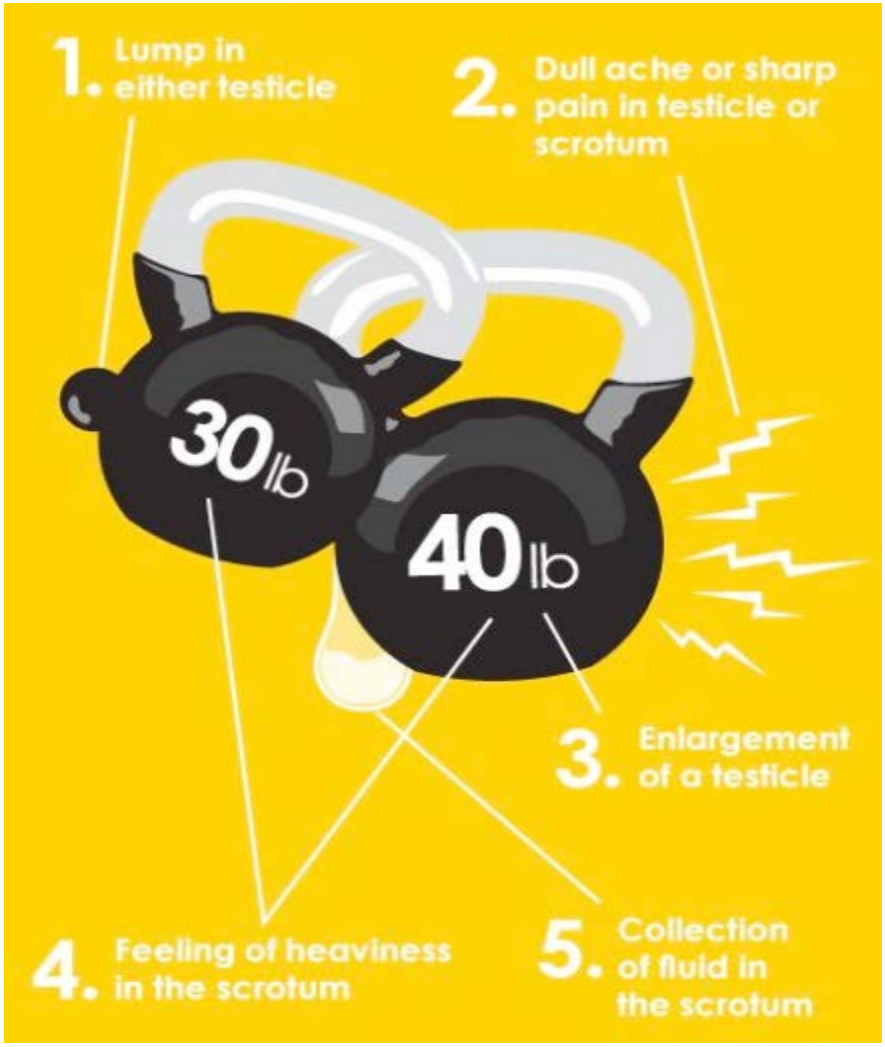
Risk factors

- 1st degree relative
- Cryptorchidism
- testicular dysgenesis
- Klinefelter's syndrome
- P/H of GCT
- Testicular cancer survivors
- H/O Intra-tubular GC neoplasia (ITGCN)

Heritability of GCT

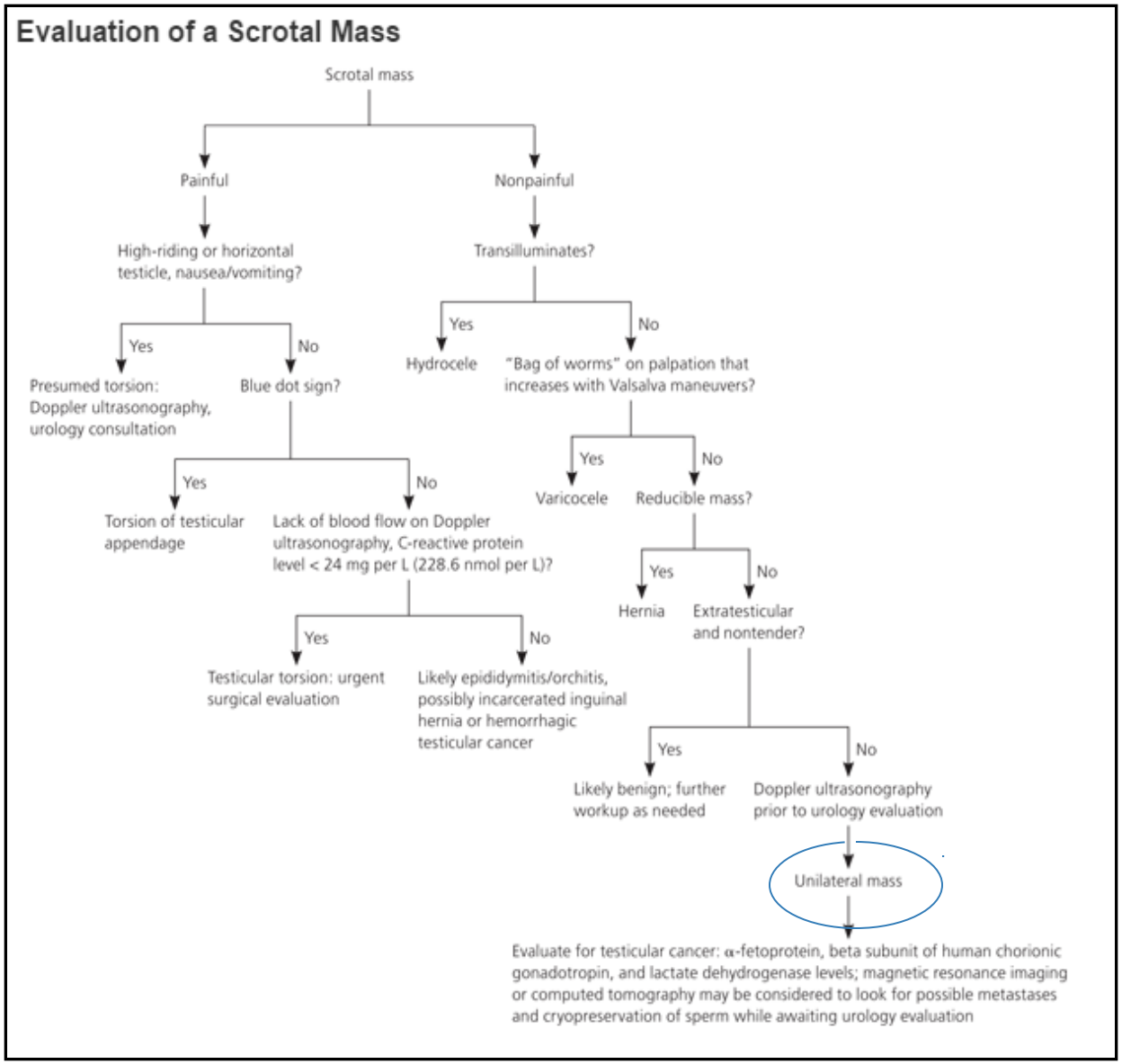
- GCTs are among the most heritable of all cancers.
- 4-6 times ↑ risk to brother
- 7-8times ↑ risk to father
- 2-3 times ↑ risk to 1st degree relatives
- The relative risk is much greater in monozygotic and dizygotic twins.
- Genetic underpinning is complex and novel e.g. KIT,TP53,RAS (seminoma) and BRAF and 12p gain (NSGCT)

Presentation



- Persisting >1-2 weeks
- Not acute/severe

Evaluation



Firm unilateral scrotal nodule presenting with/out dull aching pain
Testicular tumor

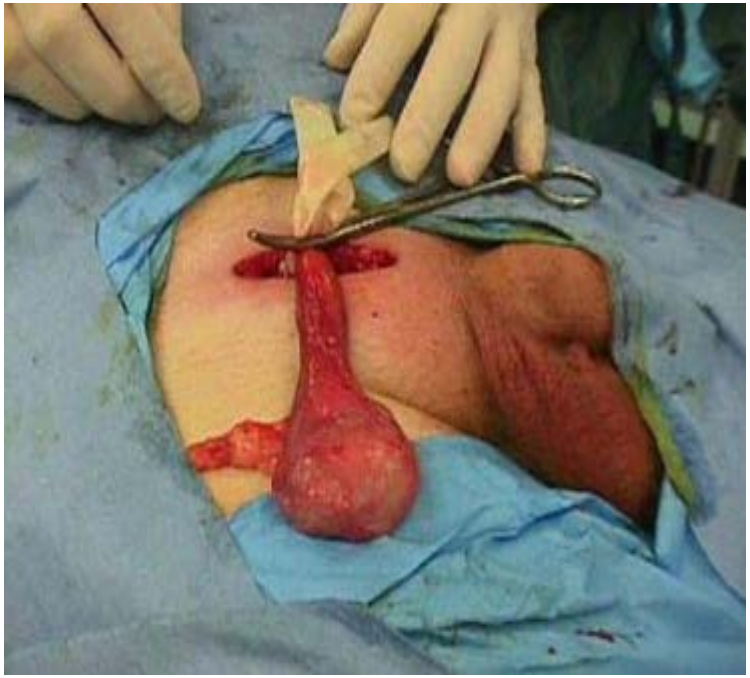
D/D

1. Epididimis
2. Orchitis
3. Hernia
4. Torsion
5. Hydrocele
6. Haematocele
7. Varicocele

USG is a must
Solid Intra-testicular mass
Call your surgeon

Primary Treatment

- Radical inguinal orchiectomy and high spermatic cord ligation is the standard diagnostic and therapeutic approach.
  - Trans-scrotal orchiectomy and biopsy is contraindicated
  - Tumor seeding to Inguinal area
  - Pelvic node +
  - High local relapse (5-8%)



Biopsy of C/ L testis?

- Low incidence of metachronus testicular cancer (1.5% in 15 yr)

- Only indicated in:
- Cryporchid or atrophic testis

- **Counsel about sperm banking**

Pathology: Seminoma is Pure

World Health Organization Histologic Classification of Testicular Germ Cell Tumors

Germ Cell Tumors
- Intratubular germ cell neoplasia, unclassified
- Other types

Tumors of One Histologic Type (Pure Forms)
- Seminoma
  - Seminoma with syncytiotrophoblastic cells
- Spermatocytic seminoma
  - Spermatocytic seminoma with sarcoma
- Embryonal carcinoma
- Yolk sac tumor
- Trophoblastic tumors
  - Choriocarcinoma
  - Trophoblastic neoplasms other than choriocarcinoma
- Teratoma
  - Dermoid cyst
  - Monodermal teratoma
  - Teratoma with somatic type malignancies

Tumors of More Than One Histologic Type (Mixed Forms)
- Mixed embryonal carcinoma and teratoma
- Mixed teratoma and seminoma
- Choriocarcinoma and teratoma/embryonal carcinoma
- Others

Source: Eble JN, Sauter G, Epstein JI, et al., eds. *Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs.* Lyon, France: IARC Press; 2004.

- Originated from intra-testicular and para-testicular cells
- 60% Seminomas
- 30% NSGCTs
- 10% Mixed
- Mixed tumors are clinically grouped under NSGCTs
- pure seminoma may have recurrence with pure NSGCT, and vice versa

Intra-tubular Germ cell Neoplasia (ITGCN) or CIN

- Precede both Seminomas & NSGCTs
- Very low incidence (0.2%)
- higher in men with impaired fertility (0.5%) & in those with crypt orchid testis (2% to 4%)

Seminomas

- Most common
- Median age 36yrs
- IHC: PLAP +/SALL4+ /CK -/Vimentin –
- Presence of syncitiotrophoblast don't alter outcome

- Spermatocytic seminomas:
  Rare, found in older age
  Bilateral
  With CIS element/without typical IHC patters

NSGCTs

- Most tumors are mixed
- Median age 27yrs
- Mixed with seminoma element don't alter prognosis
- IHC: CK+/Vimentin+/SALL4 +

- Pure Chorio Ca is rare/β HCG /poor prognosis
- Yolk Sac Tumor (Endodermal sinus tumor)
  Rarely Pure
  mixed pattern common in childhood GCT
  Elevated AFP

Patterns of spread

- Direct extension rare: Sp cord (T3)/scrotum (T4)
- Lymphatic spread commonest mode
- Landing zone is RP node
- Rt: Inter-aortocaval
- Left: Para-aortic
- Retrograde spread to iliac node in advanced cases
- 15% C/L Node (rare isolated C/L node)
- Supra diaphragmatic spread (then left SCLN) in relapse
- Pelvic and Inguinal Node + rare

Patterns of LN spread

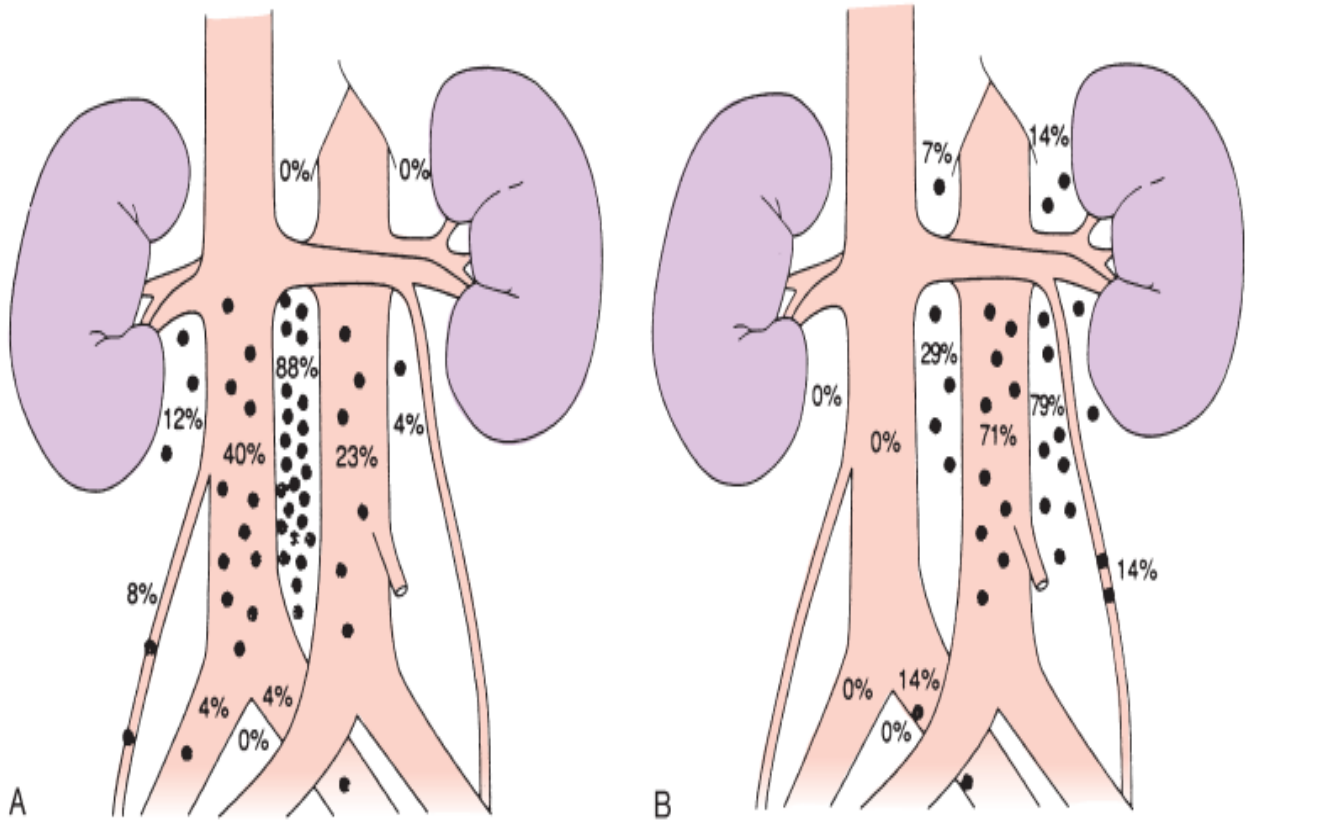


Figure 53-1 Distribution of retroperitoneal lymph node metastases in early-stage nonseminoma germ cell tumor. **A,** Right testis primary tumor. **B,** Left testis primary tumor.

Gunderson Tepper page 1129

Factors for Inguinal LN involvement

- Prior scrotal / Inguinal Sx
- Total orchiectomy with incision in Tunica albuginea
- Tm involving Tunica Vaginalis/Epid
- Crypt orchid testis

- Due to aberrant anastomosis of lymphatic vessels.

Hematological spread

- Early in NSGCTs
- Lung Parenchyma :MC (44%)
- Mediastinal node (11%)(seminomas more common)
- Neck Node (11%)
- Liver (6%)
- Others

- Metastasis to lung (IIIA) is more common and non-pulmonary visceral mets(NPVM) (IIIB) less common in seminomas.
- Embryonal carcinoma may present with lung mets without nodal involvements: CECT THX must

Evaluation : Golden Rule

- H/P exam
- Testicular USG
- Markers (AFP/β HCG/LDH)
- Blood Biochemistry
- CXR

GCT?

- Radical Inguinal Orchiectomy +/- C/L testis biopsy
- Sperm Banking discussion
- Metastatic work up
- Repeat Biomarkers (Post op)

Tumor Markers:

- Markers should be assessed prior/after orchiectomy
- Post Sx Markers are used for staging
- Markers not normalising after Sx without

Biomarkers neither helps to stage Seminoma (except stage IS) nor signify outcome like NSGCTs

- 2 to 3 days for β hCG
- 5 to 7 days for AFP
- B HCG and AFP rise in 85% case

Tumor Markers: Beta- HCG

- HCG (distinct α & β subunits)
- Normally produced by placenta
- 15% of seminomas
- False +ve in prostate ca/ UB ca/ RCC/ marijuana
- Half life 22hrs

- Sometimes there is a plateau after 4th cycle of CT (slightly > N) then fall slowly
- This persistent elevation during clinical remission doesn't need salvage Tt.

AFP

- elevated in NSGCTs (NOT in PURE seminoma)
- False + : CLD/HCC
- Half life 5days
- AFP not declining after Clinical remission: Check liver function

- GCTs that histologically appear to be pure seminoma with elevated serum AFP are given the clinical diagnosis of NSGCT, and are treated as such

LDH

- elevated 60% cases of NSGCTs

- Total LDH rise prior TT is prognostic for NSGCTs but not in seminoma

PLAP

- specific for Seminoma but without clinical relevance

Metastatic work up

- Pure seminoma (HP + normal AFP)

Abd-pelvic CECT
CXR
Chest CT: abnormal CXR or Abd CT
Bone Scan (if needed)
MR Brain (if needed)

- NSGCTs (including mixed and seminoma with elevated AFP)

Chest CT optional

Serum Biomarkers (POST OP)

Staging :AJCC/ UICC 2010

Primary Tumor (T)*

The extent of primary tumor is usually classified after radical orchiectomy, and for this reason, a pathologic stage is assigned.

pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (e.g. histologic scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion

*Note: Except for pTis and pT4, extent of primary tumor is classified by radical orchiectomy. TX may be used for other categories in the absence of radical orchiectomy.

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Pathologic (pN)

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to five nodes positive, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than five nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Distant metastasis other than to nonregional lymph nodes and lung

Serum Tumor Markers (S)

SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH < 1.5 x N* *and* hCG (mIu/mL) < 5,000 *and* AFP (ng/ml) < 1,000
S2	LDH 1.5-10 x N *or* hCG (mIu/mL) 5,000-50,000 *or* AFP (ng/ml) 1,000-10,000
S3	LDH > 10 x N *or* hCG (mIu/mL) > 50,000 *or* AFP (ng/ml) > 10,000

*N indicates the upper limit of normal for the LDH assay.

American Joint Committee on Cancer (AJCC)
TNM Staging System for Testis Cancer (7th ed., 2010)

ANATOMIC STAGE/PROGNOSTIC GROUPS

Group	T	N	M	S (Serum Tumor Markers)
Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	PT3	N0	M0	S0
	PT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/Tx	N1-3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/Tx	Any N	M1b	Any S

International Germ Cell Cancer Collaborative Group (IGCCCG) Prognostic grouping

RISK CLASSIFICATION FOR ADVANCED DISEASE (post-orchiectomy)[1]

Risk Status	Nonseminoma	Seminoma	5yr OS(%)	
			SGCT	NSGCT
Good Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Post-orchiectomy markers- all of: AFP < 1,000 ng/mL hCG < 5,000 iu/L LDH < 1.5 x upper limit of normal	Any primary site and No nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH	86	92
Intermediate Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and Post-orchiectomy markers- any of: AFP 1,000–10,000 ng/mL hCG 5,000–50,000 iu/L LDH 1.5–10 x upper limit of normal	Any primary site and Nonpulmonary visceral metastases and Normal AFP Any hCG Any LDH	72	80
Poor Risk	Mediastinal primary tumor or Nonpulmonary visceral metastases or Post-orchiectomy markers- any of: AFP > 10,000 ng/mL hCG > 50,000 iu/L LDH > 10 x upper limit of normal	No patients classified as poor prognosis		50

Source: Figure 4 from the International Germ Cell Cancer Collaborative Group: International Germ Cell Consensus Classification: A Prognostic Factor-Based Staging System for Metastatic Germ Cell Cancers. J Clin Oncol 1997;15(2):594-603. Reprinted with permission of the American Society of Clinical Oncology.

Treatment over view: seminoma

	Stage I	Stage IIA	Stage IIB/IIC/III
First line	Low risk* Preferred : • Surveillance Alternatively : ▪ Carboplatin x 1 (AUC 7) ▪ Radiotherapy (20 Gy) High risk# Preferred: • Surveillance • Carboplatin x 1 (AUC 7) Alternatively: • Radiotherapy (20 Gy)	▪ BEPx3 (or EPx4) ▪ Radiotherapy	▪ BEPx3-4 (VIPx3-4)
Residual disease	n/a	Observation Consider biopsy or resection of lesion > 3 cm, particularly if PET positive	
Relapse	Post-surveillance/carboplatin ▪ Localised: Radiotherapy ▪ Otherwise: BEPx3-4 Post-radiotherapy ▪ BEPx3 (EPx4)	Salvage chemotherapy In localised lesions: consider radiotherapy Surgery in case of a single resectable lesion	

*Low risk: absence of rete testis invasion and tumour <4 cm
#High risk: rete testis invasion or tumour ≥4 cm

ESMO guideline 2014

IS:
Stringent Imaging
BEP/EP4

IIA:
RT to PA and I/L iliac LN 30Gy
Prefer BEP3 in >1Node+

IIB:
RT may be considered in selected non-bulky cases
PA and I/L iliac LN 36Gy

IIC/III:
Consider BEP 4 in Intermediated risk group (III with NPVM)

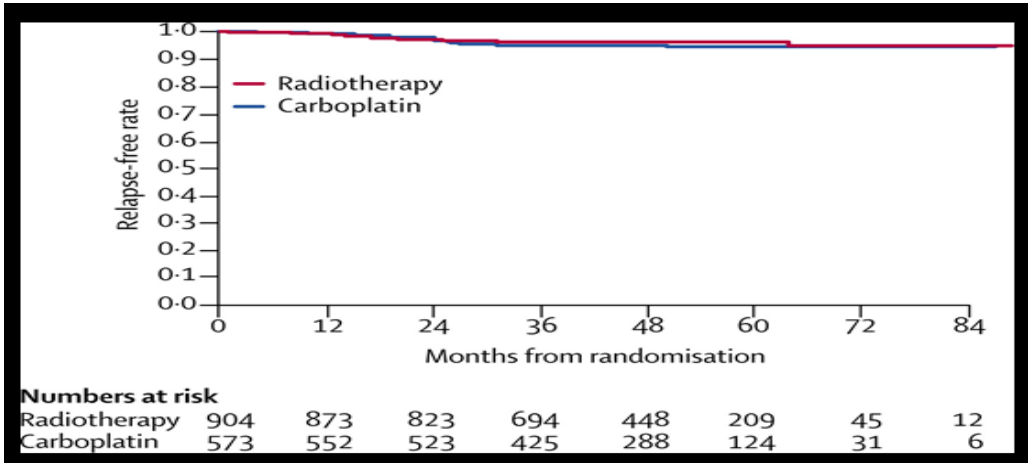
Rete testis/ Tm>4 cm criteria is doubtful in some trials

Evolution

- Historically SGCT was treated with Sx+ Inguinal + PA node RT + Prophyalactic Mediastinal RT
- Prophy Mediastinal RT abandoned 1960 for cardiac events
- Dogleg was standard with 30Gy/15#
- British MRC TE10 trial 1999 showed PA RT= Dogleg RT
- British MRC TE18 trial (2005) showed for stage I similar outcome for 30Gy/15# and 20Gy/10#.
- British MRC TE19 trial (2005) showed similar outcome of single dose AUC7 Carbo vs 20Gy/10# PA RT.
- British Columbia (2014) and Spanish group (2011) emphasized on Risk adaptive treatment approach and Active surveillance for low risk pts.

Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial

R T D Oliver, M D Mason, G M Mead, H von der Maase, G J S Rustin, J K Joffe, R de Wit, N Aass, J D Graham, R Coleman, S J Kirk, S P Stenning, for the MRC TE19 collaborators and the EORTC 30982 collaborators*



Randomized Trial of Carboplatin Versus Radiotherapy for Stage I Seminoma: Mature Results on Relapse and Contralateral Testis Cancer Rates in MRC TE19/EORTC 30982 Study (ISRCTN27163214)

R. Timothy D. Oliver, Graham M. Mead, Gordon J.S. Rustin, Johnathan K. Joffe, Nina Aass, Robert Coleman, Rhian Gabe, Philip Pollock, and Sally P. Stenning

Lancet 2005:
Updated (6.5yrs F/U) in JCO 2011

RFS similar CT vs RT
94.7% vs 96%

C/L testis GCT FS similar
99.8% vs 98.8%
CT less toxic

- RT less preferred for ling term secondary carcinogensis
  (Ann Oncol. 2013 Apr; 24(4): 878–888)

True long term adverse eventd>10yrs till not known

Risk-Adapted Treatment in Clinical Stage I Testicular Seminoma: The Third Spanish Germ Cell Cancer Group Study

Jorge Aparicio⇑, Pablo Maroto, Xavier García del Muro, Josep Gumà, Alfonso Sánchez-Muñoz, Mireia Margelí, Montserrat Doménech, Romá Bastús, Antonio Fernández, Marta López-Brea, Josefa Terrassa, Andrés Meana, Purificación Martínez del Prado, Javier Sastre, Juan J. Satrústegui, Regina Gironés, Lidia Robert and José R. Germà

[+] Author Affiliations

Corresponding author: Jorge Aparicio, MD, Servicio de Oncología Médica, Hospital Universitario y Politécnico La Fe, Bulevar Sur, s/n, E-46026 Valencia, Spain; e-mail: japariciou@seom.org.

Presented at the 46th Annual Meeting of the American Society of Clinical Oncology, June 4-8, 2010, Chicago, IL.

- Tumor size>4cm
- Rete testis invasion
- 2factors : Adjuvant Carboplatin AUC7
- 1 factor: AS

Stage IA/ IB Pure seminoma

- Primary Tt: orchiectomy
- Adj: Surveillance/CT/RT
- DFS>96% irrespective of choice

- Active surveillance:

- 5yr Relapse rate 15-20% (infra-dia LN)
- Median time 12-15months
- 5yr DFS99%

Follow up in IA/ IB pure seminomas

Table 1 Clinical Stage I Seminoma: Surveillance After Orchiectomy

	Year (at month intervals)				
	1	2	3	4	5
H&P[1,2]	Every 3–6 mo	Every 6–12 mo	Every 6–12 mo	Annually	Annually
Abdominal ± Pelvic CT	At 3, 6, and 12 mo	Every 6–12 mo	Every 6–12 mo	Every 12–24 mo	
Chest x-ray	As clinically indicated, consider chest CT in symptomatic patients.				

Table 2 Clinical Stage I Seminoma: Surveillance After Adjuvant Treatment (Chemotherapy or Radiati

	Year (at month intervals)				
	1	2	3	4	5
H&P[1,2]	Every 6–12 mo	Every 6–12 mo	Annually	Annually	Annually
Abdominal ± Pelvic CT	Annually	Annually	Annually	------	
Chest x-ray	As clinically indicated, consider chest CT in symptomatic patients.				

Stage II/ III seminoma : evolution

- Classen J (2003): Modified dogleg portal with 30Gy IIA and 36Gy IIB : excellent outcome on 6yrs F/U

- Spanish GCSG (2003) : BEP3/EP4 acceptable alternative to RT

- IGR France (2001): Risk adaptive strategy is sound option
- Tm size>3cm IIB CT
- Tm size <3cm IIB RT

IIA/ IIB (node <2/ 2-5cm)

- RT main stay Tt IIA
- Relapse rate 5% 5yr OS almost 100%
- 30Gy/15# in 2phases
- Dogleg field : PA + I/L iliac Node

- IIB (nonbulky <3cm):
- Dose is 36Gy
- Bulky prefer CT>RT

Domont J et al. Urol Oncol. 2013 Jul;31(5):697-705

IIC/ III

- Good Risk: IIC / III without NPVM
- BEP3/ EP4

- Intermediate risk : III + NPVM
- BEP4/ VeIP

F/ U

- CECT thx/Abd /Serum Markers

- Residual mass >3cm with normal markers : PET evaluation: (>6wees post CT)

- PET –ve: F/U
- Markers 2m yr1/3m yr2/6m later on
- CECT abdomen 3m,6m then clinically indicated

- PET +ve residual:
- Resection
- 2ndline CT (TIP/VeIP)

NSGCTs: Tt overview

	Stage I	Stage IIИII		
		Good	Intermediate	Poor
First line	Vascular invasion present Preferred: • Surveillance Alternatively: ▪ 1-2xBEP ▪ RPLND (rarely) Vascular invasion absent Preferred: ▪ 1-2xBEP ▪ Surveillance Alternatively: ▪ RPLND (rarely)	▪ BEPx3 (EPx4) ▪ RPLND (if marker negative stage IIA)	▪ BEPx4 ▪ VIPx4	▪ BEPx4 ▪ VIPx4
Residual disease	n/a	Resection in case of lesion > 1 cm Observation in case of lesion < 1 cm		
Relapse	Post-surveillance or post-RPLND: ▪ BEPx3-4 Surgery in case of a single resectable lesion Post-chemotherapy: ▪ Salvage chemotherapy Surgery in case of a single resectable lesion	Salvage chemotherapy Surgery in case of a single resectable lesion		

ESMO guidelines 2013

IA(T1): surveillance preferred
IB(T2-T4): Sx/CT
SX:
Nerve sparing RPLND

IS: treat as II/III

Sx to be done within 6weeks of CECT or <10days of last marker assay

PET CT is not helpful in NSGCTs

Treatment : NSGCTs IA/ IB

- Vascular invasion signifies high local relapse and significant prognostic factor for AS pts.
- VI –ve: Low risk : Active Surveillance (AS)
- VI +ve: High Risk : 2 cycles BEP

- AS/ RPLND similar outcome (cure rate >95%)
- 20-30% chance of relapse in AS pts needing CT later on
- European schools prefer 2 cycles of BEP as Sx needs special experiences

- For IB :
- 2 cycles of BEP (low relapse rate on 6yrs F/U)
- NS RPLND rarely preferred (when CT is contraindicated)

Post RPLND Tt (if done up fornt)

- pNO: AS
- pN1: AS>CT
- PN2 : CT (BEP2/EP2)>AS
- pN3: BEP3/EP4

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

Randomized Phase III Trial Comparing Retroperitoneal Lymph Node Dissection With One Course of Bleomycin and Etoposide Plus Cisplatin Chemotherapy in the Adjuvant Treatment of Clinical Stage I Nonseminomatous Testicular Germ Cell Tumors: AUO Trial AH 01/94 by the German Testicular Cancer Study Group

Peter Albers, Roswitha Siener, Susanne Krege, Hans-Uwe Schmelz, Klaus-Peter Dieckmann, Axel Heidenreich, Peter Kwasny, Maik Pechoel, Jan Lehmann, Sabine Kliesch, Kai-Uwe Köhrmann, Rolf Fimmers, Lothar Weißbach, Volker Loy, Christian Wittekind and Michael Hartmann

- 2008 (median F/U 4.7yrs)
- Similar 2yr RFS in BEP1 vs RPLND

Archivos Españoles de Urología

Management of patients with clinical stage I non-seminomatous testicular germ cell tumours: active surveillance versus primary chemotherapy versus nerve sparing retroperitoneal lymphadenectomy.

Authors: Axel Heidenreich y David Pfister.

Arch. Esp. Urol. 2012; 65 (2): 215-226

Vol. 65, Number. 2, March 2012

Clinical stage I testicular nonseminomatous germ cell tumours (NSGCT) are highly curable. Following orchidectomy a risk-adapted approach using active surveillance (AS), nerve sparing retroperitoneal lymph node dissection (nsRPLND) and primary chemotherapy is recommended by the current guidelines.

CS I is defined negative or declining tumour markers to their half-life following orchidectomy and negative imaging studies of the chest, abdomen and retroperitoneum. Low risk CS I NSGCT are defined by the absence of vascular invasion, low percentage of embryonal carcinoma (ECA) and low proliferating Ki-67 index. High risk CS I NSGCT are defined by the presence of VI, high percentage of ECA and a high Ki-67 index.

Arch. Esp. Urol. 2012; 65 (2): 215-226 According to the current guidelines, active surveillance, primary chemotherapy and nerve sparing RPLND represent 3 treatment options with the same high cure rate of about 100% but significantly different long-term complications. As demonstrated, active surveillance can be performed in low risk and in high risk NSGCT with an anticipated relapse rate of about 15% and 50%. The majority of patients will relapse with good and intermediate prognosis tumours which have to be treated with 3 to 4 cycles chemotherapy. About 25% to 30% of these patients will have to undergo postchemotherapy RPLND for residual masses. Primary chemotherapy with 1 -2 cycles PEB is a therapeutic option for high risk clinical stage I NSGCT associated with a recurrence rate of only 2-3% and a minimal acute and long-term toxicity rate. Nerve sparing RPLND, if performed properly, will cure about 85% of all high risk patients with clinical stage I NSGCT without the need for chemotherapy.

Although armchair calculations of the odds of cure and toxicity associated with the various treatment options can be performed, recommendations about the most optimal therapy in clinical stage I NSGCT remain controversial. There seems to be a consensus that active surveillance is the treatment strategy of choice for CS I low risk patients. However, there is no clear cut recommendation in high risk patients.

Each treatment has its own advantages and disadvantages which have to be discussed thoroughly with the patient. If, however, the positive results of 1 cycle of PEB can be validated, it will become the standard cytotoxic approach for clinical stage I NSGCT.

F/ U : NSGCTs IA/ IB

- H/P
- Serum Markers
- Abdomino-pelvic CT
- CXR

- 1st yr 2m
- 2nd yr 3m
- 3rd yr 6m
- 4th yr onwards annually

- AS group needs 6 monthly CECT ,other cases annually

IIA/ IIB

- Post OP Marker N: Low Risk
- RPLND (unifocal disease)/ BEP3=EP4

(Outside RP node: Multifocal)

- Post Sx CT (like Seminoma)

- Post OP Marker ↑/ Multifocal : High Risk
- BEP3=EP4

- Post CT/SX: CECT: if tm size<1: F/U
- Post CT/Sx : CECT: if tm size>1
- RPLND(if CT before)
- CT (if SX before)

Stage IS/ Multifocal/ marker +ve II/ III

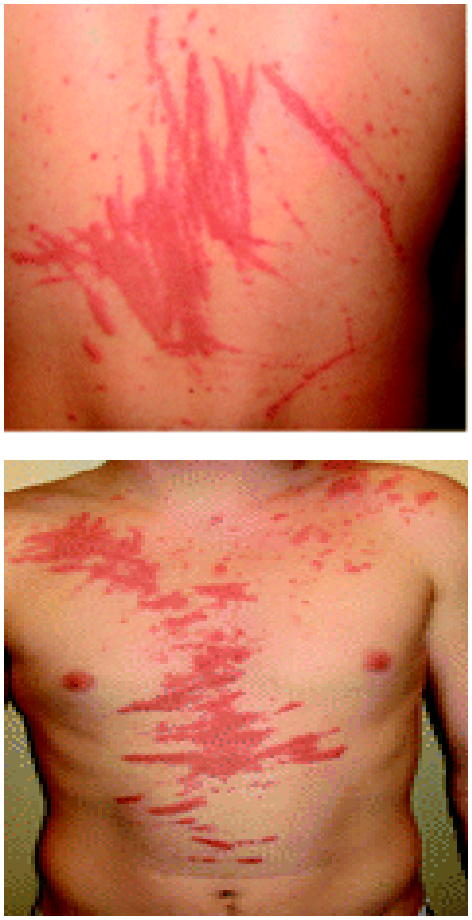
- Good prognosis:
- BEP3 = EP4
- Intermediate /poor Prognosis
- BEP4

- VIP 4(Eto/ Ifos/Cis) : when Bleomycin is contraindicated

- CECT/marker after 6weeks:
- Management of residual like IIA/IIB

Primary chemotherapy in GCT

BEP[a]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	100 mg/m^2	Day 1–5
Bleomycin	30 mg	Day 1, 8, 15
EP[b]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	100 mg/m^2	Day 1–5
VIP/PEI[c]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	75 mg/m^2	Day 1–5
Ifosfamide	1.2 g	Day 1–5



Flagellate Erythema

- Caution
- CXR/PFT (specially DLCO/VC) baseline/each cycle
- >15% decrease in parameters stop Bleomycin

Salvage/ 2nd line therapy of advanced disease

Parameter	Score points				
	0	1	2	3	Score
Primary site	Gonadal	Extragonadal	–	Mediastinal non-seminoma	
Prior response	CR/PRm-	PRm+/SD	PD	–	
PFI, months	>3	≤3	–	–	
AFP salvage	Normal	≤1000	>1000	–	
HCG salvage	≤1000	>1000	–	–	
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; non-seminoma or mixed tumours = 0					
Final prognostic score (−1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)					

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

Prognostic score for patients with relapsing non-seminoma or seminoma

Lorch et al. ASCO 2010

Chemotherapy choices

- Conventional dose TIP
- High dose TI Carbo Eto (with HSCT)

- High Dose CT preferred in one retrospective study in high risk relapse group.

- Pico et al 2005 compared HDCT (Carbo/Eto/Cyclo + HSCT) with conventional TIP without any outcome difference.

- Choice is still debatable

2ndline Chemotherapy

VIP/PEI[c]	(Repeat cycles every 3 weeks)	
Cisplatin	20 mg/m^2	Day 1–5
Etoposide	75 mg/m^2	Day 1–5
Ifosfamide	1.2 g	Day 1–5
TIP[d]	(Repeat cycles every 3 weeks)	
Paclitaxel	250 mg/m^2	Day 1
Cisplatin	25 mg/m^2	Day 2–5
Ifosfamide	1.5 g	Day 2–5
VeIP[e]	(Repeat cycles every 3 weeks)	
Vinblastine	0.11 mg/kg	Day 1 + 2
Ifosfamide	1.2 g/m^2	Day 1–5
Cisplatin	20 mg/m^2	Day 1–5
TI-CE[f]	(TI cycles 1–2 every 2 weeks)	
Paclitaxel	200 mg/m^2	Day 1
Ifosfamide	2.0 g	Day 2–4
	(CE cycles 3–5 every 3 weeks)	
Carboplatin	AUC = 7	Day 1–3
Etoposide	400 mg/m^2	Day 1–3
CE[g]	(Two cycles, may be preceded by VeIP)	
Carboplatin	700 mg/m^2	Day 1
Etoposide	750 mg/m^2	Day 1–3

[d]Four cycles TIP, typically as conventional dose salvage chemotherapy.
[e]Four cycles VeIP, typically as conventional dose salvage chemotherapy.
[f]Two cycles TI before stem cell harvesting, thereafter three cycles CE as high-dose treatment.
[g]Two cycles CE as high-dose treatment, may be preceded by cyto-reductive VeIP.

Palliative Chemotherapy:

Gem/OX
Gem/Pacli
Gem/Ox/Pacli
Etoposide (oral)
?Sunitinib

Late relapse

- Relapse >2years occurring at least after 3cycles CT
- Occurs in 4% patients
- Often present with AFP+ YST or teratoma
- Do not respond well with CT
- In marker –ve relapse : Post OP H/P check

- Treatment:
- If possible resection
- Individualized CT (as upfront or post op)

RT Technique

- Pre RT counseling
- Semen analysis and Sperm banking

- Patient position
- Supine arms by the side of body
- Pelvic or fit may be used
- Keep Penis out of the field
- Clamshell on uninvolved testis
- Legs separated with towel roll
- Simulation CT(3D Plan)

Testicular shielding

- Normally testis receives 1.5 Gy dose from dogleg fields
- Attempt should be made to prevent testis dose <1% of midplane dose
- Commonly used device is Clamshell shield
- Lead device (1cmm thick cup) to shield C/L testicles
- Mean dose of C/L testicles

	PA	PA + IL iliac
Without shield	1.86 cGy	3.89 cGy
With shield	0.65 cGy	1.48 cGy

2D technique

- **Stage I: PA node**
- Borders:
- Sup:

  Classical :

  T9- T10 junction

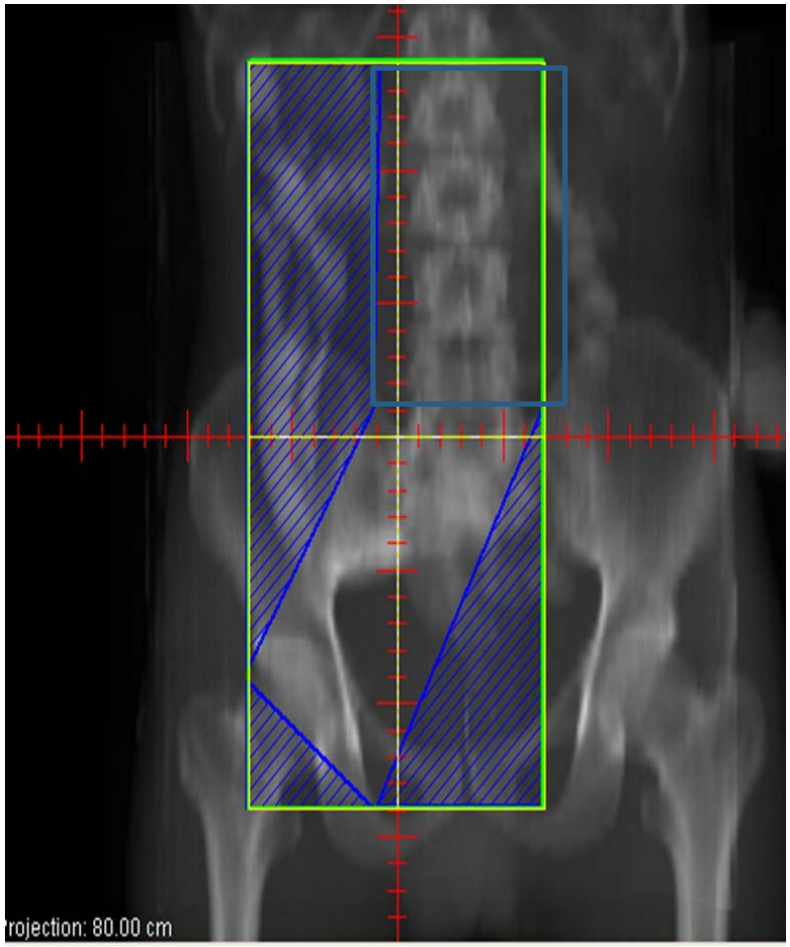
  Modified by Classen

  T10-11

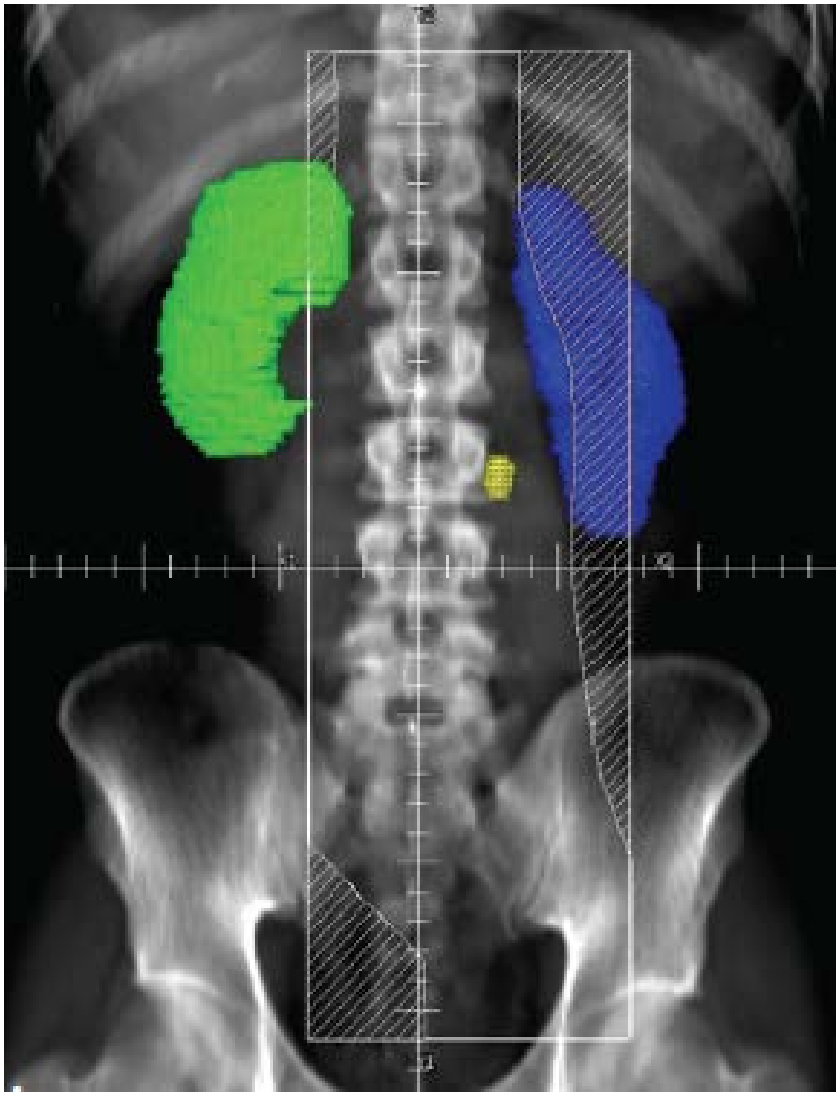
- Inf: L5-S1 junction
- Lat: tip of Tr process

- Portal AP-PA

May need renal block



- If left sided Tumor widen the left lateral border to include renal hilar area

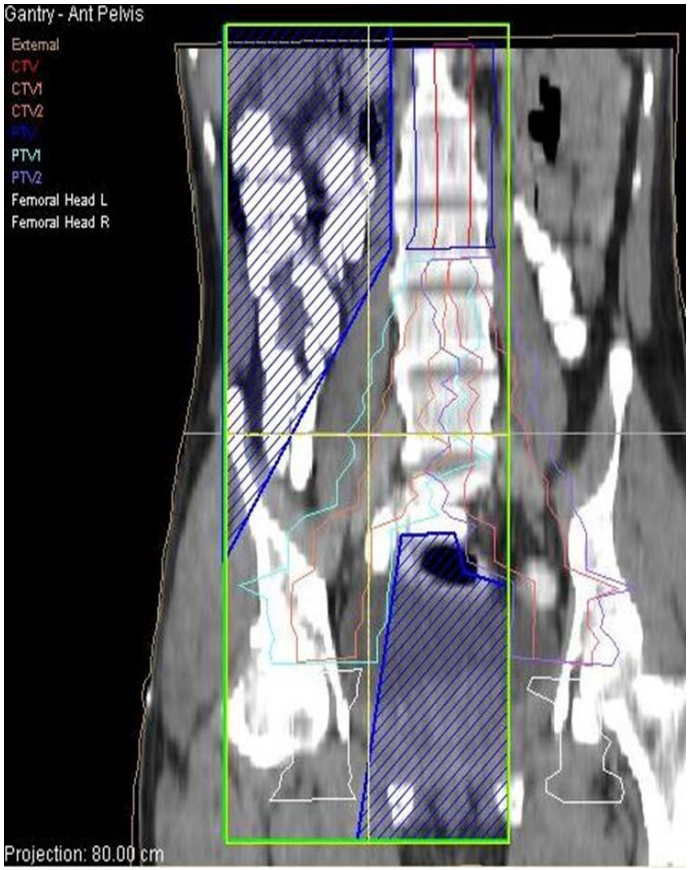


3D technique

- Aorta & IVC contoured with 1.2-19.9 cm margin to include all paraaortic, aorto-caval, paracaval, pre-aortic nodes

- PTV : 0.5cm margin

- Alteration of Lymph channels
- I/L iliac & inguinal LN along with surgical scars need to be treated



RT dose:

1. 25Gy/20#/1.25Gy/4weeks (north America) or
2. 20Gy/10#/2Gy/2weeks (Europe)

- No added advantage of giving I/L iliac in addition to PA node. (MRC UK)
- 30Gy vs 20 Gy dose had no difference in Local relapse and survival. (MRC UK 2008)

IIA and IIB: 2D technique

- RT contraindicated in:
- IBD
- Horse shoe kidney
- Prior H/O RT

- Target : PA + I/L Iliac LN
- Classical Dogleg/ Hockey stick (not used)
- Modified Dog leg (Classen et al.)
- Extended Dog leg (not used)
  - 2phases without gap
  - Dose:
  - IIA: 30Gy/15#/3weeks
  - IIB: 36Gy/18#/3.5weeks

Radiotherapy for Stages IIA/B Testicular Seminoma: Final Report of a Prospective Multicenter Clinical Trial

By Johannes Classen, Heinz Schmidberger, Christoph Meisner, Rainer Souchon, Marie-Luise Sautter-Bihl, Rolf Sauer, Stefan Weinknecht, Kai-U. Köhrmann, and Michael Bamberg

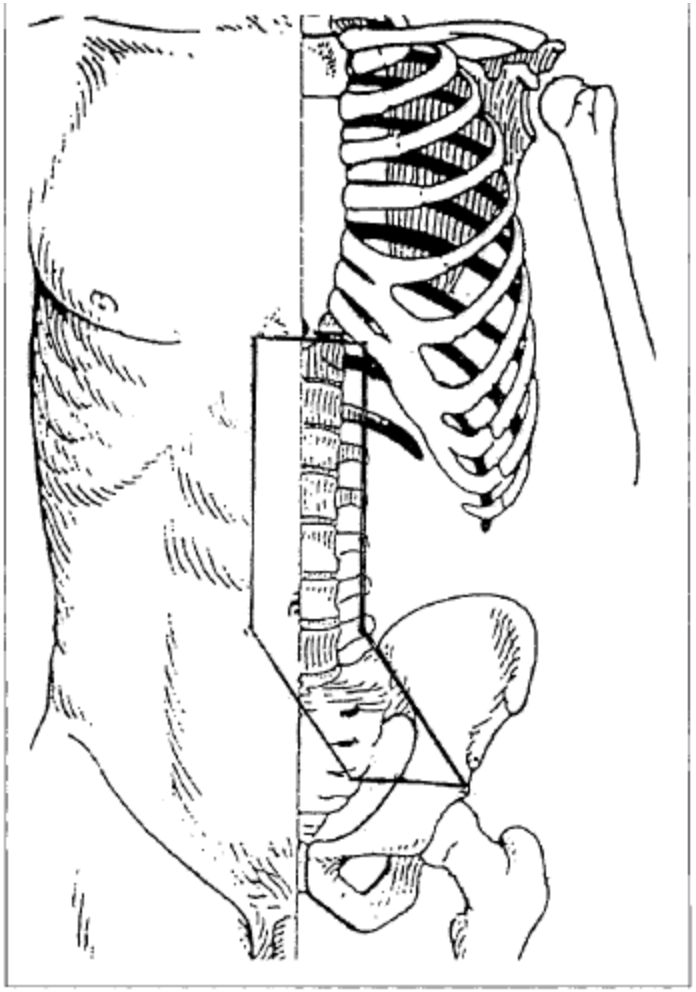


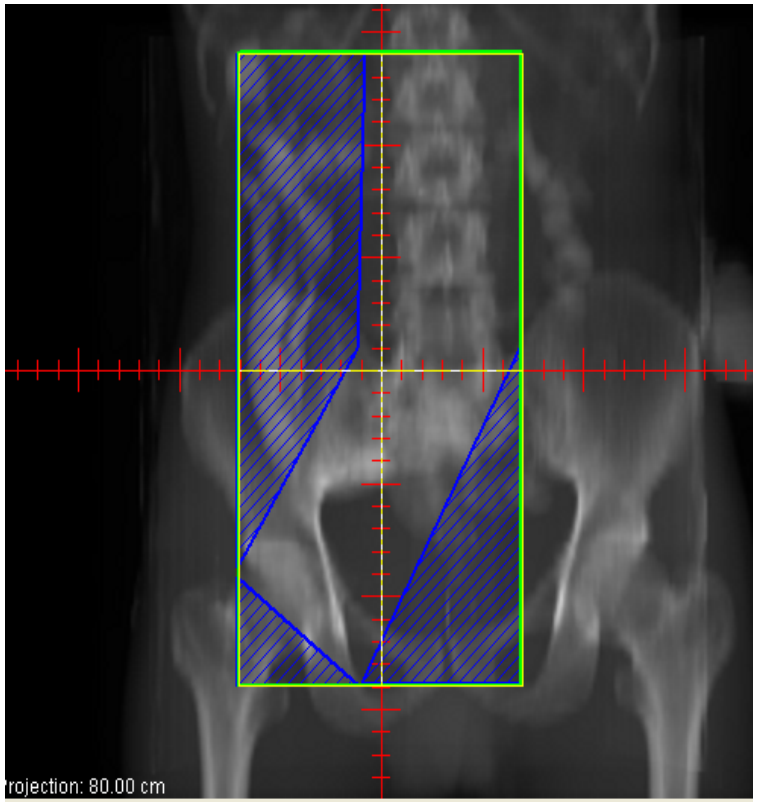
Fig 1. Treatment portals used for treatment of stage IIA and IIB seminoma.

Radiotherapy was applied through ventro-dorsal opposing fields covering macroscopically enlarged lymph nodes, as assessed by CT with a 2-cm safety margin, together with para-aortic/paracaval and ipsilateral high iliac lymph nodes (hockey-stick portals). The upper border of the field was posed at the cranial rim of the 11th thoracic vertebra, and the lower field margin was set to the cranial rim of the ipsilateral acetabulum (Fig 1). The lateral field margins for the para-aortic region were defined by the ends of the lateral vertebral processes, resulting in a width of the fields between 9 and 11 cm. The lateral borders for the iliac region were defined by a line from the upper rim of the acetabulum to the end of the lateral process of the fourth lumbar vertebra. The para-aortic and iliac regions were treated in one field. Individualized absorbers were used for shaping of the fields. All radiation portals were assigned using treatment simulators. Irradiation was performed with 4- to 20-MV photons of linear accelerators. Both opposing fields were treated every day for 5 days per week with a fraction of 2.0 Gy per day as specified in the International Commission on Radiation Units and Measurements (ICRU) 29 report for opposing fields. A total dose of 30 Gy was applied over 15 days for patients with stage IIA disease. For patients with stage IIB disease, the dose was increased to 36 Gy. A boost treatment was not performed.

J Clin Oncol 21:1101-1106.

2D (IIA/ IIB)

- Sup border: T10-11
- Inf: top of acetabulum
- Lat:
- C/L side (below PA field):
- Line joining Tr Pr of L4 (C/L) and obturator foramen
- I/L side(below PA node)
- Line joining Tr Pr of L4 (I/L) and supero-lat part of acetabulum
- Others area to be blocked



Classical dogleg field : Historical

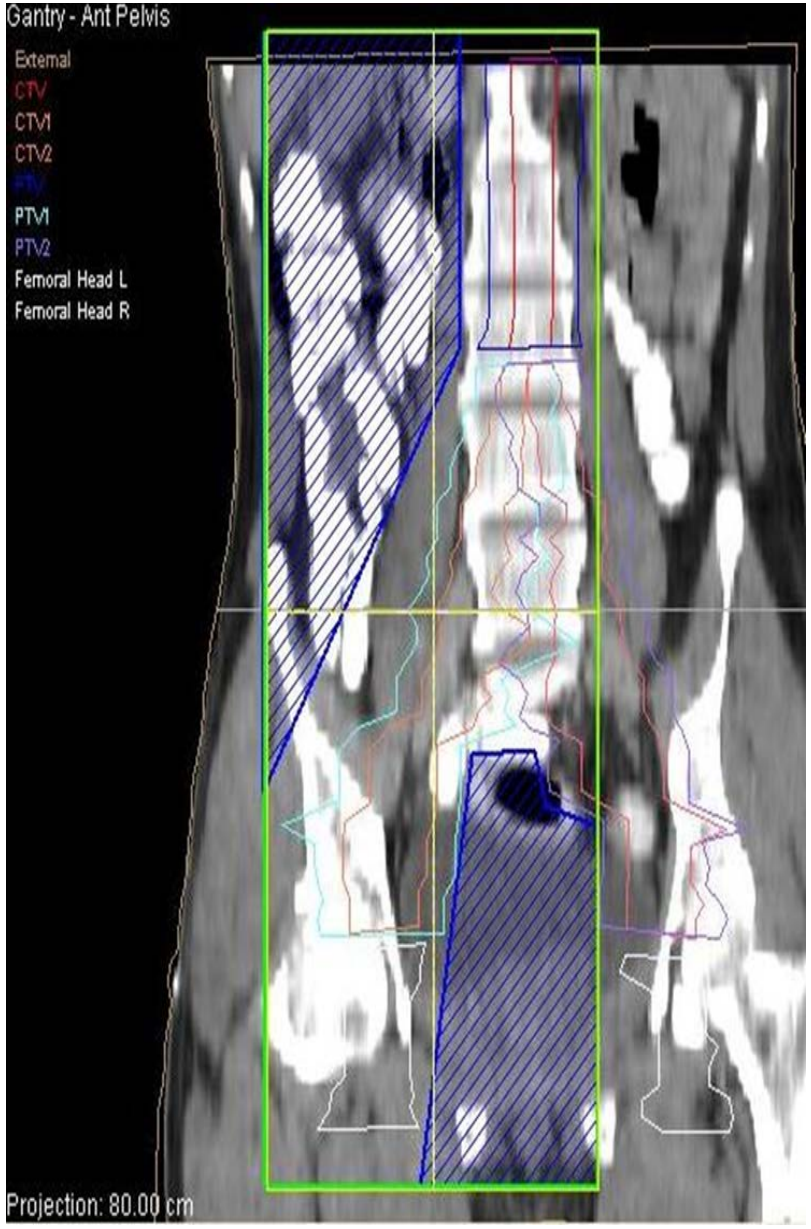
- Sup border : T9/T10 junction
- Inf border : top of obturator foramen
- width : 9-10cm
- On left Lat border is extended to include renal hilum (width 11-12cm)

- Left Kidney may be shielded

- at Mid L4 level field is extended to include Ext Iliac LN (width 11-12cm)

- Proper shield configures the shape of Dogleg


THERAPLANPLUS External Beam Planning - Version 3.8
Beam : Post Pelvis
Tray: Med
Patient Name : Germ Cell Tumor Patient ID : RT/XXX/16 Anatomy : PELVIS OCT
Plan : Phase 1 No. of beams : 2 Norm : 0.00
Modified : RADIOTHERAPY 13-Jun-2016 12:46:57
Plan Database : C:\TPP_DB\PLAN_E.MDB
UM Database : C:\TPP_DB\OLCHUM_SAMPLE-1.MDB
Scale: 0.665:1
Approved by
14-Jun-2016 14:56:13


Gantry - Ant Pelvis
External
CTV
CTV1
CTV2
PTV
PTV1
PTV2
Femoral Head L
Femoral Head R
Projection: 80.00 cm

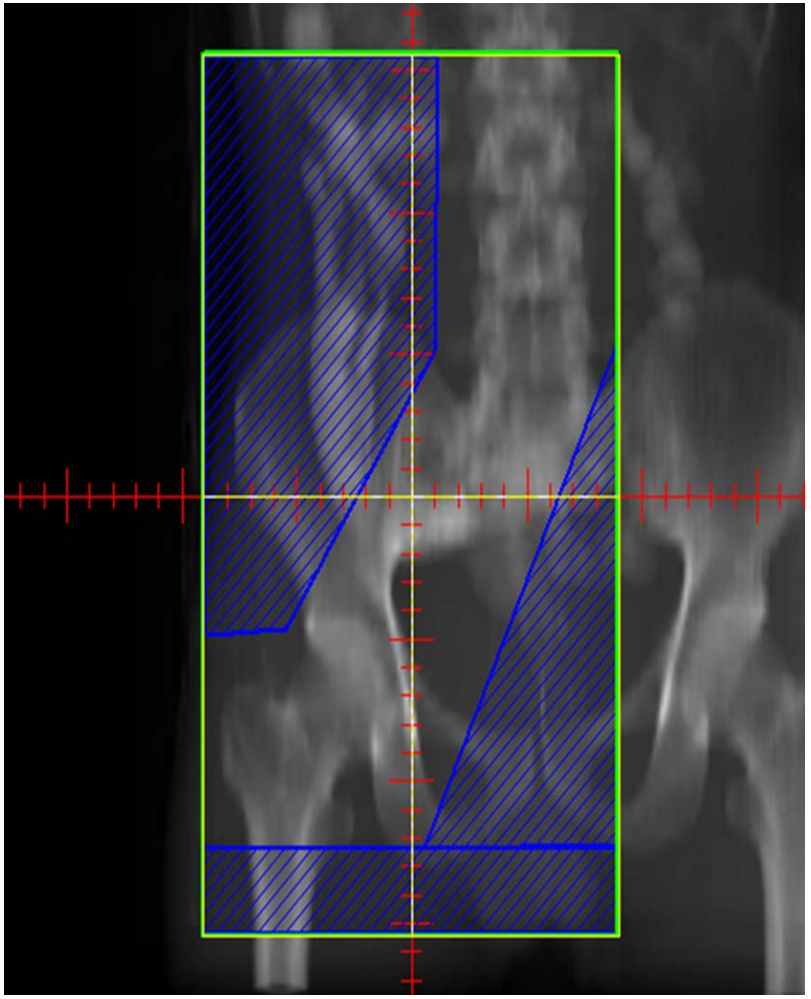
3D technique

- Contouring to be done from T10-T11 to top of acetabulum
- Nodes to be contoured
- PA:
- Contour IVC aorta with 1.2-1.9 cm margin to include all paraaortic, aorto-caval, paracaval, pre-aortic nodes
- Pelvic:
- Common Iliac
- External iliac (I/L)
- Proximal int iliac (I/L)

IIA/ IIB seminomas

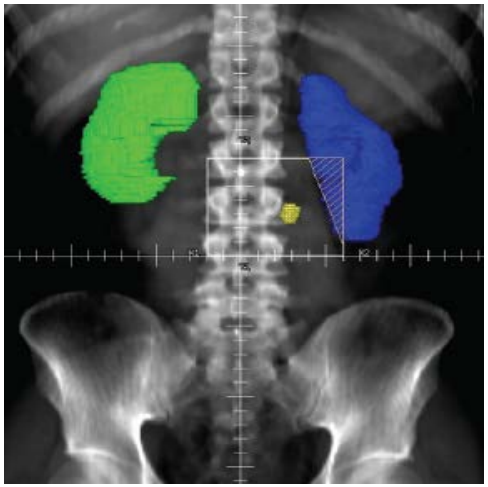
- Inguinal Node + Inguinal scar may be included with a H/O inguinal Sx (Inguinal herniorraphy/orchiopexy).

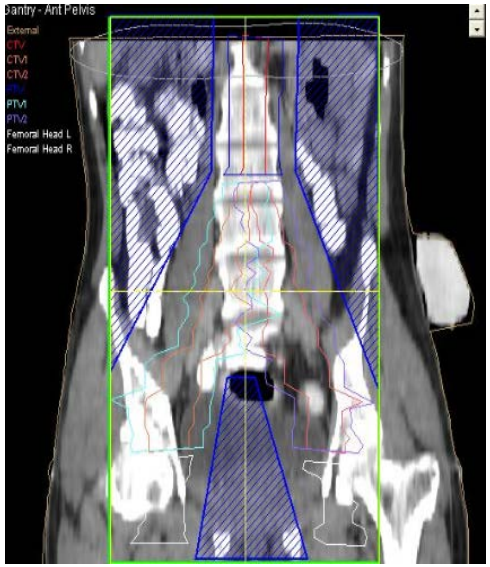
- Extended Dog leg field is used.



Bulky RP node (>5cm)increases risk for C/ L iliac Node.

- Additional TT:
- RT: Inverted Y field
- RT: boost to GTV (25Gy + 10Gy)
- Sequential / Conc. (PMH Canada)
- Chemotherapy in Bulky II





Conformal RT: IMRT

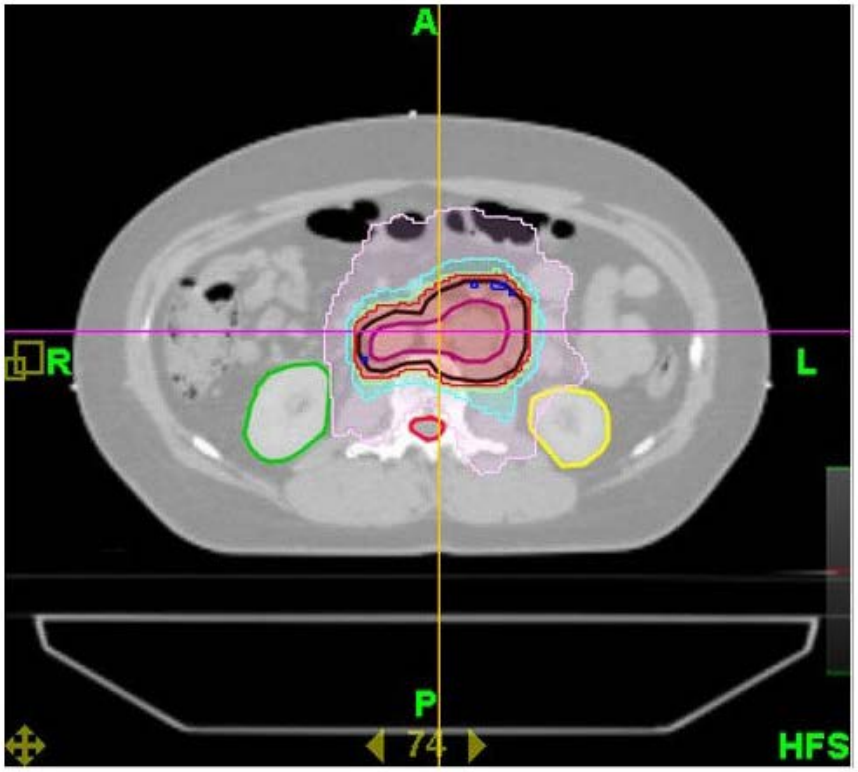


Figure 1
Axial view showing planning target volume and isodose distribution using TomoTherapy, sparing kidneys and spinal cord in the case of stage I seminoma.

▹Boujelben N. Radiation Oncology 2011

OAR constraints

- Testis:
- 0.5 Gy causes temporary azoospermia (reverts <1yr)
- 2Gy causes permanent sterilization

- Kidney:
- D50 ≤ 8Gy (both kidney)
- D15 ≤ 20Gy (if one kidney is present)

Treatment sequel

- Post Tt Life expectancy >40yrs
- Long term F/U mandatory

- Cardiac late effects:
- 7folds risk od CVS disorder (due to cisplatin)
- Dyslipidemia and metabolic syndrome common in GCT survivers

- Need:
- Diet/ exercise/cessation to tobacco
- Cardiac and metabolic screening

Chemo induced neurotoxicity

- 20-40% patients may have Cisplatin induced painful neuropathy
- Cumulative dose of Cispatin and additional use of paclitaxel are risk factors
- Therapies are not so much helpfull

Hypogonadism and Infertility

- Depends on type & duration of therapy
- In a study successful paternity at 15years
- 81% with surveillance,
- 77% after RPLND,
- 65% after RT,
- 62% after CT , and
- 38% after high-dose salvage CT

- Hypogonadism also found
- May need
- Sperm banking
- Testosterone supplementation

Ototoxicity

- 15-20% may have permanent B/L SNHL
- Depends on cumulative dose, dose intensity and genetic underpinning
- No effective treatment option

Psychological issues

- 10-30% patients suffer from moderate to severe grade anxiety and depression
- The issue may be short term and long term
- Sexual dysfunction potentiate depression

Second malignancy

- Acute Leukemia occur within 2-4 years
- Depends on cumulative dose of Etoposide

2course	<1000mg/m2	RR 0.5%
3-4 Course	1500-2000mg/m2	RR <1%
>4 course/HDCT	>20000mg/m2	RR 6%

- 11q- is associated with Etoposide induced AL
- AL in mediastinal GCT is separate entity
- i12 p associated Megakaryocytic AL

- Other SM occur late: around 20years: stomach,Pancreas,UB
- Second GCT in C/L testicles occur 2% patients (RT related)

- Single AUC7 dose Carboplatin apparently decreased incidence, but need longer follow up

Other testicular cancers

- **Sex cord gonadal/stromal tumors**
- Leydig & Sertoli Cell Tumor:
- MC
- A/W steroid hormone hyper secretion
- CT/RT not helpful (?Mitotane may help)

- Granulosa Cell Tumor:
- Rare
- Sx TOC

- Gonadoblastoma:
- May have GCT element
- Aggressive
- CT helpful

- **Lymphoma:**
- B/L
- Systemic disease a/w CNS involvement

The balls are in your court