Management of Testicular Tumors-Seminoma

Quick Review of Staging

- **pT1**: Limited to testis and epididymis (upto T. albuginea)
- **pT2**: LVSI ±T. vaginalis involvement
- **pT3**: Spermatic Cord
- **pT4**: Scrotum

N stage

- **pN1: ≤ 2cm + ≤ 5 nodes**
- **pN2: >2 cm, ≤ 5 cm or, >5 nodes none more than 5cm**
- **pN3: > 5cm**

M Stage

- **M1a** - Non regional nodal or pulmonary metastases
- **M1b** - Nonpulmonary visceral masses

Serum Markers

	LDH	HCG mIU/ml	AFP ng/ml
S0	N	N	N
S1	<1.5 x N	< 5000	< 1000
S2	1.5-10x N	5000 to 50000	1000 to 10000
S3	>10x N	> 50000	>10000

Stage Grouping

Group	T	N	M	S (Serum
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

Summary of Stage Grouping

- **Stage I:** no Dz beyond testis/scrotum (i.e., T1-4N0M0S0-3)
- **Stage II:** regional nodal involvement and S0-S1 tumor markers (IIA = N1, IIB = N2, IIC = N3)
- **Stage III:** S2-S3 tumor markers with N+ Dz, or M1 Dz




A Patient presented with Painless Testicular Mass. What to do next?

- **Testicular ultrasound:**

❖ to confirm the presence of a intra testicular mass

❖ to explore the contralateral testis.

- CBC, RFT, LFT
- CXR-PA
- Serum Markers
- USG Abd & Pelvis

Sperm Banking

- Must be discussed in patients of reproductive age.
- Up to 52% patients will become Permanently Infertile after Treatment

Indications of Testicular Biopsy

- Presence of only macrocalcification on USG
- C/L macrocalcification
- C/L cryptorchid testis or marked atrophy

- Only microcalcifications : Biopsy **NOT** necessary.

Perform Surgery: High Inguinal Orchiectomy

- Further management : Histology and Stage
- Classify into pure seminoma or nonseminoma
- Non seminoma includes mixed seminoma tumors and seminoma histology with elevated AFP), and the stage.

Post Orchiectomy Tests

- Post Orchiectomy Serum Marker Status: Decides Staging
- Usually performed after 3 weeks of Surgery
- When a patient presents with rapidly increasing beta-hCG and symptoms related to disseminated disease, chemotherapy initiated immediately w/o biopsy diagnosis.

Post Orchiectomy Tests

- CE CT Abdomen & Pelvis

- A **Chest CT** is indicated if :

✓ the abdominopelvic CT shows retroperitoneal adenopathy or,

✓ the CXR shows abnormal results.

- Brain MRI and Bone Scan. If clinically indicated.

Strategy for Stage I

- **Stage I A, B:**

❑ Surveillance (Preferred for pT1,2)
❑ Single-agent Carboplatin
(AUC=7 x 1 cycle)
❑ RT to PA and I/L illiac nodes (20 Gy in 10 #)

- **Stage IS:**

Repeat serum marker & assess with abdo/pelvic CT scan for evaluable dz.

Uncommon and generally treated with radiation.

SURVEILLANCE FOR STAGE I

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.				

During Surveillance:

- Testicular ultrasound for any equivocal exam in C/L testis.
- **If Recurrence, treat according to extent of disease at relapse**

Risk Adapted Strategies

- Initial studies: **T>4 cm and rete testis invasion** as a risk factor in predicting relapse in Stage I.
- A validation study by Chung et al revealed that tumor size >4 cm and rete testis invasion were not predictors of relapse.
- Hence, Risk adapted strategy is discouraged.

Carboplatin Dose Calculation

Calvert formula: 7 X (glomerular filtration rate [GFR, mL/min] + 25 mg)

$$GFR = \frac{(140 - Age) \times Body\ weight}{72 \times S.\ Cr} \quad (\times 0.85 \text{ for Women})$$

Use of this dosing formula, as compared to BSA, allows compensation for patient variations in **pretreatment renal function** that result in:

- Underdosing (in patients with above average renal function) or
- Overdosing (in patients with impaired renal function).

PRINCIPLES OF RADIOTHERAPY FOR PURE TESTICULAR SEMINOMA

- Linear accelerators with >6 MV photons should be used when possible.
- The mean dose (Dmean) and dose delivered to 50% of the volume (D50%) of the kidneys, liver, and bowel are lower with CT-based AP-PA 3D-CRT than IMRT.
- As a result, the risk of second cancers arising in the kidneys, liver, or bowel may be lower with 3D-CRT than IMRT, and IMRT is not recommended.

- Radiotherapy should start once the orchiectomy wound has fully healed.
- Patients should be treated 5 days per week.
- Patients who miss a fraction should be treated to the same total dose and with the same fraction size, extending the overall treatment time slightly.

C/I of RT

- Horseshoe (pelvic) kidney,
- Inflammatory bowel disease, or
- A history of RT.




- All patients, with the exception of those who have undergone bilateral orchiectomy, should be treated with a scrotal shield.

- The legs should be separated by a rolled towel of approximately the same diameter as the scrotal shield and its stand.

C/L TESTICULAR SHIELDING

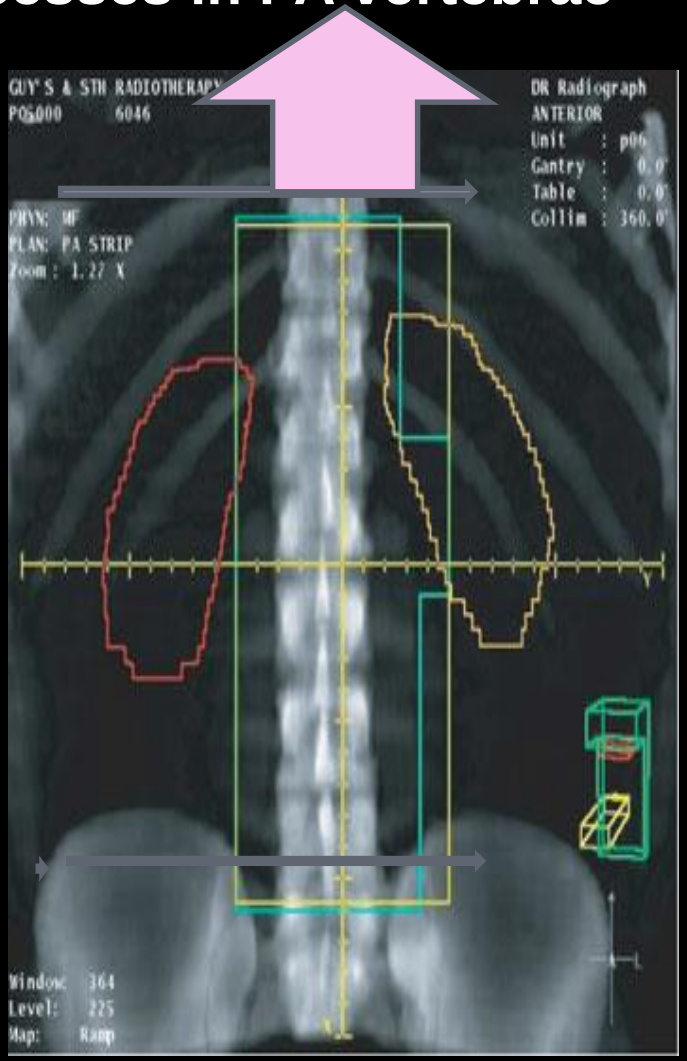
– C/L testis shielded with a lead clamshell device, which consists of a cup that is 1 cm thick.

– This shields the testicle from low-energy scattered photons and effectively reduces the testicular dose by a factor of 4.

- If scrotal irradiation is necessary because of previous scrotal surgery or involvement of the Scrotum, electron therapy is used to treat the scrotal sac and lower inguinal nodes on the affected side.

Para Aortic Field in Stage I Seminoma

10 cm covers the transverse processes in PA vertebrae



upper border of T10 or T11

PARA-AORTIC NODAL IRRADIATION FOR OF LEFT TESTIS

L5 Vertebrae

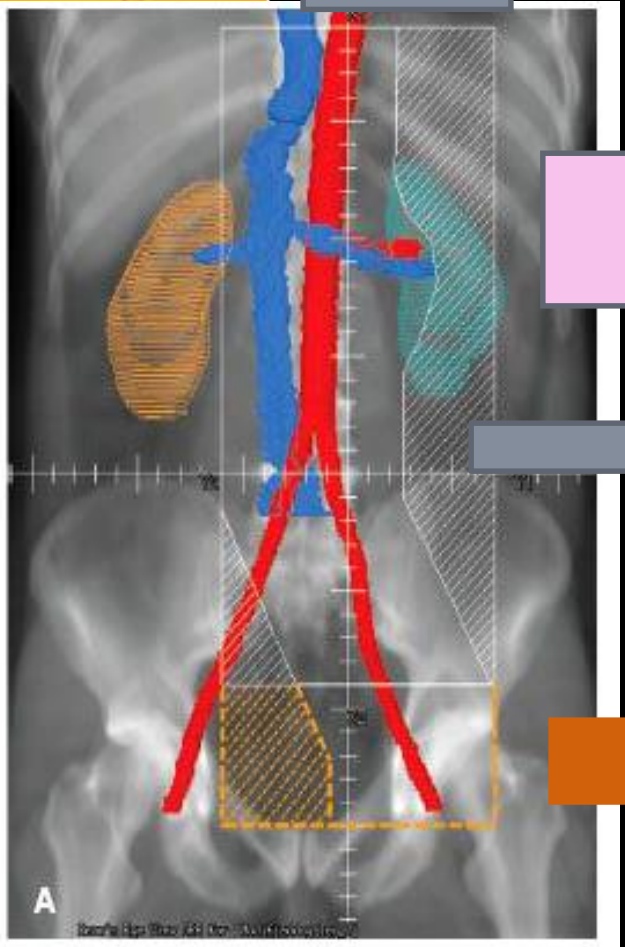
Para Aortic Field- Modified

- Recent nodal mapping studies : fields should target the RP nodes but not necessarily the i/l renal hilar nodes.
- Superior border : bottom of body T11
- Inferior border : inferior border of body L5
- Lateral border: 10 cm wide, encompassing tips of transverse processes of PA vertebrae.

Dog Leg Field

10 cm wide in the para-aortic region and usually covers the transverse processes

upper border of T10 or T11



left renal hilum is included for left-sided tumors (only)

At the **mid-L4** level, the field is extended laterally to cover the i/l external iliac

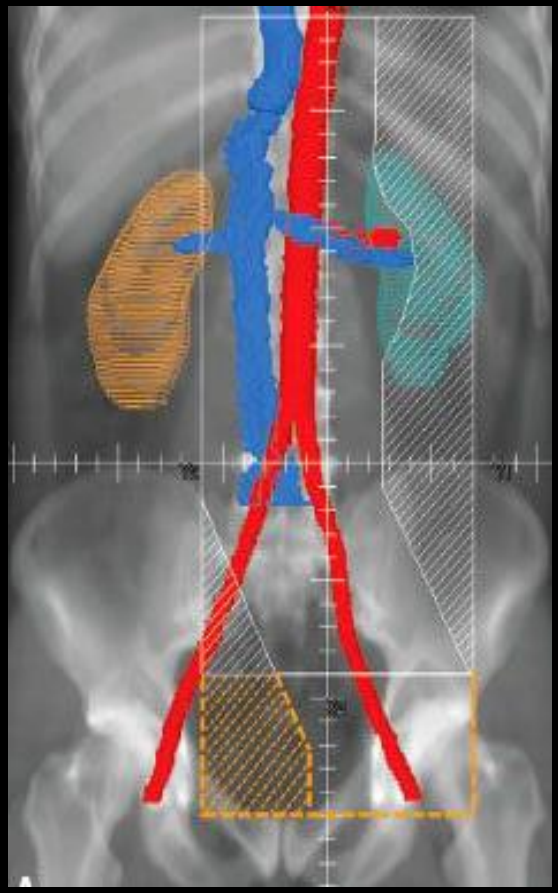
Traditionally, the inferior border was placed at the superior obturator foramen (indicated in orange) to include all external iliac nodes

Dog Leg Field- Modified

- Superior border :bottom of body T11.
- Inferior border : top of the acetabulum.

- The medial border for the lower aspect of the modified dog-leg fields extends from the tip of the c/l transverse process of L5 toward the medial border of the i/l obturator foramen.

- The lateral border for the lower aspect of the modified dog-leg fields is defined by a line from the tip of the i/l transverse process of L5 to the superolateral border of the i/l acetabulum.



3D Planning

- 3D planning is preferred due to potential of marginal miss, with 2D planning based on bony anatomy .
- 3D planning improves target definition and kidney/small bowel shielding.

3D PLANNING

Para-aortic field:

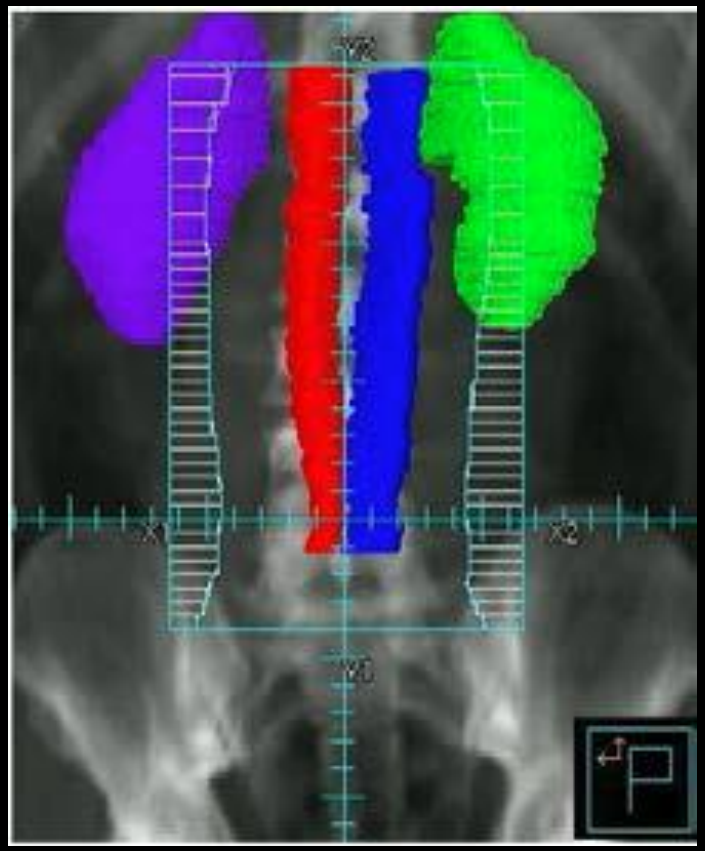
- Contour IVC and aorta separately from 2 cm below the top of the kidneys down to the point where these vessels bifurcate.
- Use a 1.2 cm expansion radially around IVC and a 1.9 cm expansion around the aorta, excluding bone and bowel.

Dogleg field:

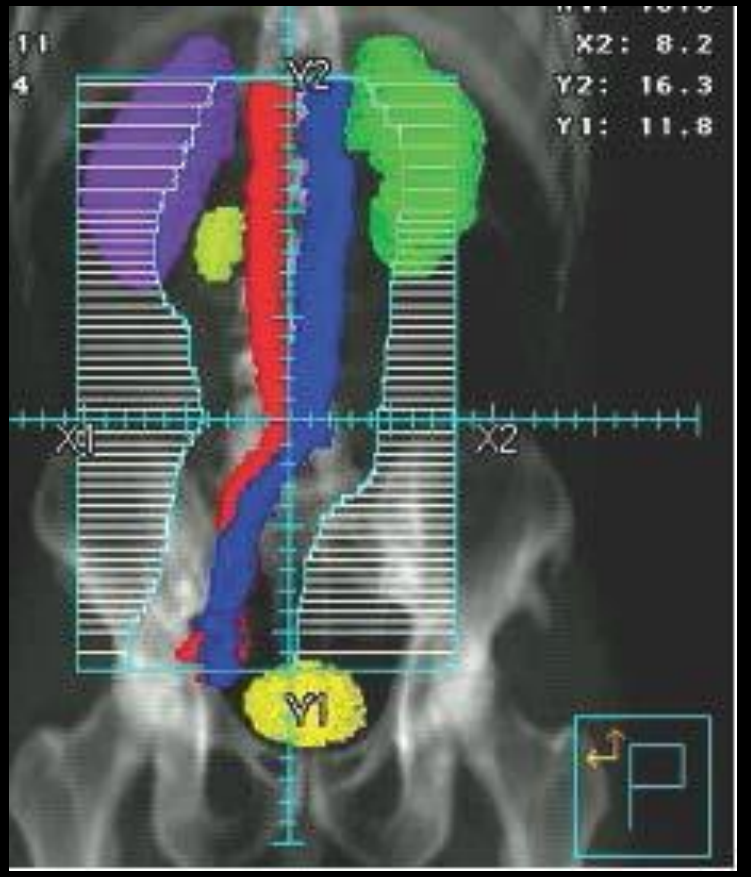
- In addition to PA field, contour the ipsilateral common, external, and proximal internal iliac veins and arteries down to upper border of acetabulum.
- Use a 1.2 cm expansion on the iliac vessels, excluding bone and bowel.

- PTV=CTV+0.5 cm
- 0.7 cm margin on PTV to block edge to take penumbra into account

3D CRT Fields



PA Field



Dog Leg Field

DOSE CONSTRAINTS

- Kidneys: D50% ≤8 Gy, mean dose ≤9 Gy.
- If patient has only one kidney, then D15% ≤20 Gy.

STRATEGIES TO REDUCE RADIOTHERAPY MORBIDITY

REDUCTION OF RADIATION FIELD SIZE

- MRC TE10 :-478 patients randomised to traditional dog-leg or para-aortic radiotherapy

REDUCTION IN DOSE

- MRC TE18 :- 625 patients randomised to 30 Gray in 15 # over 3 weeks or, 20 Gray in 10 # over 2 weeks.

MRC TE10 (Fossa et al 1999)

- Survival at 3 years, 99% for PA vs 100% for DL.
-
-
-
-

CONCLUSION:

Adjuvant radiotherapy confined to the paraaortic LNs is associated with decreased haematologic, GI and gonadal toxicity, at nearly similar risk of pelvic recurrence

MRC TE 18 (Jones et al 2001 & 2005)

- 625 patients
- 5 year relapse free survival 97.0% after 30Gy
  96.4% after 20Gy
- **Better Quality of Life scores for acute effects in lower dose arm:-**20 Gy arm had decreased

CONCLUSION :
Standard radiotherapy for stage 1 seminoma should be:- 20 Gy in 10 fr. over 2 weeks to PA strip (unless previous inguino/pelvic/scrotal surgery when “dog-leg” field is used)

MRC/EORTC (Oliver et al. 2005,08)

Carboplatin vs. RT, 2005 →

- 1,477 patients were randomly assigned to receive RT or 1 injection of carboplatin.
-
- nd
- ewer new secondary testicular GCTs with chemo (2 patients vs. 15 with RT).

CONCLUSION:
A single dose of carboplatin is less toxic and as effective in preventing disease recurrence as adjuvant radiotherapy in men with stage I pure seminoma after orchiectomy.

- Independent of the treatment modality, the risk of recurrence is Stage I Seminoma is highest in the first 2 years and decreases after that.

Stage IIA Seminoma

RT

- RT (Dog Leg Field) to a dose of 30 Gy
- Preferred Modality

CT

- EP for 4 cycles or
- BEP for 3 cycles for multiple positive lymph nodes

Stage IIB Seminoma

RT

- RT in select non-bulky cases (N< 3cm)

Dog Leg Field

- Phase I: 20 Gy
- Phase II: to a dose of 36 Gy

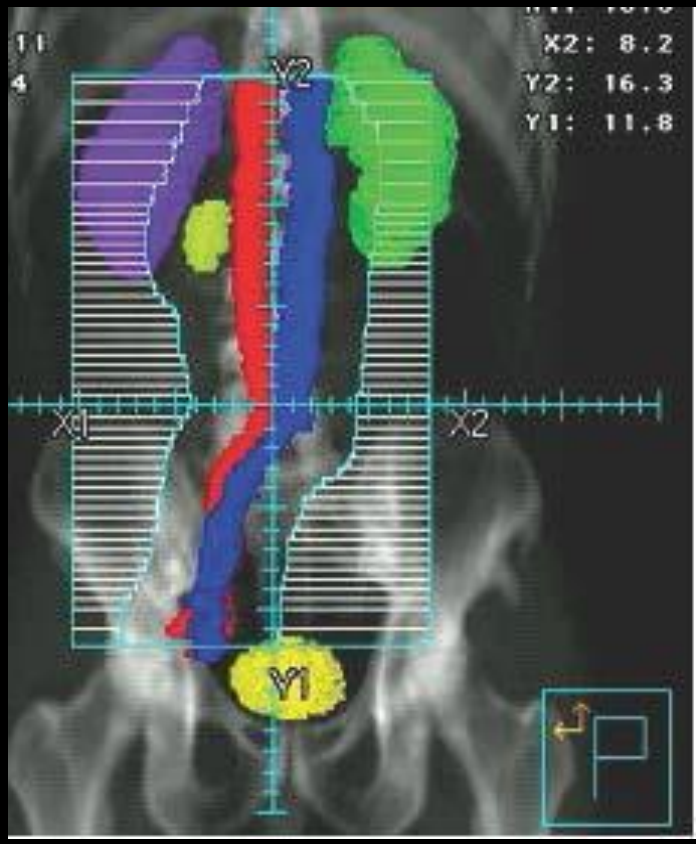
CT

- Preferred Modality

- EP for 4 cycles or,
- BEP for 3 cycles

For Stage II Seminoma

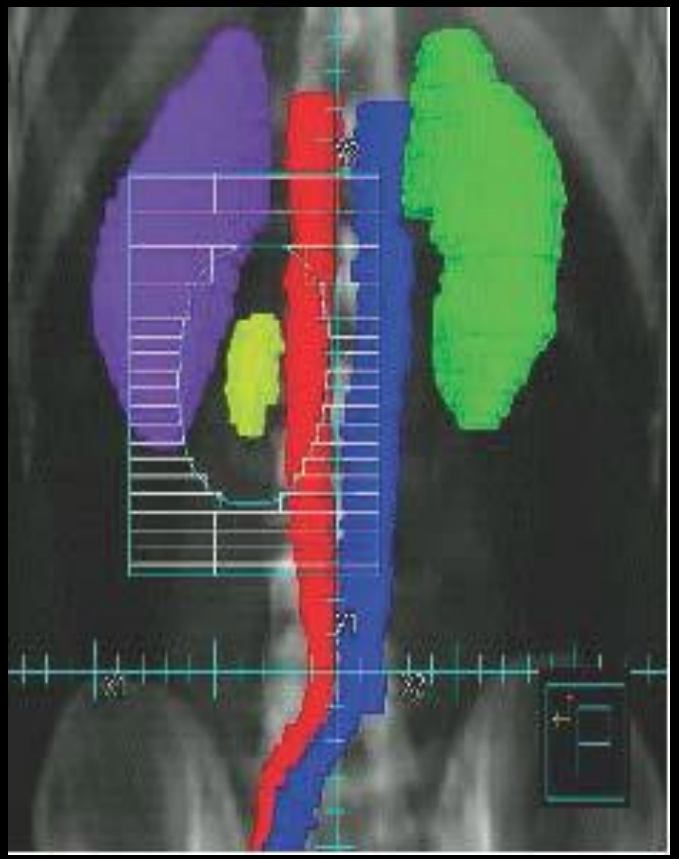
- GTV node = positive lymph nodes seen on imaging.
- CTVnode = GTVnode + 0.8 cm, excluding bone and bowel
- PTVnode = CTVnode + 0.5 cm.
- Incorporate a 7 mm expansion around the PTVs to block edge to account for beam penumbra.



Cone Down:

- Dose: The second phase of the radiotherapy consists of daily 2-Gy fractions to a cumulative total dose of

- 30 Gy for stage IIA and
- 36 Gy for stage IIB.



Stage IIC & III Seminoma

Good Risk

- EP→4 CYCLES or,
- BEP→3 CYCLES

Intermediate Risk

- BEP→4 CYCLES

Risk Classification-IGCCCG Criteria

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

Risk Status	Nonseminoma	Seminoma
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
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
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

Source: Figure 4 from the International Germ Cell Cancer Collaborative Group: International Germ Cell Consensus

Dosing of CT

EP
Etoposide 100 mg/m^2 IV on Days 1–5
Cisplatin 20 mg/m^2 IV on Days 1–5
Repeat every 21 days[1]

BEP
Etoposide 100 mg/m^2 IV on Days 1–5
Cisplatin 20 mg/m^2 IV on Days 1–5
Bleomycin 30 units IV weekly on Days 1, 8, and 15 or Days 2, 9, and 16
Repeat every 21 days[2]

Pediatric Dose of Bleo: 0.25 to 0.50 units/kg

Follow Up for Stage II & III

Table 3 Clinical Stage IIA and Non-Bulky IIB Seminoma: Surveillance after Radiotherapy

	Year (at month intervals)				
	1	2	3	4	5
H&P[1,2]	Every 3 mo	Every 6 mo	Every 6 mo	Every 6 mo	Every 6 mo
Abdominal/ Pelvic CT	At 3 mo, then at 6–12 mo	Annually	Annually	As clinically indicated	
Chest x-ray[3]	Every 6 mo	Every 6 mo	------		

Table 4 Bulky Clinical Stage IIB and Stage III Seminoma: Surveillance Post-Chemotherapy with No Residu and Normal Tumor Markers

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[2]	Every 2 mo	Every 3 mo	Every 6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT[4]	• Abdominal/pelvic CT at 3–6 months, then as clinically indicated • PET scan as clinically indicated				
Chest x-ray[3]	Every 2 mo[5]	Every 3 mo[5]	Annually	Annually	Annually

[1]Serum tumor markers optional.
[2]Testicular ultrasound for any equivocal exam.
[3]Chest x-ray may be used for routine follow-up but chest CT is preferred in the presence of thoracic symptoms.
[4]Patients with PET-negative residual mass measuring >3 cm following chemotherapy should undergo an abdominopelvic CT every 6 months for the first year then annually for five years.
[5]Add chest CT if supradiaphragmatic disease present at diagnosis.

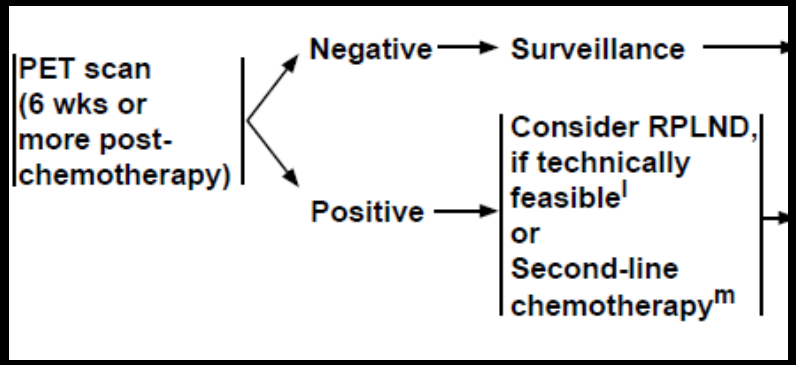
F/U Results

No residual mass

or residual mass ≤3 cm and normal markers

- Surveillance

Residual mass (>3 cm) And normal markers



Management of Progressive Disease




Conventional-Dose Chemotherapy Regimens

VeIP

Vinblastine 0.11 mg/kg IV Push on Days 1–2
Mesna 400 mg/m^2 IV every 8 hours on Days 1–5
Ifosfamide 1200 mg/m^2 IV on Days 1–5
Cisplatin 20 mg/m^2 IV on Days 1–5
Repeat every 21 days[1]

TIP

Paclitaxel 250 mg/m^2 IV on Day 1
Ifosfamide 1500 mg/m^2 IV on Days 2–5
Mesna 500 mg/m^2 IV before ifosfamide, and then 4 and 8 hours after each ifosfamide dose on Days 2–5
Cisplatin 25 mg/m^2 IV on Days 2–5
Repeat every 21 days[2]




High-Dose Chemotherapy Regimens

Carboplatin 700 mg/m^2 (body surface area) IV
Etoposide 750 mg/m^2 IV
Administer 5, 4, and 3 days before peripheral blood stem cell infusion for 2 cycles[3]

Paclitaxel 200 mg/m^2 IV over 24 hours on Day 1
Ifosfamide 2000 mg/m^2 over 4 hours with mesna protection on Days 2–4
Repeat every 14 days for 2 cycles followed by
Carboplatin AUC 7–8 IV over 60 minutes Days 1–3
Etoposide 400 mg/m^2 IV Days 1–3
Administer with peripheral blood stem cell support at 14- to 21-day intervals for 3 cycles[4]

THANKS