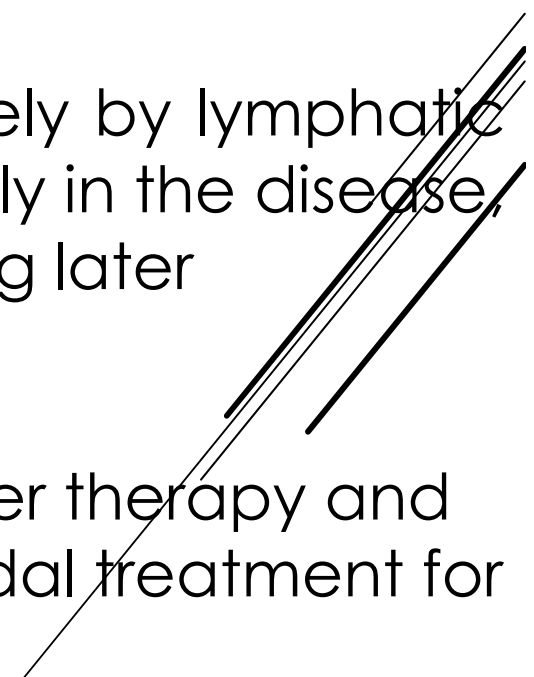


TREATMENT IN TESTICULAR TUMORS



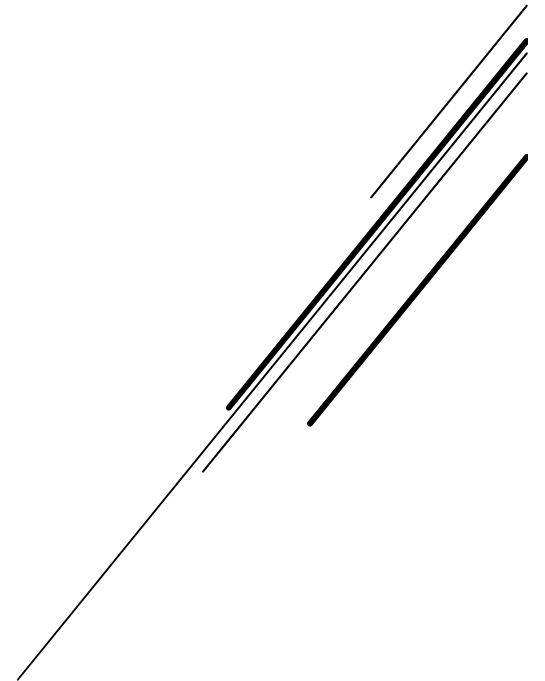
Dr.(Prof) Mohammad Ashraf Teli
Srinagar, Kashmir

TESTICULAR TUMORS

- Natural history of testicular tumors is fairly well understood and consequently management of these tumors has evolved on sound Scientific lines resulting in high cure rates approaching 100% for patients with low stage and low risk disease .
 - Spread of seminomatous GCT is defined largely by lymphatic spread to the retroperitoneal lymph nodes early in the disease, with haematogenous dissemination developing later
 - Represents one of the major successes in cancer therapy and provides a model for successful use of multimodal treatment for solid tumors
- 

NATURAL HISTORY (NSGCT)

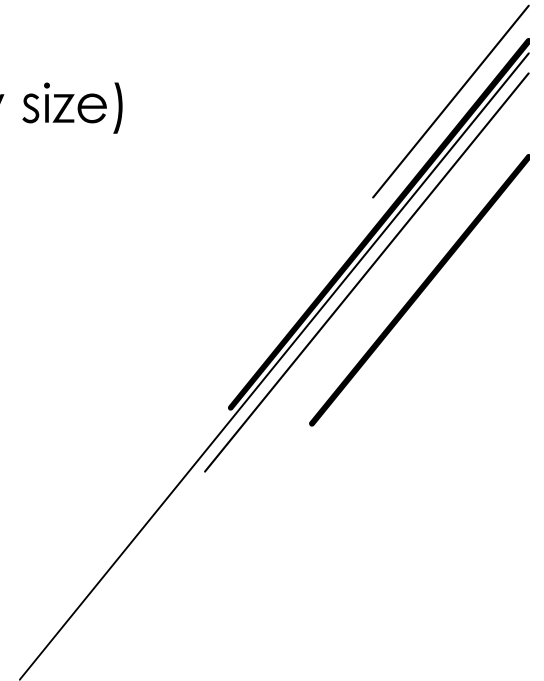
- Age specific incidence peak – 10 years earlier than seminoma
- More aggressive
- Increased incidence of distant metastases at presentation
 - stage I- 20 %
 - stage II-20-30%
 - stage III-50%
- Hematogenous spread – more common
- Higher incidence of systemic relapse
- Relatively radio-resistant (radio-curable-!)



- **USG** –Bilateral testicular ultrasound exam.----- contralateral testis (30% risk of ITGCN)
- **Bipedal lymphangiography**
 - Sensitivity -70%; specificity – 60%
 - Demonstrate architectural abnormalities within normal sized l.n
 - Not add to the diagnostic accuracy
 - Invasive hence dis favoured
 - Historical importance
- **PET** – sensitivity- 70%; specificity- 100%
 - unable to demonstrate lesions <5 mm & teratoma (any size)
 - Has role in evaluating residual RPLN following CCT
 - optional investigation with expanding role---??
- **MRI – chest & abdomen** (if contraindication to CT)
- **CT/ MRI brain** (if CNS symptoms)
- **Bone scan** (if elevated ALP or symptoms)

SPECIAL STUDIES

- Semen analysis & sperm banking

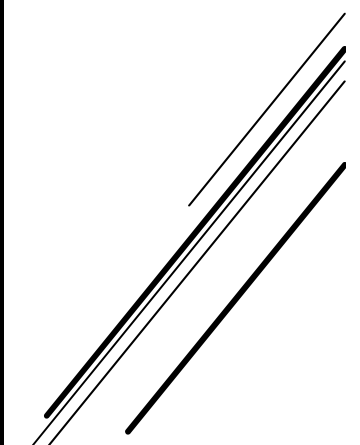


ROLE OF TUMOUR MARKERS

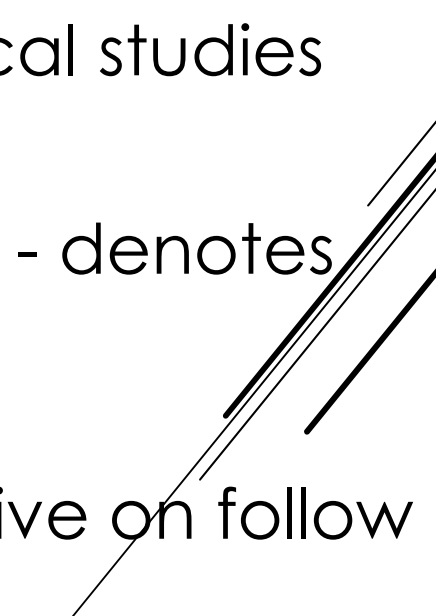
- ▶ Marker elevation seen in 80 to 85% of Testicular Tumors
- ▶ Diagnosis - Markers give clue to the Diagnosis & Histology of Tumor
- ▶ Help infer clinical behavior, monitor therapy, detect residual /or recurrent disease
- ▶ Post Orchiectomy Elevated marker levels denotes Residual Disease /or higher Stage Disease

TUMOR MARKERS IN TESTICULAR TUMORS

Tumor Marker	Half life	Normal value	Comments
Beta-HCG	2-22hrs	<5 IU/L	100 % - Choriocarcinoma 60% - Embryonal cell carcinoma 55% Teratocarcinoma 25% Yolk Cell Tumour 7%-15% Seminomas -correlates with tumor burden; so prognostic value
LDH	1day	105 - 333 IU/L	-poor specificity -Not diagnostic -prognostic marker -correlates with tumor burden
PLAP	1 day		serum levels are elevated in 50 to 70% of higher stage seminomas.
AFP	5Days	20ng/ml	Raised in embryonal cell carcinoma Raised levels exclude pure seminoma



ROLE OF TUMOUR MARKERS

- ▶ Levels of Marker Elevation Appears to be Directly Proportional to Tumor Burden
 - ▶ Markers are detected earlier than radiological studies
 - ▶ Detection of an elevated AFP in Seminoma - denotes presence of Non-Seminomatous elements
 - ▶ Negative Tumor Markers status turning positive on follow up usually indicates - Recurrence of Tumor
- 
- A decorative graphic consisting of several parallel diagonal lines of varying thicknesses, extending from the bottom right towards the top right of the slide.

WORKUP

PRIMARY TREATMENT^b

PATHOLOGIC DIAGNOSIS

Suspicious
testicular
mass

- H&P
- Alpha-fetoprotein (AFP)
- beta-hCG^a
- LDH
- Chemistry profile
- Testicular ultrasound

- Discuss sperm banking, if clinically indicated
- Radical inguinal orchiectomy
- Consider inguinal biopsy of contralateral testis if:
 - ▶ Suspicious ultrasound for intratesticular abnormalities
 - ▶ Cryptorchid testis
 - ▶ Marked atrophy
- Consider testicular prosthesis

Pure seminoma (pure seminoma histology and AFP negative; may have elevated beta-hCG)

[See Postdiagnostic Workup and Clinical Stage \(TEST-2\)](#)

Nonseminomatous germ cell tumor (NSGCT) (includes mixed seminoma/nonseminoma tumors and seminoma histology with elevated AFP)

[See Postdiagnostic Workup and Clinical Stage \(TEST-6\)](#)

▶ High inguinal orchiectomy


Diagnostic as well as a therapeutic modality.

{Removes primary tumor ; Confirms histopathological diagnosis.
guides about prognostic factors- tumor size/rete testis/cord
invasion/ LVI.}

**Further Management guided on the basis of histology, stage
and risk factor stratification.**

STAGING SYSTEMS

Many staging systems .

- **GIBBS & BODEN CLASSIFICATION** one of the earliest systems 1950s.
 - Clinical staging system – **Royal Marsden Hospital**. Most commonly followed for seminomas.
 - **UICC & AJCC Staging** –Clinico-pathological staging based on histological findings of primary tumor, nodes, physical examination, radiological exam & tumor markers.
- 

GIBBS & BODEN STAGING

Stage IA Tumor limited to testis not involving cut ends of spermatic cord.

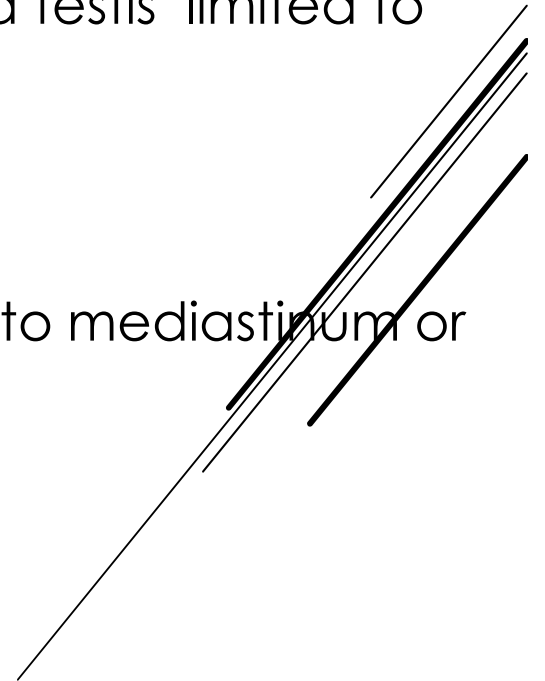
Stage IB - Tumor clinically limited to testis involving cut ends of spermatic cord.

Stage II- Clinical or radiological evidence of spread beyond testis limited to regional lymphatics below diaphragm.

Stage III – extension beyond diaphragm.

III A – Extension beyond diaphragm but still confined to mediastinum or S/C nodes.

III B – extra nodal spread.



AJCC,TNM classification & Staging

Primary tumor (Defined after radical orchiectomy)

PTX- primary tumor not accessible, (Orchiectomy not performed)

pT0- No evidence of tumor-histological scar in testis)

pTis- Intratubular GCT-Ca.in Situ

pT1- Tumor limited to testis/Epididymis/Tunica albuginea without LVI/Vascular invasion,

pT2- Tumor with Tunica vaginilis involvement /LVI/Vascular invasion

pT3- Tumor with infiltration of spermatic cord +- LVI/Vascular invasion.

pT4- Tumor involving the scrotum +-LVI/Vascular invasion

Regional Lymph Nodes (N)

Pathological Lymph Node (pN)

NX-Regional nodes not (cannot) be assessed

pNX-

N0-No regional nodal involvement

pN0-

N1-Nodal metastases with size of <2 Cms

pN1-nodal involvement in up to 5 nodes +ve for metastases

N2-Nodal metastases with size <=5 Cms

pN2->5 nodes + ve/extr anodal extension

N3-Nodal metastases with size > 5 Cms

pN3-

Serum tumor marker status (S)

Distant Metastases (M)

MX-Presence of Distant metastases cannot be assessed

M0-No DM

M1-DM present

M1a-Non-regional nodal met/Pulmonary metastases

M1b-DM to sites other than under M1a category

	LDH	B-hCG (mIU /ml)	AFP(ng/ml)
Sx	NA/Not perform	NA/NP	NA/NP
S0	Normal limits	Normal limits	Normal limits
S1	<1.5 X ULN +	<5000 +	<1000
S2	<=1.5-10 X ULN	5000-50,000	1000-10,000
S3	>10 X ULN	>50,000	>10,000

STAGING - ROYAL MARSDEN HOSPITAL

- ▶ **I - No evidence of metastases beyond testis.**

- ▶ **IM- Rising serum markers with no other evidence of metastases.**

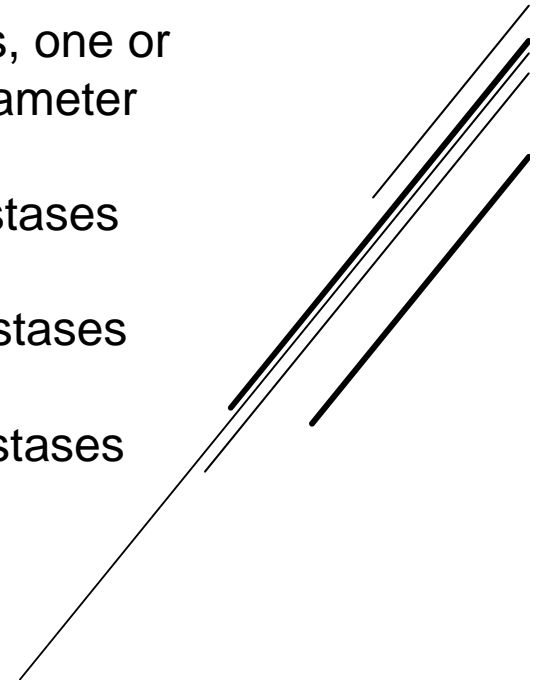
- ▶ **II - Abdominal node metastases**
 - A <2 cm in diameter
 - B 2–5 cm in diameter
 - C >5 cm in diameter

- ▶ **III - Supra-diaphragmatic node metastases**
 - M-Mediastinal
 - N-Supraclavicular cervical axillary
 - O-No abdominal node metastases
 - ABC- Node size defined as in Stage II

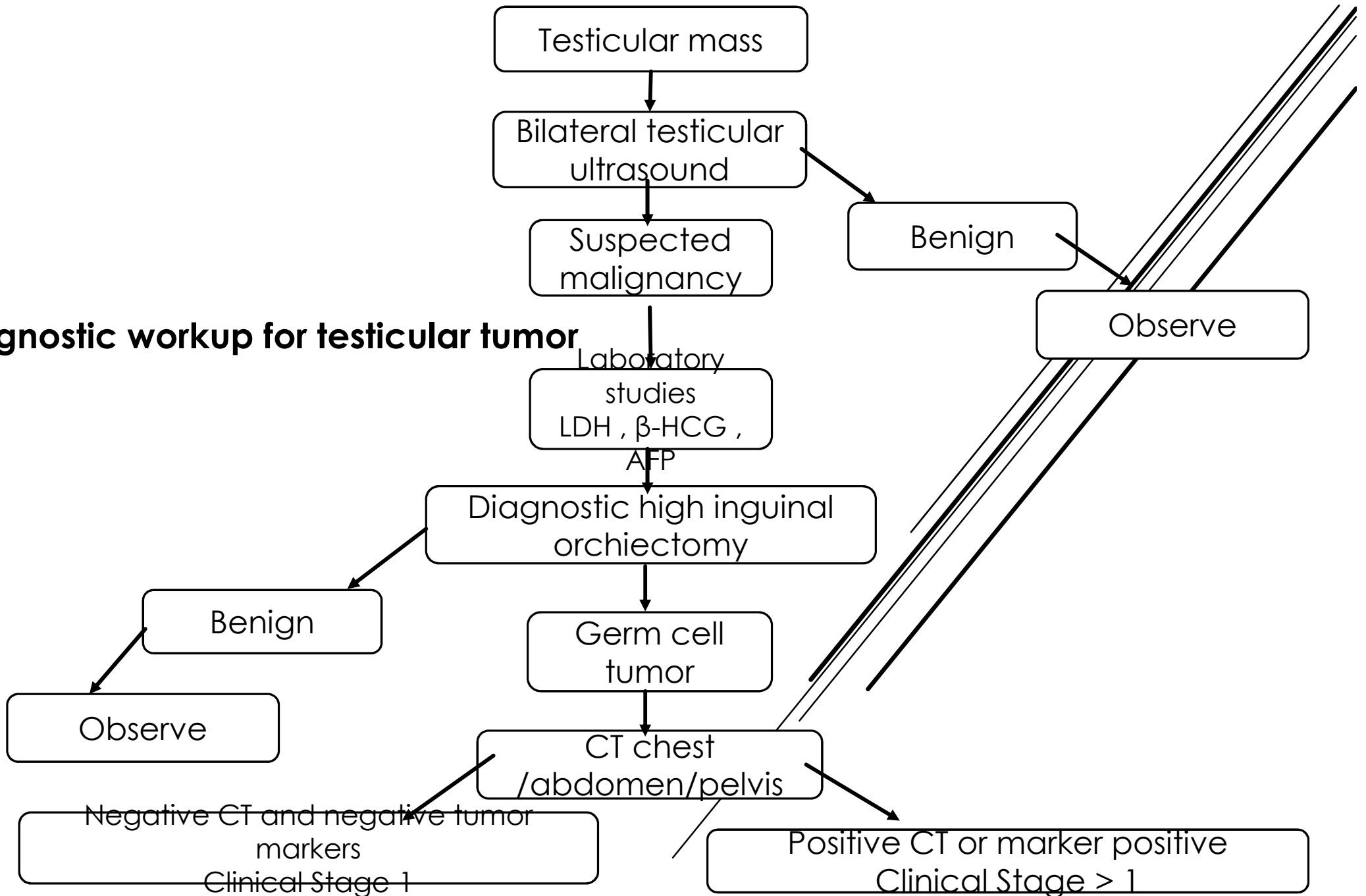
•IV - Extra-lymphatic metastases

Lung

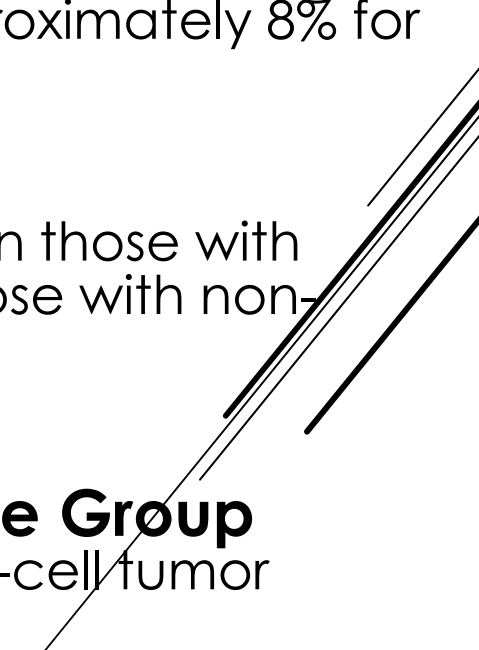
- L1 ≤ 3 metastases
 - L2 >3 metastases all < 2 cm in diameter
 - L3 >3 metastases, one or more > 2 cm in diameter
-
- H +Liver metastases
 - Br +Brain metastases
 - Bo +Bone metastases



Diagnostic workup for testicular tumor



PROGNOSTIC FACTORS

- ▶ **T stage** is not useful in predicting risk of relapse in stage I, **tumor size >3cm** and **rete testis invasion** are of independent prognostic value.
 - ▶ The relapse risk for **stage II** seminoma after radiation therapy depends on the bulk of retroperitoneal disease. The relapse risk is approximately 8% for stage IIA, 14% for stage IIB, and 28% for stage IIC.
 - ▶ In **metastatic disease**, differentiation is made between those with metastatic disease to non-regional nodes or lung and those with non-pulmonary metastases.
 - ▶ The **International Germ Cell Cancer Collaborative Group (IGCCCG)** based on 6,000 patients with metastatic germ-cell tumor developed a widely accepted risk stratification.
- 

INTERNATIONAL CONSENSUS RISK STRATIFICATION OF TESTICULAR GERM CELL TUMORS

Prognostic stratification	seminomas	Non-seminomas
Good	Any site with no non-pulmonary metastases with normal AFP	Testicular/retroperitoneal primary with no non-pulmonary metastases and AFP < 1000 ngs/ml, HCG <5000 IU/L or <1000 ngs/ml LDH <1-5 X ULN
Intermediate	Any site with non-pulmonary metastases with normal AFP	Vide supra with AFP >1000-10,000 ngs/ml or HCG >5000-50,000 IU/L or LDH 1-5 to 10 X ULN
Poor	Non- existent	Mediastinal primary or Non-pulmonary visceral metastases or AFP,or HCG levels higher than for intermediate risk group.

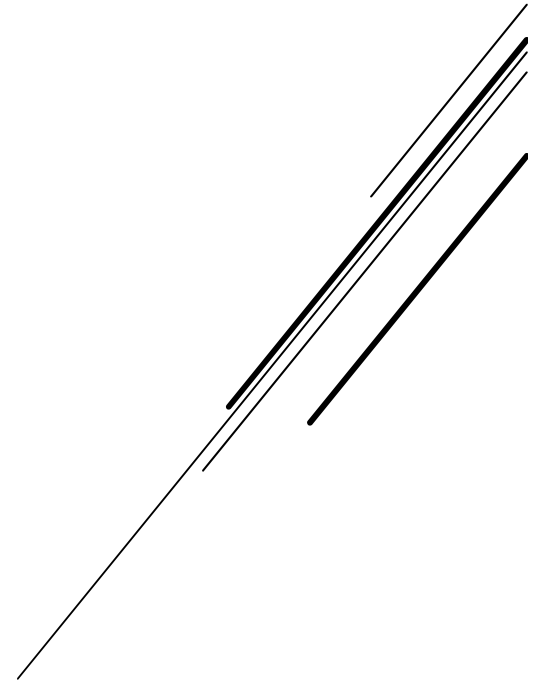
RISK CLASSIFICATION FOR ADVANCED DISEASE
(post-orchietomy)¹

Risk Status	Nonseminoma	Seminoma
Good Risk	Testicular or retroperitoneal primary tumor and No nonpulmonary visceral metastases and <u>Post-orchietomy markers</u> - 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 <u>Post-orchietomy markers</u> - 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 <u>Post-orchietomy markers</u> - 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

INTERNATIONAL RISK STRATIFICATION VISA VIS SURVIVAL

	5-YEAR (OS)		5-YEAR(DFS)	
RISK GROUP	SEMINOMAS	NON-SEMINOMAS	SEMINOMAS	NON-SEMINOMAS
GOOD	86	92	82	89
INTERMEDIATE	72	80	67	75
POOR	--	48	--	41

STAGE WISE TREATMENT OPTIONS



Stage 0 germ cell tumors

In this stage, the tumor in the testicle is carcinoma in situ (CIS)/(ITGCN), the cancer has not spread outside the testicle, and the levels of tumor markers (like HCG and AFP) are not elevated.

If this stage is diagnosed after surgery to remove the testicle, no other treatment is needed.

If the CIS is found after a testicular biopsy (such as for fertility problems), surveillance is recommended. The patient may be watched closely with repeat physical exams, ultrasound of the testicle, and blood tests of tumor marker levels. Treatment may not be needed as long as there are no signs that the CIS is growing or turning into an invasive cancer. If CIS is treated, it is with surgery (orchidectomy) or with radiation therapy to the testicle---??.

If tumor marker levels are high, the cancer is not really stage 0 – even when only CIS is found in

the testicle and there are no signs of cancer spread. These cases are treated like stage IS cancers.

Stage -1

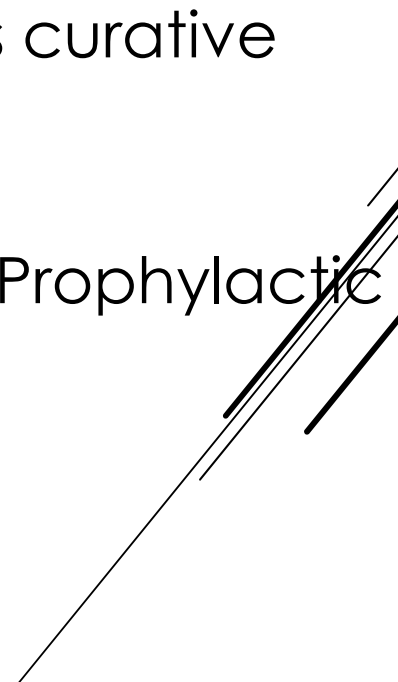
Stations at risk-

- The lymphatic drainage directly to the Para-aortic lymph nodes, predominantly at L1-L3
- The L testicular V drains to L Renal V, so lymphatic drainage primarily to LN around the left renal hilum.
- Crossover drainage from right to left occurs routinely but left to right nodal drainage occurs in only 15% to 25% of cases.
- 20% stage I patients harbor micro mets in RPLN.
- Pelvic lymph node involvement is present in 1% to 3% of cases.
- Inguinofemoral lymph node involvement is rare and limited to factors leading to altered lymphatic drainage of the testis -very extensive local disease, i, and gross scrotal contamination

Treatment options-(Stage-1)

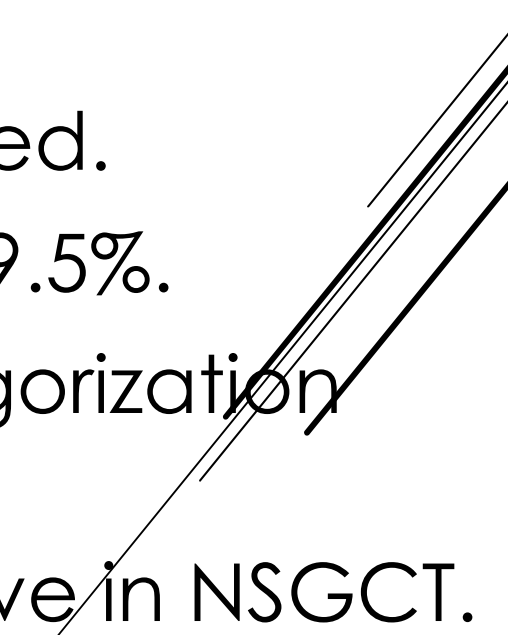
- **RADIOTHERAPY**
- **SURVEILLANCE**
- **CHEMOTHERAPY**

Radiotherapy

- Highly sensitive - Very low dose – 20Gy-30Gy is curative
 - Predictable sequential nodal spread.
 - 20% stage I harbor micro metastases in RPLN, Prophylactic PLN treatment reduces chance of recurrence.
 - Rate of infield recurrence very low- 0.2%
 - After RT, RFS- 97% & DFS- >99%
 - Thus, **Treatment of choice?**
- 

SURVEILLANCE

Rationale

- ✓ Only 15-20% have micro metastases in RPLND ----
- over treat 80%.
 - ✓ Highly effective Radiotherapy and CCT available for salvage of relapse.
 - ✓ Treatment sequelae of RT/CCT avoided.
 - ✓ Equivalent results-OS unchanged- 99.5%.
 - ✓ Better risk factor stratification/ categorization established.
 - ✓ Surveillance strategy proved effective in NSGCT.
- 

DISADVANTAGES

Long natural history , median time to relapse – 1.5 yrs, continued relapse at >4yrs, and as late as 10 yrs.

No reliable **markers** like NSGCT.

Psychological impact- FEAR OF RELAPSE, 1/5 (15-20%) relapse.

More **costly**. 20-25 times RT alone.

Need **commitment** from both patient and clinician.

PROGNOSTIC FACTORS

TUNICA ALBUGINEA INVOLVEMENT.
LVI
INVOLVEMENT OF EPIDIDYMIS.
INVOLVEMENT OF SPERMATIC CORD.

OS 92-99% AT 5-10YRS
CSS- 100%
RELAPSE RATE – 0.5-5%

INFIELD RELAPSE IS RARE-<**0.2%**
MOST PTS RELAPSE IN **2YRS** OF TREATMENT. PMH SERIES MEDIAN TIME WAS **18 M** & LATEST RELAPSE AT **6 YRS**, SO CLOSE F/U UP TO 10 YRS.

MOST COMMON SITES OF RELAPSE ARE **PELVIC NODES IF NOT IN FIELD, MEDIASTINUM, LUNGS, L. SCLN.**

UNCOMMON RELAPSES - **INGUINAL NODES DUE TO PREDISPOSING FACTORS, BRAIN, TONSIL.**

SUPRA DIAPHRAGMATIC RELAPSES CCT IS THE TREATMENT, WHILE INGUINAL NODES RT

CHEMOTHERAPY

- ▶ **Less toxic alternative** to RT- single agent Carboplatin 1-2 cycles 400mg/m² (7 AUC)
- ▶ **OLIVER**- 1 to 2 cycles of carboplatin in 78 patients, f/u-44 months, only one relapse.
- ▶ **MRC TE-19/EORTC 30982-**
 - ▶ Phase III RCT- 1447 patients, follow-up-- 8 years
 - ▶ Adjuvant RT vs. carboplatin 7AUC X 1
 - ▶ **RT - RR-3.4% CCT - RR-4.6%**



Advantages

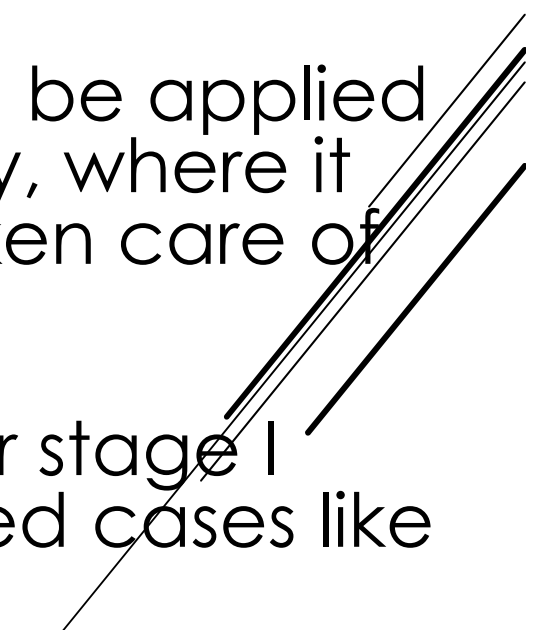
- ✓ Easy and less time for Rx completion.
- ✓ spermatogenesis recovery fast and mild a/c toxicity.
- ✓ Reduction of c/I testicular tumour.
- ✓ Definite advantage in select cases where RT is C/I- Inflamm bowel d/s, horse shoe kidney and pelvic kidney, previous h/o RT.

Disadvantage-

- ✓ Long term side effects are unknown.
- ✓ Post CCT recurrence – RT/CCT treatment may be more toxic.
- ✓ For surveillance CT abd-pelvis will be required as different relapse pattern.



CLINICAL STAGE	PRIMARY TREATMENT ^j	FOLLOW-UP	
Stage IA, IB	Surveillance for pT1-pT3 tumors (category 1) (preferred)	See Follow-up for Seminoma, Table 1 (TEST-A 1 of 2)	Recurrence, treat according to extent of disease at relapse
	or		
	Single-agent carboplatin (AUC=7 x 1 cycle or AUC=7 x 2 cycles)	See Follow-up for Seminoma, Table 2 (TEST-A 1 of 2)	Recurrence, treat according to extent of disease at relapse
	or		
	RT ^k (20 Gy, preferred or 25.5 Gy) ^l	See Follow-up for Seminoma, Table 2 (TEST-A 1 of 2)	Recurrence, treat according to extent of disease at relapse
Stage IS		Repeat elevated serum tumor marker and assess with abdominal/pelvic CT scan for evaluable disease ^m	Recurrence, treat according to extent of disease at relapse

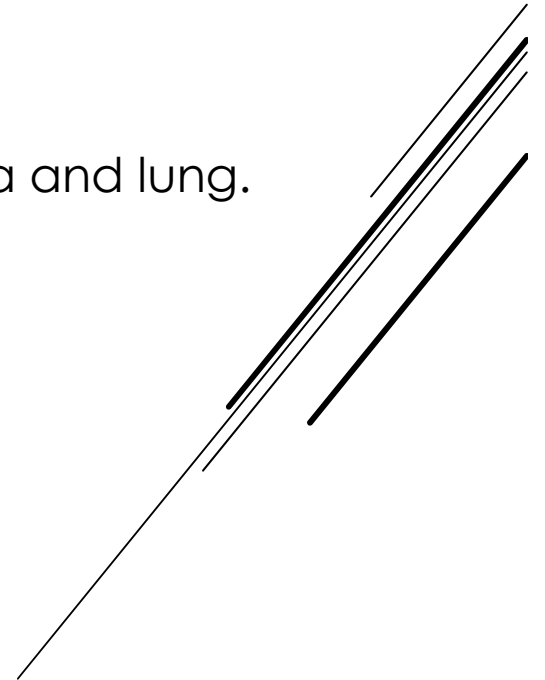
- ▶ 100% patients of Stage 1 are cured regardless of post Surgical treatment.
 - ▶ **RT** is a long tested approach for treatment with convincing results, (except for isolated incidence of 2nd non testicular malignancy) & **still remains treatment of choice.**
 - ▶ **Surveillance** is an **attractive option** & can be applied in careful and limited clinical settings only, where it doesn't compromise survival & cost is taken care of
 - ▶ **CCT** is equally **potential modality** as RT for stage I disease with special use for highly selected cases like Inflammatory bowel disease.
- 

STAGE II

- ▶ **15-20%** of seminoma.
- ▶ **70% of stage II are II A/B.**

- ▶ **Three groups** depending on diameter of PALN (most important prognostic indicator) defined by largest LN mass on CT.
- ▶ **IIA**-<2cm OSR- 96-100%
- ▶ **IIB**-2.1-5cm OSR- 96-100%
- ▶ **IIC**->5cm OSR>90%
- ▶ Relapse is most commonly in mediastinum, supraclavicular fossa and lung.

- ▶ **Rx Options-**
 - **RADIOTHERAPY-** Rx of choice in IIA/B
 - historical in II C
 - **CHEMOTHERAPY** -experimental in stage II A/B
 - Rx of choice in II C



STAGE II A/B

Relapse rate of 8-11%

Sites- mediastinum, supraclavicular fossa and lungs.

CCT was able to salvage 80% of relapses in stage IIA/B

CSS- 96-100% at 5 yrs.

Patients with bulky disease, >5 cm (stage IIC)

High failure following RT -31%.

Considerable variation in RR in diff series but OSR >90%.

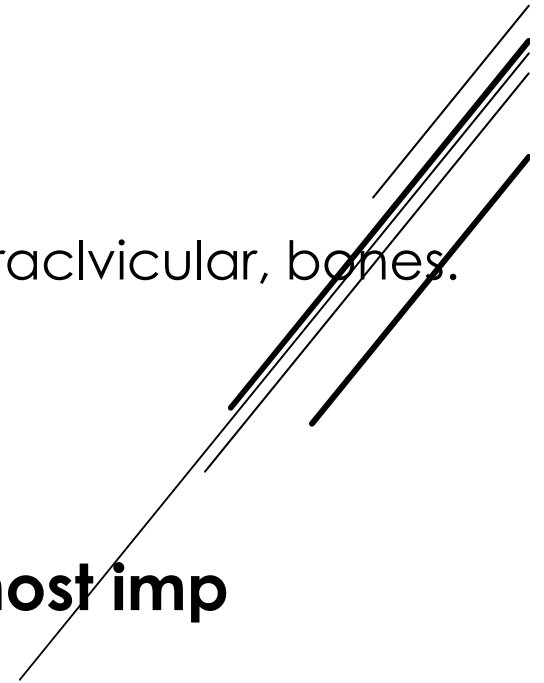
MC site of relapse - mediastinum (if no prophylactic RT), supraclavicular, bones.

Stage IIC pts with >10 cm,

Regardless of RT technique 50% pts relapsed.

Not all relapses were salvaged.

All the studies showed tumor bulk at RPLN to be most imp prognostic factor.



COMBINATION CT IN IIC

Indications-

- Tumor bulk- extending 10 cm with multiple enlarged lymph nodes from L1-5 with max transverse dia - 4 cm.
- Location of disease- more laterally risking kidney/liver
- Anatomic variants- horse shoe kidney/pelvic kidney

➤ **IIC- CCT is considered treatment of choice.**

➤ **Results- progression free survival- 90%**

➤ **BEP- 3 cycles**

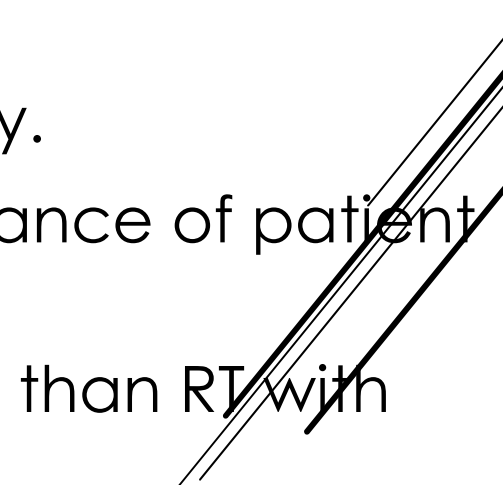
➤ **EP- 4 cycles**

▶ **30-50%** have residual mass on CT, of this **15%** have +ve histology esp **>3cm(30%) bartholomew hospital.**

▶ **further discussion with Stage III disease.**

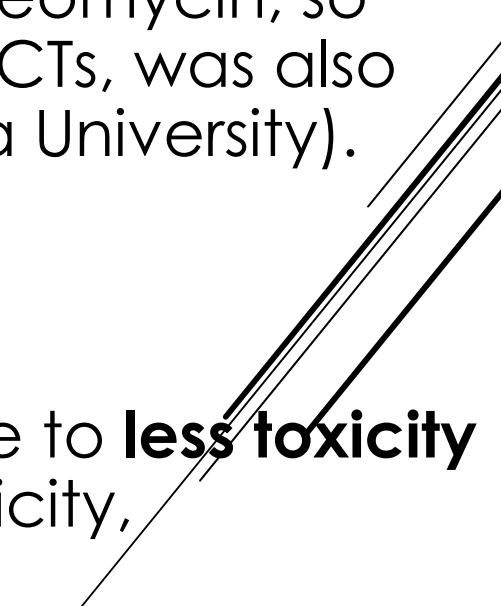


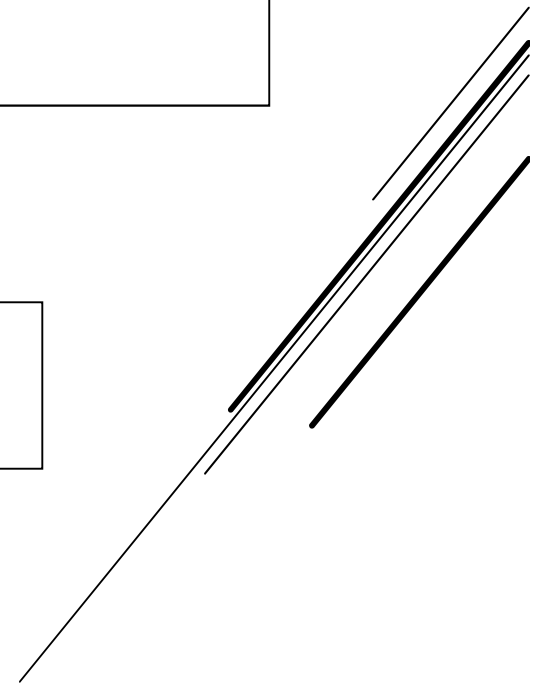
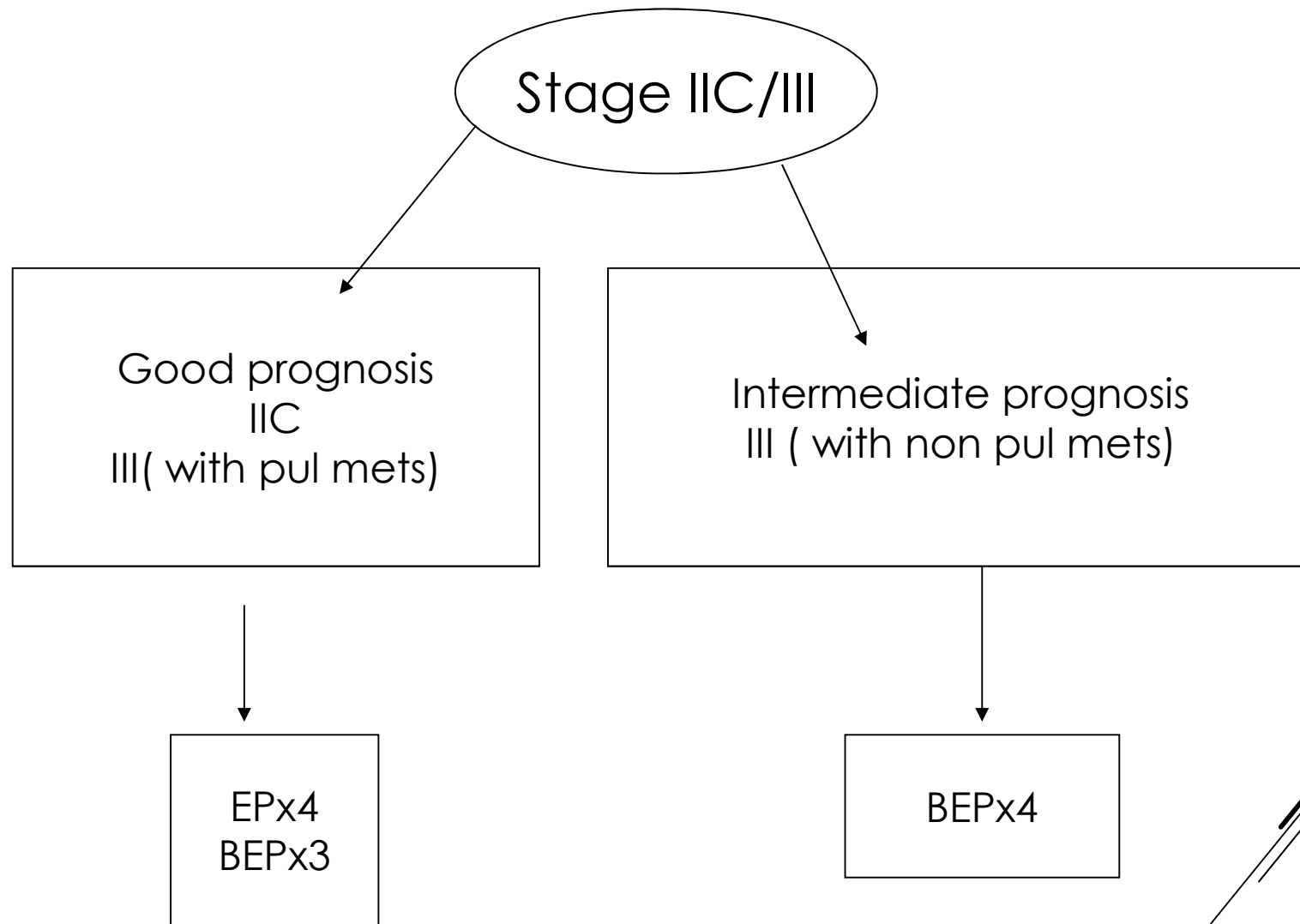
▶ **Current trend-**

- ▶ The risk of failure is low for most patients in stage IIA/B.
 - ▶ Failures easily salvageable by CCT.
 - ▶ 5- 10 cm LN have high risk of failure and may argument for prophylactic RT.
 - ▶ Dose in such cases should be in range of 25 gray.
 - ▶ Side effects of extended RT field decrease tolerance of patient to further CCT, if needed.
 - ▶ So in Bulky disease (IIB) CCT should be preferred than RT with extended fields.
- 

STAGE III

Combination CT is the treatment of choice.

- ▶ The combination of cisplatin, vinblastine, and bleomycin, so successful in the treatment of patients with NSGCTs, was also effective in the treatment of seminoma (Indiana University).
 - ▶ Earlier **PVB** regime was used.
 - ▶ Currently **BEP/EP** have replaced PVB regime due to **less toxicity maintaining equal efficacy**. (neuromuscular toxicity, myelosuppression, pul fibrosis, raynaud's phen)
- 



CHEMOTHERAPY PROTOCOLS

▶ **PVB x 3 wkly, 4 cycles**

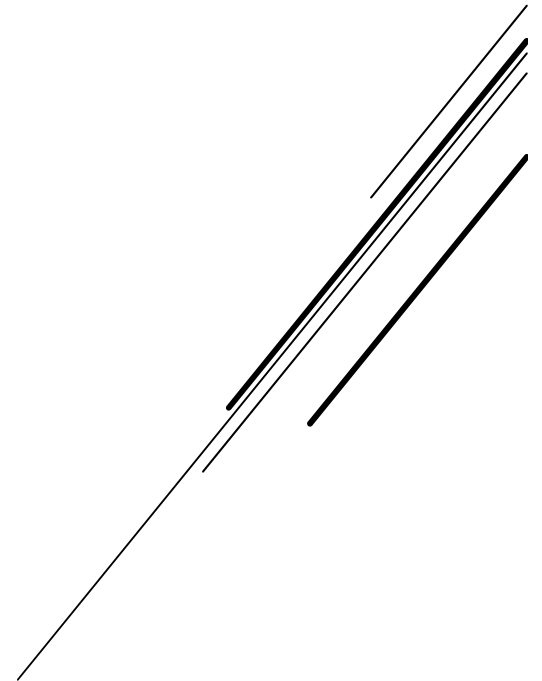
- ▶ Cisplatin- 20mg/m² D1-5
- ▶ Vinblastine- 0.15mg/kg D1-2, reduce dose by 20% if prior RT given.
- ▶ Bleomycin- 30 units D-2,9,16

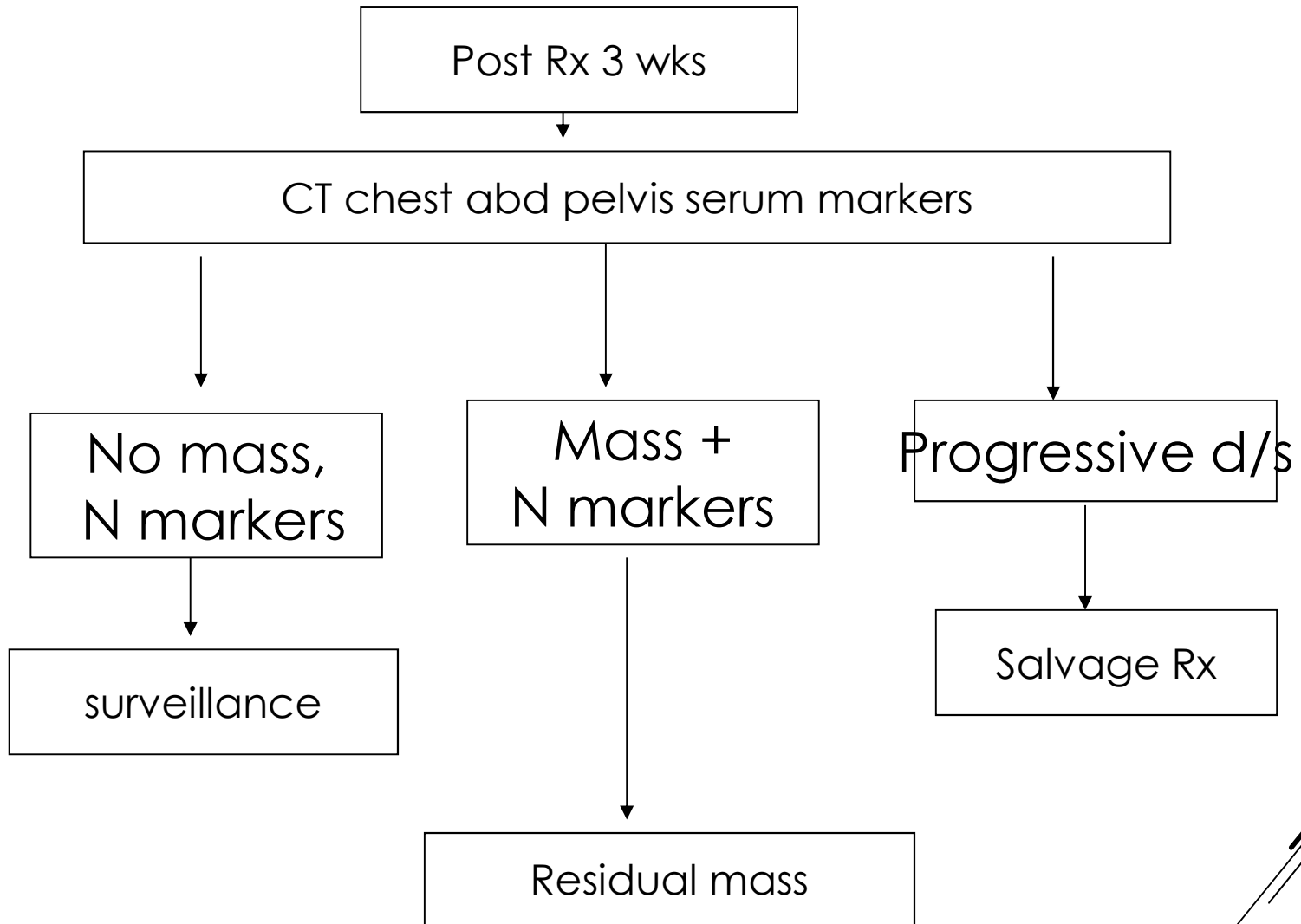
▶ **BEP- 3 wkly X 3cycles/4 cycles.**

- Bleomycin 30 U /day, D- 2,9,16 /
- Etoposide- 100mg/m²/day, D-1-5
- Cisplatin- 20mg/m²/day, D1-5/

▶ **EP- 3wkly X 4 cycles**

- Etoposide-16 100 mg/m² IV days 1-5
- Cisplatin-20 mg/M² IV days 1-5

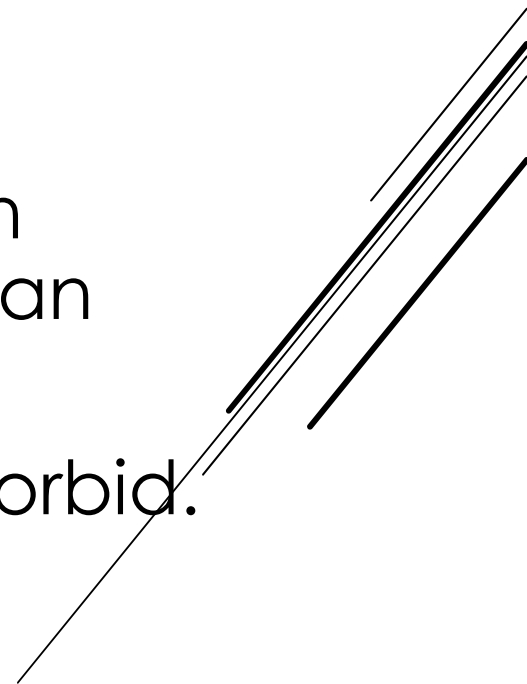




RESIDUAL RPLN

▶ Residual mass post RT, CCT in Stage IIC and III
Ms Common and **Rx** of this is **controversial**.

- ▶ Possibility of **NSGCT** component, so biopsy/FNAC and serum markers always recommended.
- ▶ Role of PET CT evolving
- ▶ **Options- Observation/surgical/CCT/RT**
- ▶ Stable mass is usually fibrosis/necrosis with minority only active d/s. so **observation** can be relied here
- ▶ **Surgery** technically difficult and highly morbid.
- ▶ **MSKCC**- 104 pts of residual mass, Surgery/multiple Biopsy
 - ▶ No mass <3 cm had viable tumor while 30%>3cm



FOLLOW-UP GUIDELINES

Seminomas

A) Stage(s)-1A,1B,1S(Post radiation)

F-up year	Clinical exam,X-ray chest (monthly interval)	Abd.Pelvic CT-Scan (monthly interval)
-----------	---	--

1	3	12
2	4	12
3-5	6	12

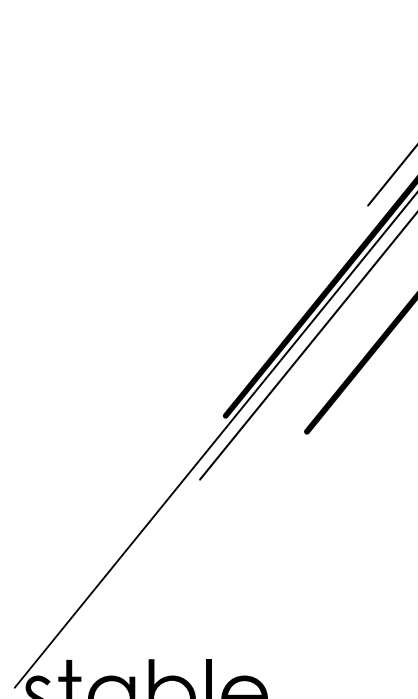
B-Stage 11A,11B(post RT),11C,111 (post CT)

1	2	after 4 th month 3 moths till stable later 12
2	3	
3	4	
4	6	

every

monthly

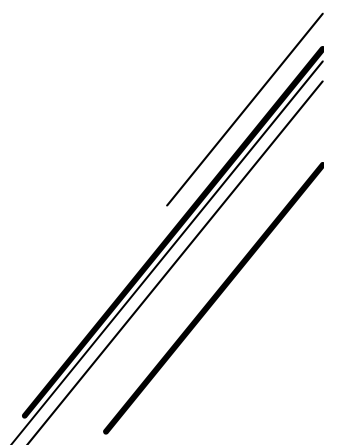
SURVEILLANCE POST CCT

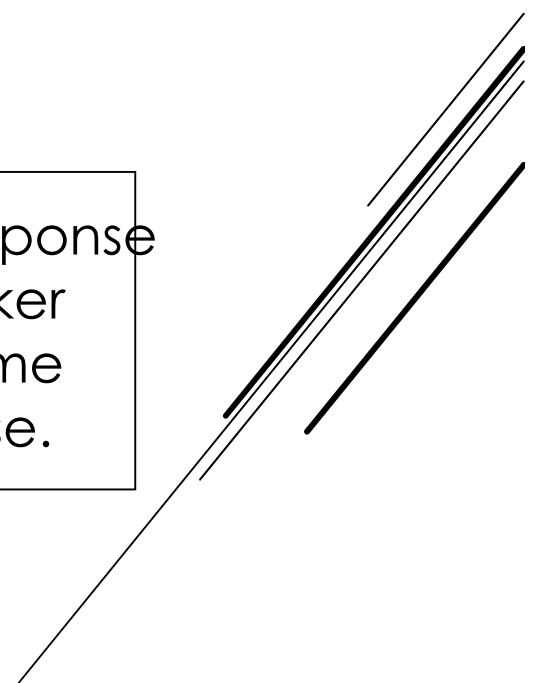
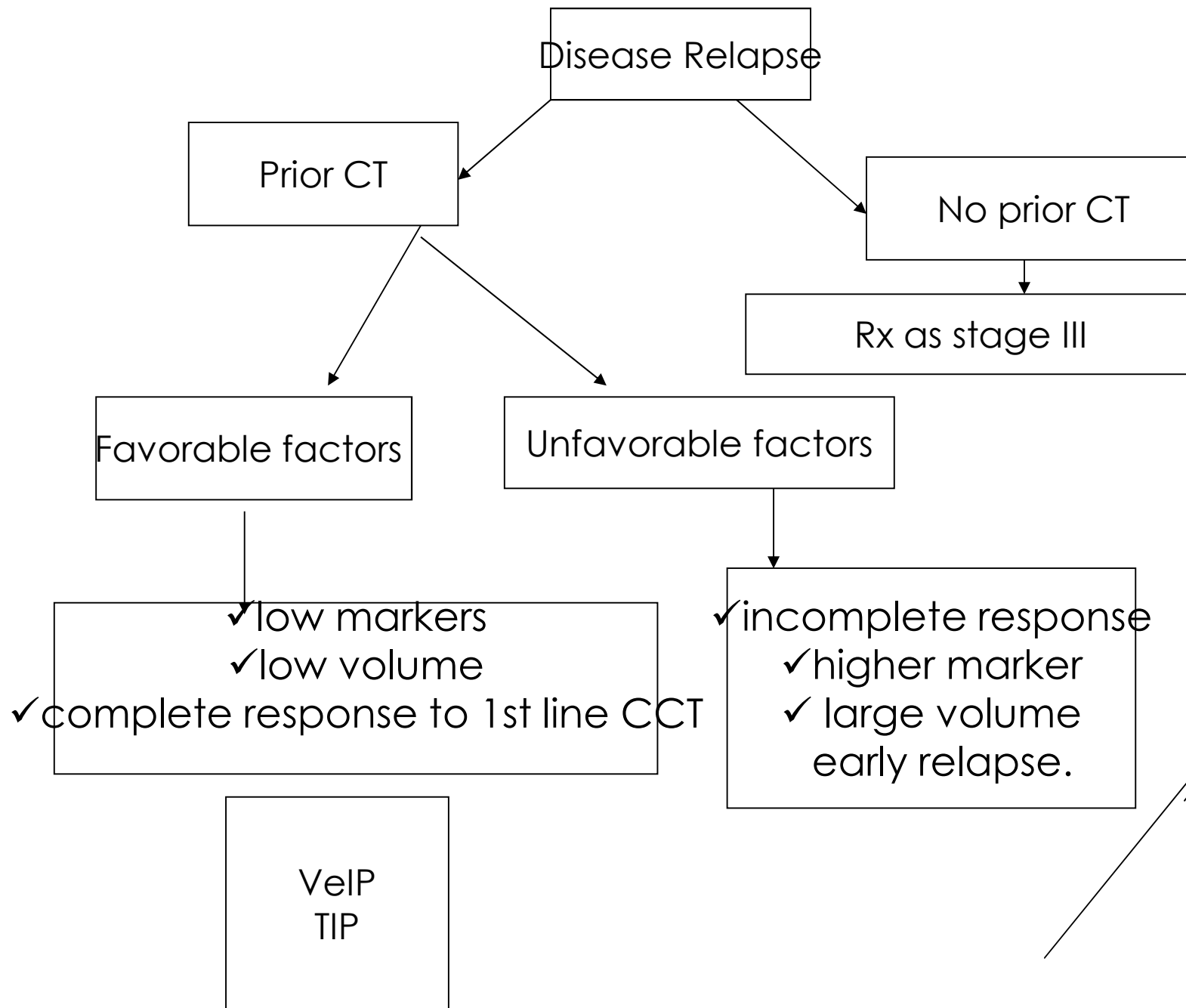
- ▶ History and physical examination and CXR at each visit.
 - ▶ Serum markers- AFP, B-HCG, LDH-
 - 2m X 1 year,
 - 3m X 2nd year,
 - 4m X 3rd year,
 - 6m X 4th year,
 - annually there after.
 - ▶ CECT abd. pelvis at 4th month, or till stable disease.
- 

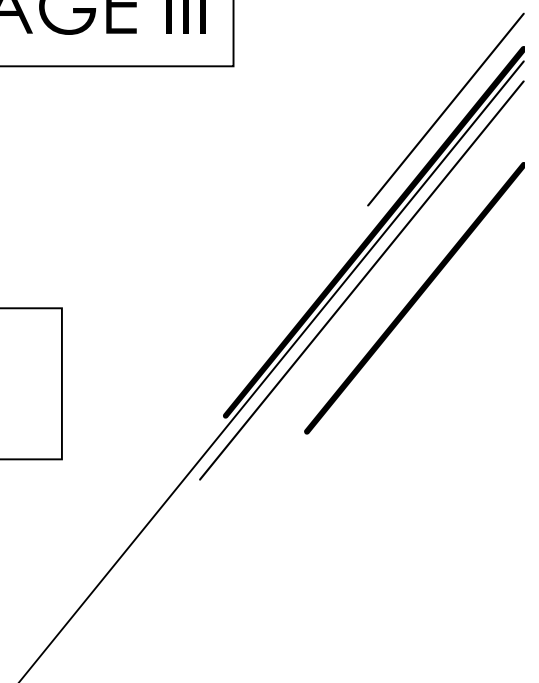
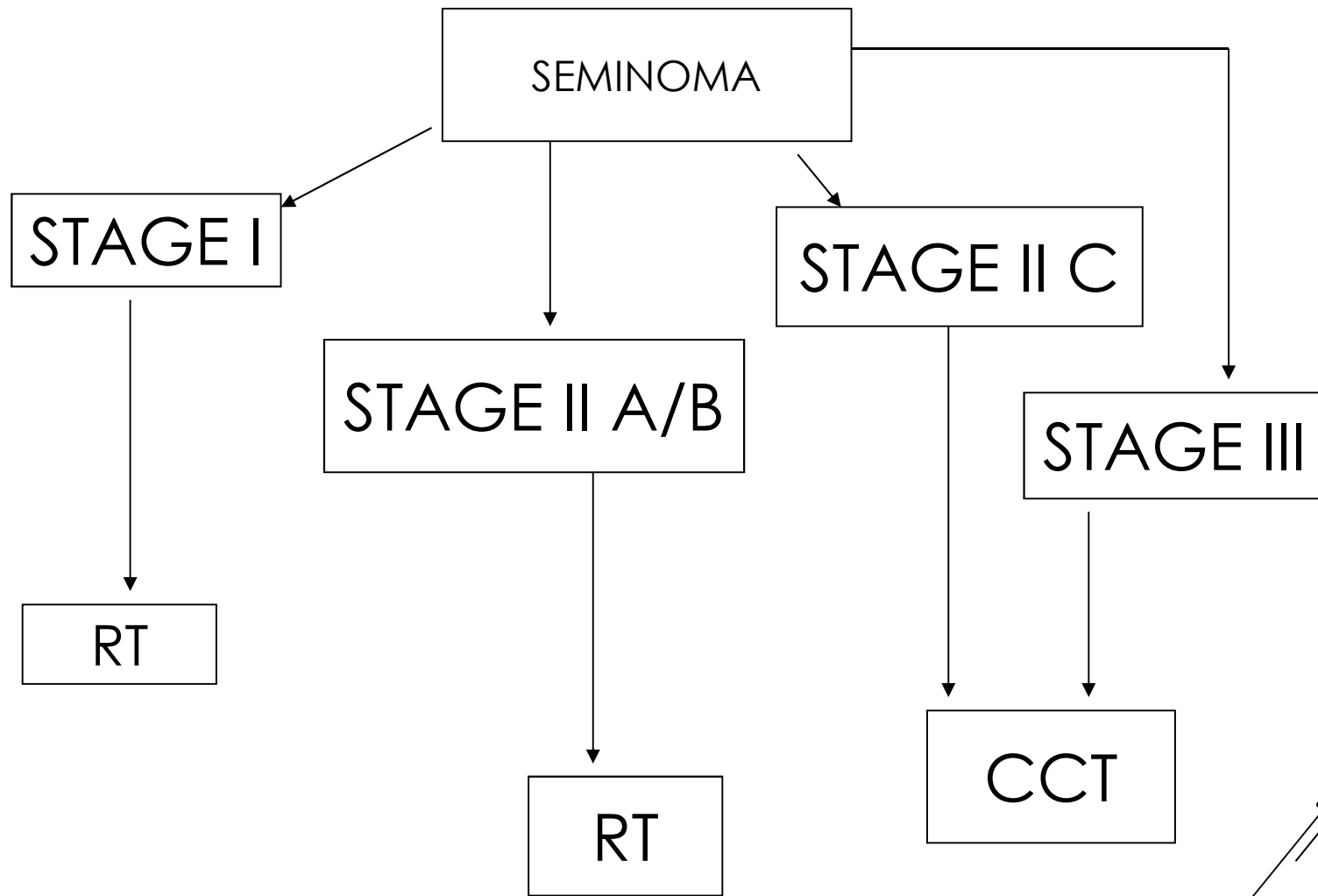
F.UP SCHEDULE

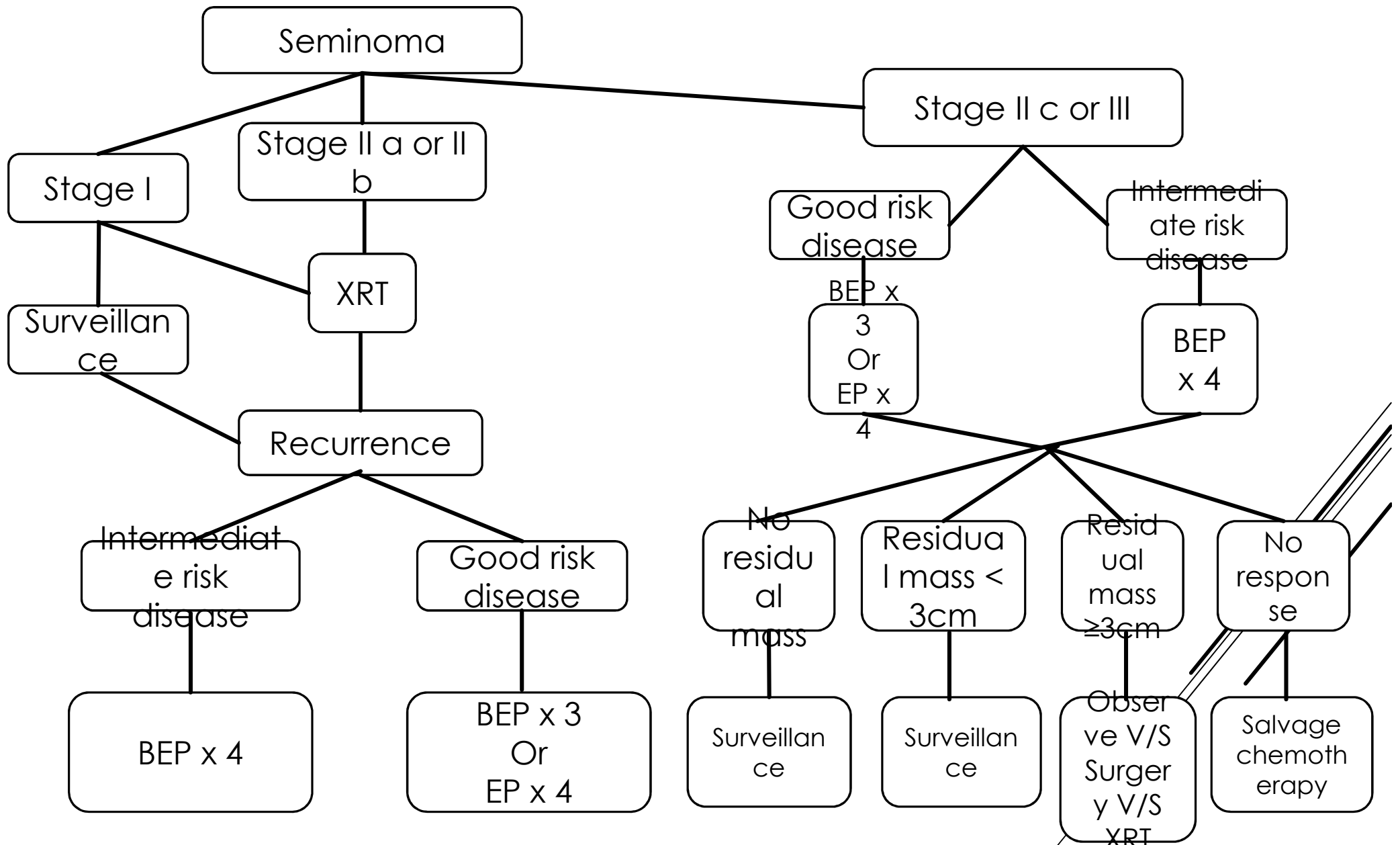
- ▶ Contemplated in compliant patients with understanding of risk of late relapse.
- ▶ Monitored for at least 10 yrs

	Month4	Month 6	Month 8	Month 12
Yrs 1-2	Markers Cxr, ct abd-pel		Markers Cxr, ct abd-pel	Markers Cxr, ct abd-pel
Yrs 3-5		Cxr, ct abd-pel		Cxr, ct abd-pel
Yrs 6,7		Cxr, ct abd-pel		Cxr, ct abd-pel
Yrs 8-10				Cxr, ct abd-pel



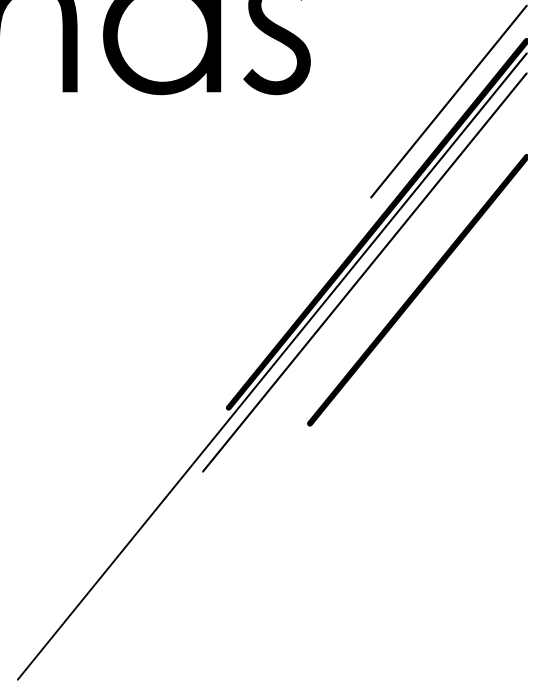






Treatment algorithm for seminoma. XRT , Abdominal / Retroperitoneal irradiation.

Non-Seminomas




▶ MANAGEMENT AFTER ORCHIECTOMY

options – Surveillance

RPLND

Adjuvant chemotherapy

- ▶ With **cure rates approaching 100%** (In properly defined risk groups) with all three approaches , there is currently ***no international consensus***
 - ▶ Further treatment approach depends on **prognostic information** from orchiectomy specimen
 - vascular invasion – **most imp.**
(recurrence rates 48% vs. 15 %)
 - presence of >50% embryonal ca cells
 - high proliferative index
 - absence of yolk sac elements
- 

SURVEILLANCE

Since majority of patients of NSGCT with good risk stratification factors will not recur after orchiectomy, surveillance is a reasonable option, since we have effective CCT for the 30% that recur

SURVEILLANCE PROTOCOL

physical exam/ CXR/ tumor markers

monthly- 1st year

2 monthly- 2nd year

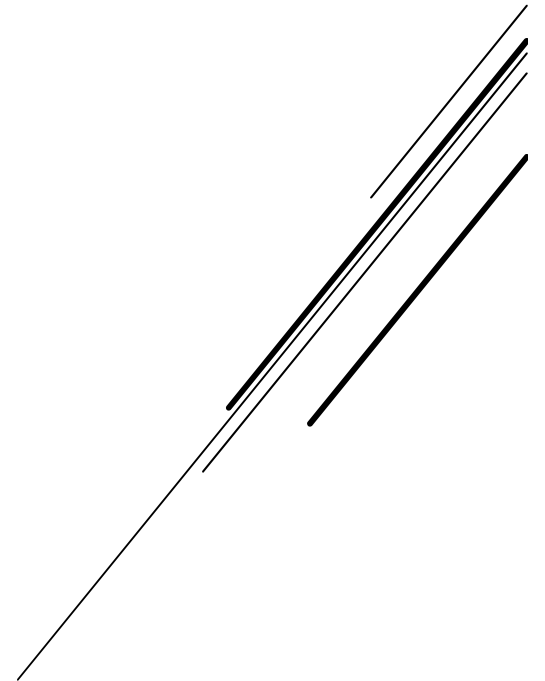
3-6 monthly-thereafter

Contrast CT abdomen/Pelvis-

3 monthly-first 2 years

6monthly thereafter

Surveillance period-5 -10 years



ADVANTAGE

Treatment is reserved for patients that require it, thus for **70% of stage-I patients who are unlikely to relapse** after primary orchiectomy unnecessary surgery or CCT can be avoided.

DIS-ADVANTAGE

- Maintaining strict follow-up, requires----- **highly motivated Patient**
- late relapse
- Patient with relapsed metastatic disease require 3/4 cycles of combination CT compared with 2 cycles in adjuvant setting

Recommended for motivated cases with good risk category.

RPLN D

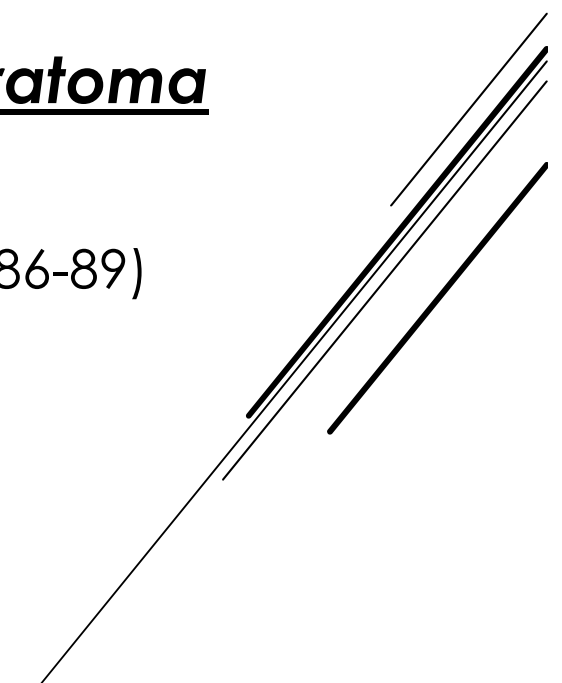
- ▶ 30% cases of stage- I have RPLN involvement
→upstaged to stage II
- ▶ RPLND →p stage- I –95% cure rates
p stage- II –50% cure rate with RPLND alone
80% cure rates in patients with microscopic
disease alone
- ▶ Post RPLND relapse rates (<10%), appearing in lungs,
- ▶ ***(Heidenreich A et al;Ther Adv Urol;2012 August;4(4):187-205***

- provides actual staging information (30% diagnosed with stage I on the basis of CT subsequently have involved RPLN at surgery)
- therapeutic & diagnostic
- recurrences within retro-peritoneum is rare after RPLND, thus subsequent follow up does not require routine abdominal CT
- eliminates long term concern for **growing teratoma syndrome** in the retro-peritoneum

(Vladislav Gorbatiy et al ; Ind J Urol.2009;25(2)186-89)

DISADVANTAGES

- post operative morbidity
- infertility/ retrograde ejaculation
- 15% cases relapses in lung → require chemo despite RPLND



ADJUVANT CHEMOTHERAPY

INDICATIONS

- *High risk patient (Vascular Invasion +)*
- *low risk cases – not willing for regular surveillance f-up*

RATIONALE-

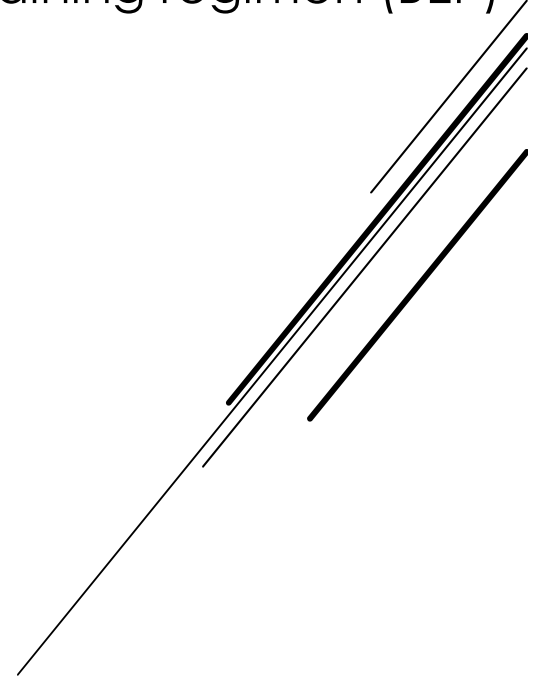
2 cycles of combination chemotherapy with cisplatin containing regimen (BEP) reduces the recurrence rates from 48% to <5%

REGIMEN

BEP - **cisplatin** - 20 mg/m² D1-5
etoposide - 100 mg/m² D1-5 3 wkly for 2 cycles
bleomycin - 30 IU D 2,9,16

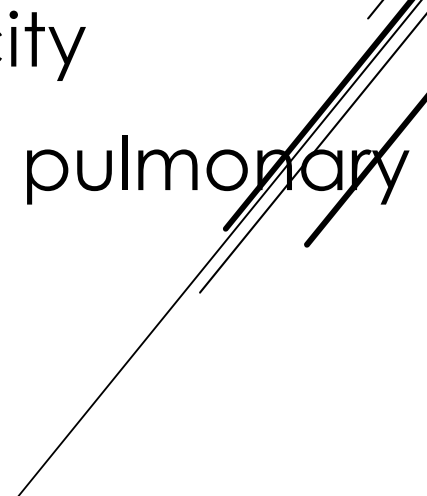
BOP -bleomycin - 30 IU D1
vincristine - 2mg D1 3 weekly for 2 cycles
cisplatin – 100mg/m² D1

BOP has similar response rates but more toxic (neuropathy)



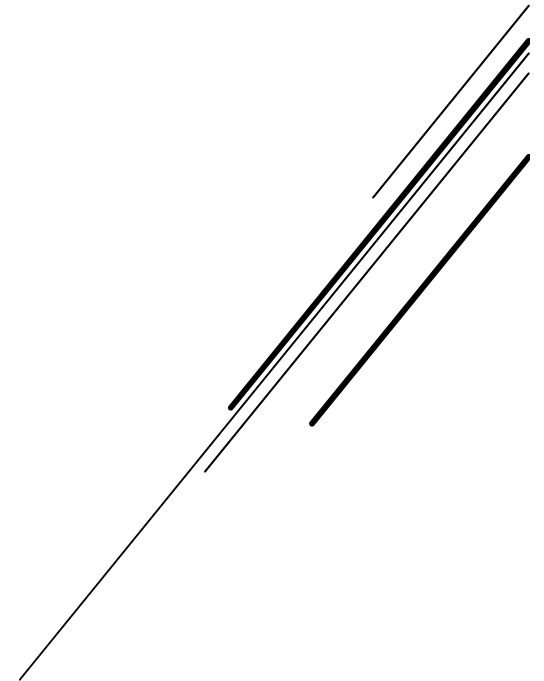
- 97% of patients will remain relapse free and overall cure is 99%
- prevents recurrence in all sites unlike Surgery, which addresses the retro-peritoneum only
- offers re-assurance to patients → remove psychological stress

DISADVANTAGES


- nephrotoxicity/ neurotoxicity/ oto-toxicity
 - myelo-suppression/ myeloid leukemia/ pulmonary fibrosis
 - cardiovascular & fertility problems
 - ***over-treating 70% of cured patients***
- 

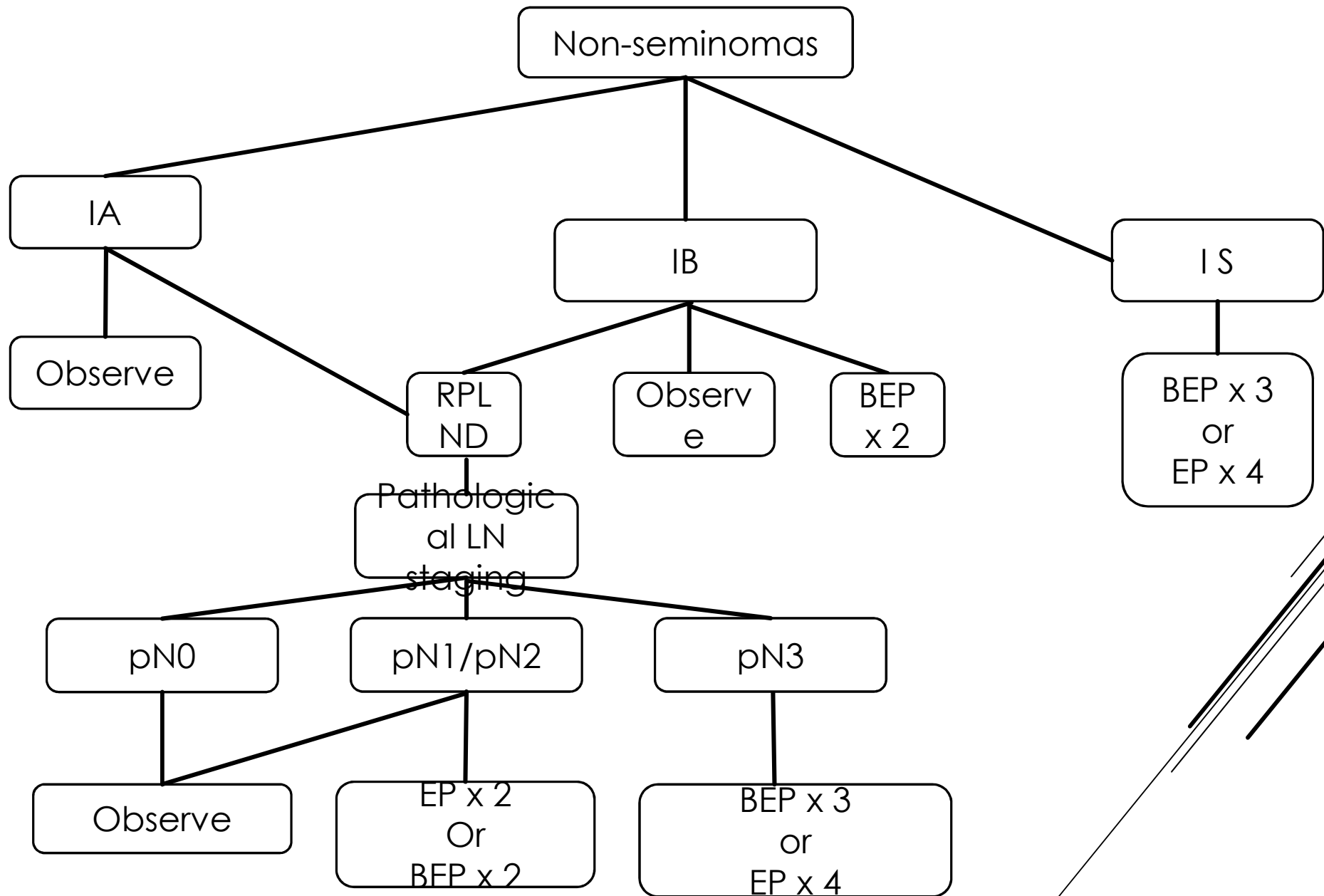
STAGE - I S

- ▶ No clinically detectable metastases but persistent/elevated Tumor Marker(S) el
- ▶ **Relapse risk – 100%**
- ▶ Treatment of choice – Combination CT
 - BEP × 3 cycles
 - EP × 4 cycles



SUMMARY – STAGE I

- ▶ CS I NSGCT can be effectively managed with surveillance, RPLND, or primary chemotherapy. No randomized trials have been conducted to evaluate whether one approach is superior.
 - ▶ **Surveillance** offers 70% of patients the benefit of avoiding any post-orchietomy therapy but is associated with a higher risk for relapse and a more burdensome follow-up schedule.
 - ▶ **RPLND** lowers the risk for relapse and offers patients the best chance of avoiding chemotherapy and late relapse. RPLND carries a risk for acute and chronic complications. One limitation to RPLND is that 15% of average-risk and up to 30% of high-risk patients end up receiving chemotherapy after RPLND either for PS II disease or for subsequent relapse.
 - ▶ **Primary chemotherapy** offers the benefit of the lowest relapse rate achievable with a single post-orchietomy treatment modality but is associated with toxicity.
- 



Treatment algorithm for non-seminomas : stages I a , I b , and I S.

Bethesda Handbook of Clinical Oncology ;11nd Ed ,Lippincott Williams & Wilkins

STAGE II A & IIB

- ▶ Further treatment depends on
 - tumor markers estimates
 - size of lymph nodes

- ▶ Treatment options
RPLND / CCT

- ▶ Indiana University Data
 - nodes ≤ 2 cm \rightarrow relapse risk - 25%
 - nodes > 2 cm \rightarrow relapse risk - $> 50\%$

Overall Cure rates – 98%



RPLND in stage

IIA/IIB SURGERY - Bilateral RPLND

ADVANTAGES OF RPLND

- Excellent long term control of retro-peritoneum
- Avoids later surgery for growing teratoma syndrome

DISADVANTAGE OF RPLND

- 1/3 cases relapses → require chemotherapy
- morbidity
- Retrograde ejaculation

INTERGROUP TESTICULAR PROTOCOL – Patients in pathological stage II were randomly assigned to either close FU or to receive 2 cycles of adjuvant CCT. Recurrences in close FU arm – 39 as compared to 5 in adjuvant CCT arm.

Adjuvant CCT post RPLND in stage II reduces further recurrence

TREATMENT GUIDELINES – IIA/IIB

IIA , marker -ve

(a) RPLND

-p stage I → follow up

-p stage IIA/B → follow up / 2 cycles of BEP

or (b) follow up every 6 weeks

Regression – further follow up

-No change – further follow up or RPLND

-Progressive – 3 cycles of BEP+/- resection of residual mass
or RPLND

▶ **IIA , marker +ve ; IIB**

3 cycles of BEP f/b resection of residual tumor



STAGE IIC & III

Cure rates **80%**

- Stratified into 3- **risk groups** according to **IGCCCG**
 - good risk
 - intermediate risk
 - poor risk
- Mainstay of treatment is **CCT**
- **Good prog.** → Use regimens with max. efficacy & min. toxicity
- **Poor & intermediate** → more effective therapy needed; toxicity is secondary issue

GOOD RISK PATIENTS

- ▶ Attempts to reduce toxic effects have involved
 - reducing the no. of cycles
 - omitting bleomycin
 - substituting carboplatin for cisplatin

NUMBER OF CYCLES

SEG -1989 compared **BEP × 4 vs BEP × 3** in good risk pts

result – equivalent control rates and survival

BEP × 3 – less toxic, significant improvement in QOL

Consensus:- 3 cycles are sufficient

INTERMEDIATE & POOR PROGNOSIS PTS

- **BEP** is the *treatment of choice* for most patients
- 40-50% of pts will not be cured
- Clinical trials have tried to evaluate cure rates of different other regimens

2ND LINE CCT

INCORPORATION OF IFOSFAMIDE & PACLITAXEL

VIP

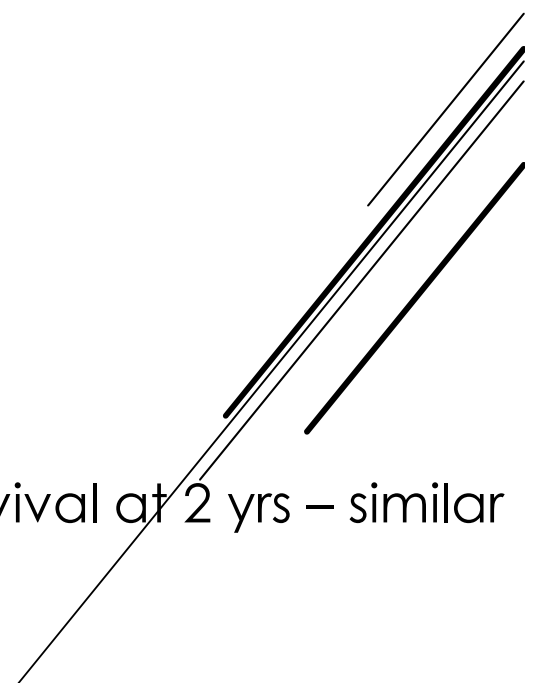
etoposide 75 mg/m² D1-5

ifosfamide 1.2gm/m² D1-5

cisplatin 20mg/m² D1-5

Nichols et al compared VIP vs BEP (n=204), failure free survival at 2 yrs – similar
; higher BM toxicity with VIP

3 weekly; 4 cycles



TIP

paclitaxel 250 mg/m² D1

Ifosfamide 1.2 gm/m² D1-5

Cisplatin 20 mg/m² D1-5

T-BEP

de wit and colleagues combined BEP with escalating doses of paclitaxel (phase I/II) (poor & intermediate)

of 13 pts with evaluable disease, all achieved CR and all were disease free at 18 months post CCT

EORTC phase II/III study (ongoing) – T-BEP vs BEP

DOSE ESCALATION

Although certain trials have indicated that high dose cisplatin improves outcome, no randomized studies have shown an improvement over the doses used in BEP

Indiana University-

BEP100 vs BEP200 – CR 73% vs 68%

no added benefit ; increased toxicity

DOSE INTENSIFICATION

Kaye et al (n=391) BEP/EP vs BOP/VIP-B

(CR- 57% vs 54%) ; increased toxicity; no benefit in outcome with use of prophylactic hematological growth factors

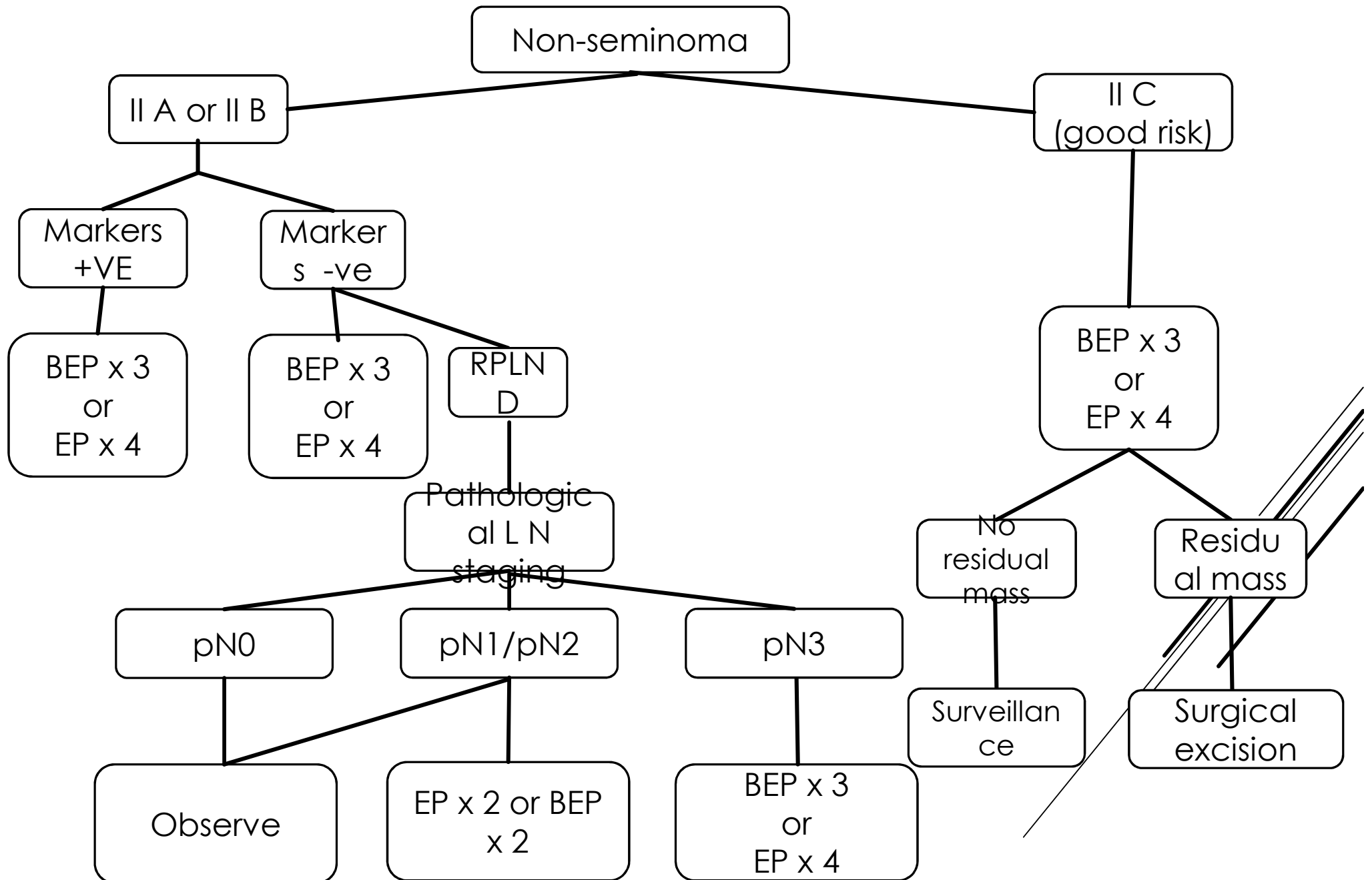
Other phase II studies

CBOP/BEP

POMB/ACE



BEP x 4 - IS THE BEST FIRST LINE REGIME



Treatment algorithm for non-seminoma : stages II A , II B , and II C (high risk disease)

RESIDUAL DISEASE

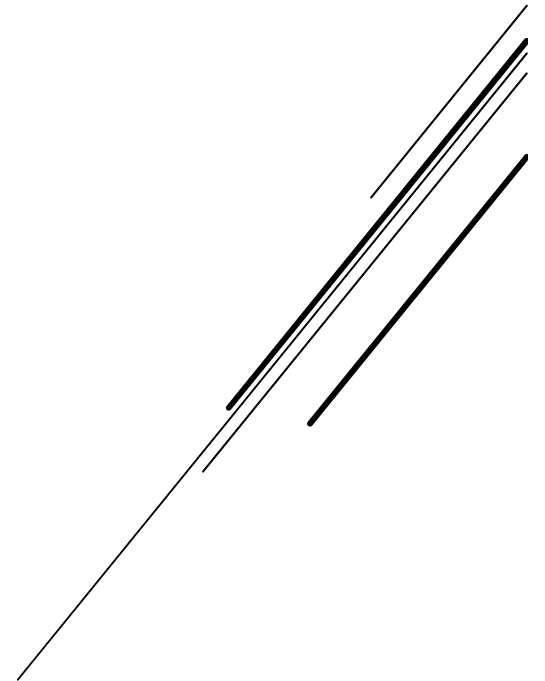
- ▶ **30% patients have residual radiographic abnormalities after completion of CCT**

RD

- a) with normal tumor markers
- b) with increased tumor markers

Treatment options

- salvage CCT
- surgical resection



Factors predicting presence of viable tumor in residual disease

- presence of terato-carcinoma in orchiectomy specimen
- pre operative markers (stabilization vs resolution)
- size of post CCT residual mass

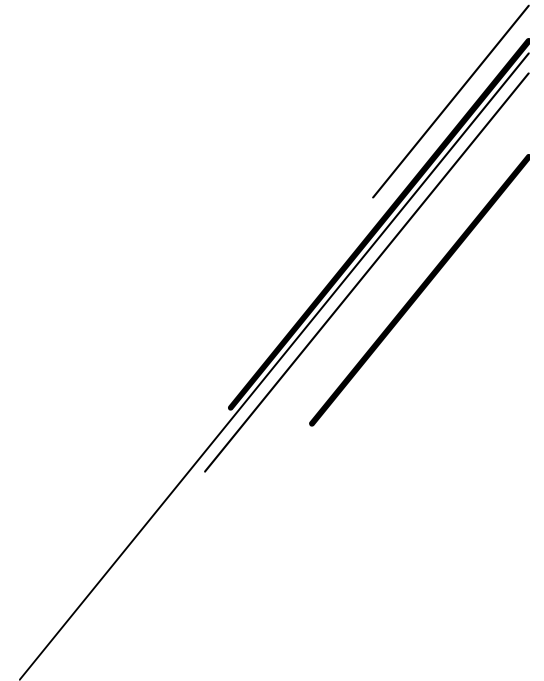
CT – not reliable

PET – better , but FN in small size(<1-2Cms)

TREATMENT OPTIONS - CCT/ RPLND

STRATEGY

- with increased markers → **salvage CCT**
- with normal markers → decision based on:
 - possibility of viable ca
 - biological potential of teratoma
 - morbidity of RPLND



RPLND (post CCT)

- bilateral dissection
- sometime necessary to perform adjunctive procedure like en bloc nephrectomy, bowel resection, en bloc resection of a great vessel.
- high morbidity
- eliminates the risk of growing teratoma syndrome

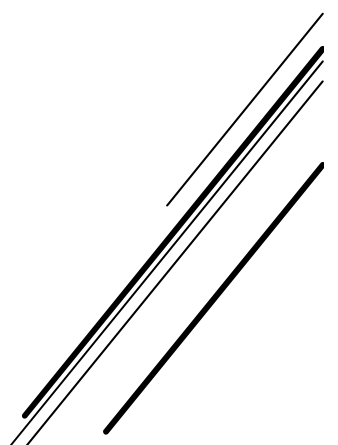
RETROPERITONEAL SPECIMEN

a) Necrosis/ teratoma → relapse risk (5% / 10%)

no additional therapy

b) viable tumor → high risk of relapse & decreased DFS

2 additional cycles of EP (cure rates -70%)



▶ Residual disease in lung or mediastinum

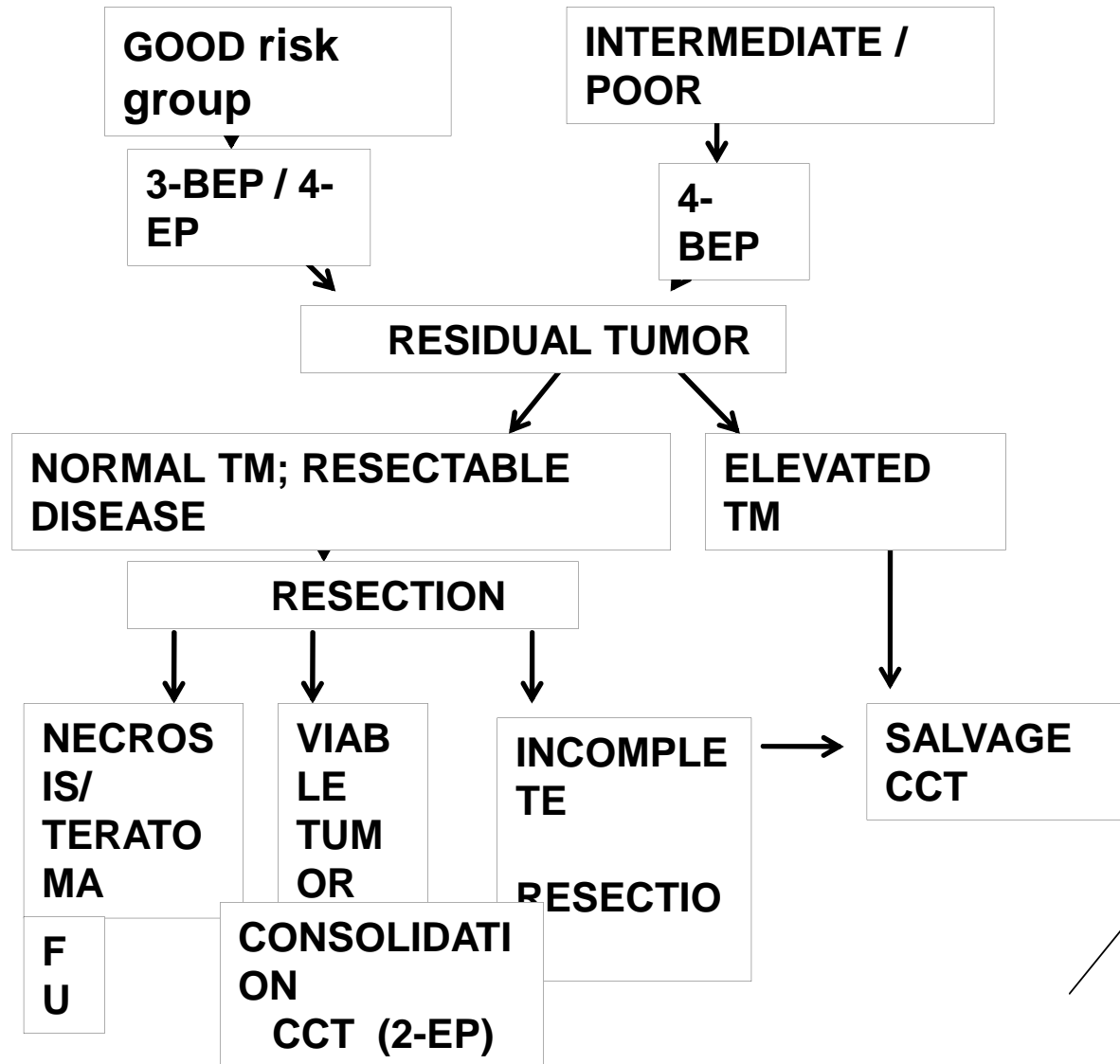
likelihood of teratoma or viable tumor (highest in mediastinum) - Higher

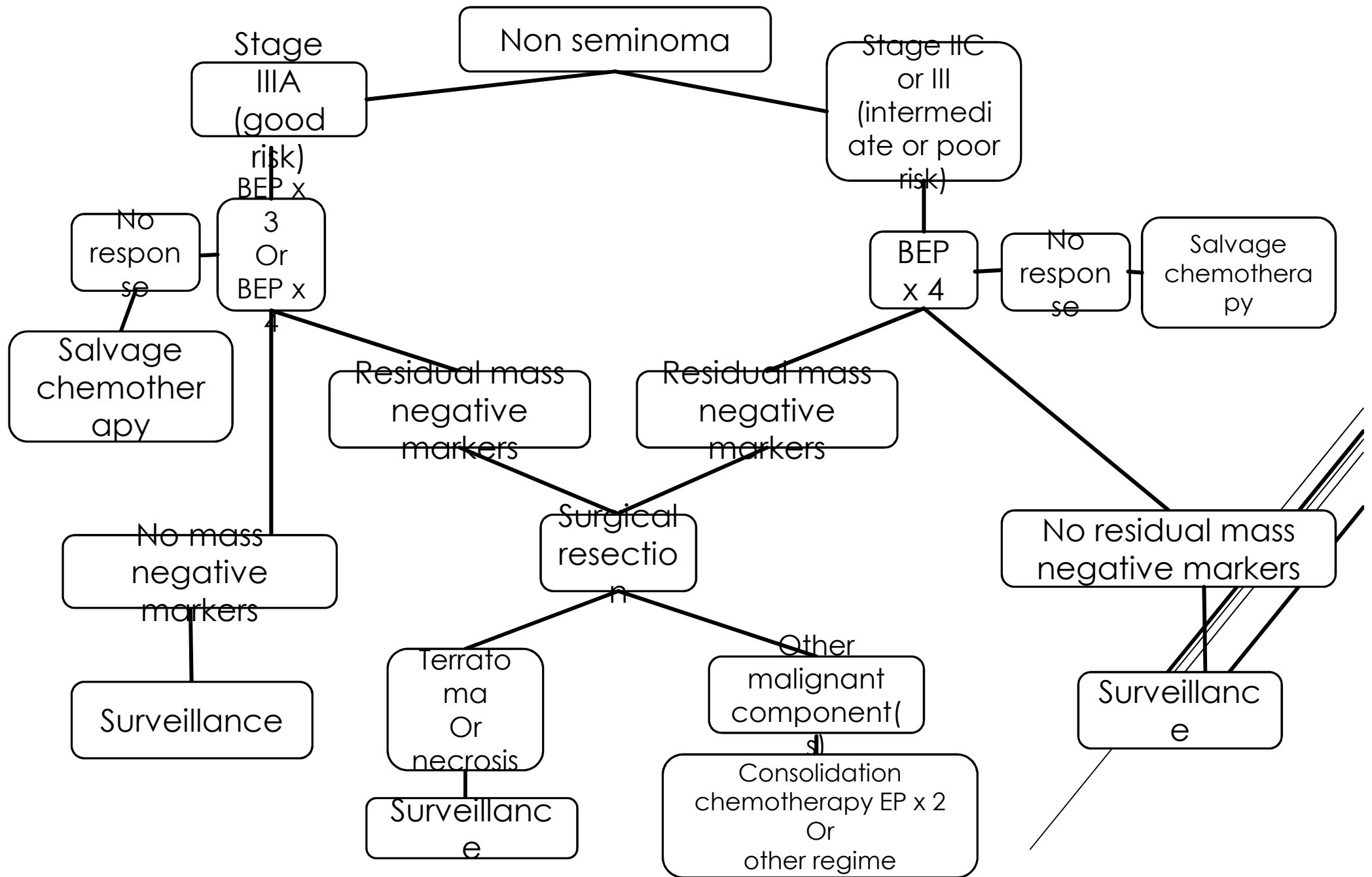
- Size of pre treatment/ and post CCT pulmonary nodule does not correlate with final histology

treatment → ***surgical resection***




STAGE IIC / III





Treatment algorithm for non-seminoma : stages II C (intermediate and poor risk disease)

RELAPSE / REFRACTORY DISEASE - SALVAGE CCT

- 20-30% with advanced tumors relapse or fail to achieve CR with conventional cisplatin based CCT
 - 2nd or 3rd line CCT offers possibility of cure (cure rates 0 -70 %)
 - **Salvage CCT**
 - conventional dose
 - high dose
 - **Prognostic factors**
 - primary site (testis/RP/mediastinal)
 - CR with initial CCT (35-40% 3 yr survival vs 10% 3 yr survival in PR with initial cct)
 - high HCG level
 - progressive disease within 4 weeks of cisplatin therapy
(cisplatin resistance)
- 

• HIGH DOSE CCT

Rationale

- chemosensitivity with dose response phenomena
- young pt (can tolerate high dose)
- rare bone marrow mets

significant morbidity and mortality

Prognostic factors – Beyer et al

Addition of PET CT in this context is proving very helpful (BJC,2002,86;506-11)

PROGNOSTIC SCORING FOR OVERALL SURVIVAL AND FAILURE-FREE SURVIVAL OF PATIENTS RECEIVING HIGH-DOSE CHEMOTHERAPY FOR RELAPSED OR REFRACTORY GERM CELL TUMORS

Factor*	Scoring Scheme		Risk Estimate		
	Points	Sum of Points	Risk Group	2-yr FFS (%)	2-yr OS (%)
Progressive disease	1	0	Good	51	61
Primary mediastinal tumor	1	1–2	Intermediate	27	34
Cisplatin-refractory disease	1	> 2	Poor	5	8
Absolute cisplatin-refractory disease	2				
hCG > 1,000 IU/L	2				

hCG > 1,000 IU/L

2

Absolute cisplatin-refractory disease

2

Cisplatin-refractory disease

1

> 2

Poor

5

8

NEVER

DRUGS

Oxaliplatin

- favorable toxicity profile
- active in cisplatin resistance
- RR- 13%

▶ Gemcitabine

- with paclitaxel showed 21% response in pts with refractory tumors
- with oxaliplatin yielded a RR of 44% in cisplatin refractory pts
(Bookmeyer et al)
- 50% RR with cisplatin in less heavily treated pts

Irinotecan

Paclitaxel based high dose CT with autologous stem cell rescue

(Margolin KA et al, Biol Blood Marrow transplant, 2005; 11(11):903-11

CNS METS

▶ Associated with

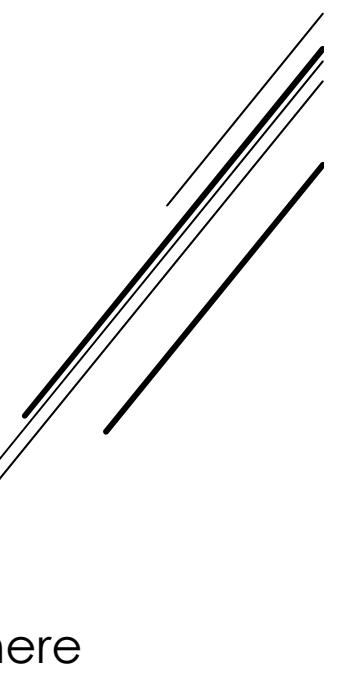
- NSGCT (testis, retroperitoneum vs mediastinum)
- choriocarcinoma
- high HCG
- pulmonary mets

▶ Types

- brain mets (more common)
- epidural mets
- leptomeningeal mets

▶ Presentation

- initial presentation
- isolated recurrence in brain after response of disease elsewhere
- with systemic recurrence / refractory disease (poor prognosis)



FOLLOW-UP GUIDELINES

Non-Seminomas

A) Stage(s)-1A,1B,

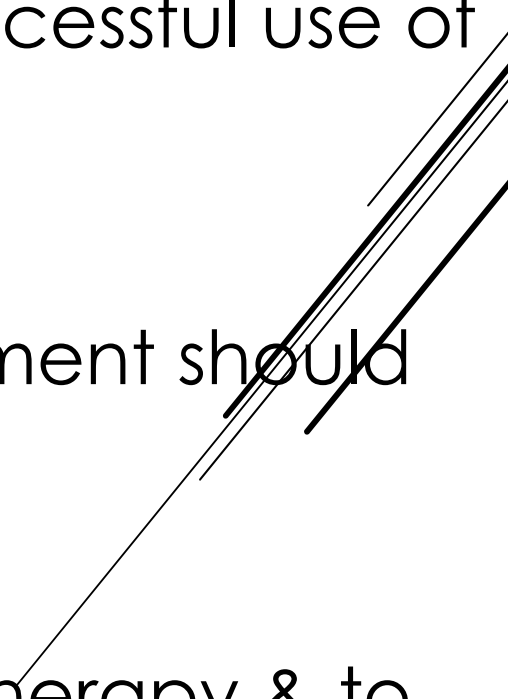
F-up year _____	Clinical exam,X-ray chest (monthly interval)_____	Abd.Pelvic CT-Scan (monthly interval)
--------------------	--	--

1	1-2	3-4
2	2	3-4
3	3	4
4	4	6
5	6	12
6+	12	12

B-Stage 11A,11B,11C,111 (post CT/RPLND and complete response)

1	1-2	6
2	2	6

CONCLUSIONS


- ▶ Curable in more than 80% of patient's with 100% cure rates in cases with low stage
 - ▶ Represents one of the major successes in cancer treatment and provides a model for successful use of multimodal approach
 - ▶ With a variety options, the plan of treatment should be individualized for each pt.
 - ▶ The trend is to reduce the morbidity of therapy & to increase responsiveness in poor risk advanced pts.
- 

Concerns after Treatment for Testicular Cancer?

- Fertility and Hormone Concerns in Boys and Men With Testicular Cancer
- Recurrence/relapse and fear of Second malignancy?
- Lifestyle Changes
- Emotional Health aspects

Managing Cancer as a Chronic Illness with concern and vigil about reduction of late

▶ **Current thrust--**

- ▶ **With such effective treatment available, the trend is to reduce the morbidity of therapy by a variety of techniques.**
 - ▶ **From full Dog Leg 30 Gy to Para Aortic 20 Gy to single cycle Carboplatin to Surveillance.**
 - ▶ **Development of more effective chemotherapy drugs & combinations**
 - ▶ **The key to this would be meticulous refinement in Risk Stratification and individualistic tailored treatment policy .**
- 

Thanks

