INDIAN COLLEGE OF RADIATION ONCOLOGY (ICRO)
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Management of Non Seminomatous Testicular tumours

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Most neoplastic scrotal masses ultimately prove to be germ cell tumours and are recognisable with routine haematoxylin and eosin-stained sections

What is new in 2016?

- ITGCN is now GCNIS
- Germ cell neoplasia in situ
- Does not involve entire tubule

- Add ‘Intratubular’ if it involves entire tubule
  - Intratubular seminoma
  - Intratubular embryonal

New classification

GCT derived from GCNIS

GCT unrelated to GCNIS

Sex cord Stromal

Misc tumors

Hematolymphoid

Tumors of collecting duct and rete testis

NON SEMINOMATOUS GERM CELL TUMOURS: WHAT DO WE DISCUSS

- How they present, staging and risk grouping
- Management modalities with respect to stage and risk group
- New advances
- Summarise management

AGE AT PRESENTATION

Congenital / <6 mths	Children >6 mths	Young men	Older men
• Juvenile granulosa cell tumour	• YST • Teratoma • Sex cord-stromal tumours	• GCT – seminomatous • Sex cord-stromal tumours	• Spermatocytic tumor • Sex cord-stromal tumours • Metastasis • Lymphoma

PREVIOUS HISTORY

Undescended testis

Previous diagnosis of a germ cell tumour or GCNIS or IT GCT

Possibility of a GCT very high

Previous or current carcinoma, lymphoma or leukaemia

Likely secondary tumour

GROSS PATHOLOGY

Seminomas	Non-seminomatous germ cell tumours	Teratoma	Sex cord stromal
• Nodules of homogenous white or tan tissue	• Zones of haemorrhage or necrosis	• Cystic • Tooth • Cartilage	• Yellow or tan

Tumor markers

LDH : Seminomas and non-seminomatous GCT

AFP : YST ; correlates with the amount of tumour in mixed germ cell tumours.

hCG : choriocarcinoma and in seminoma and mixed germ cell tumours as syncytiotrophoblast cells are commonly present in a scattered fashion

Inhibin : Leydig cell tumour, Sertoli cell tumour

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

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

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

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

Serum Tumor Markers (S)

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

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

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 Classification: A Prognostic Factor-Based Staging System for Metastatic Germ Cell Cancers. J Clin Oncol 1997;15(2):594-603.

NCCN Guidelines Version 2.2015
Testicular Cancer

TREATMENT MODALITIES FOR NON SEMINOMATOUS GERM CELL TUMOURS

- Surveillance
- Chemotherapy
- Surgery
- Radiotherapy for Brain metastases

Which cases to put under Surveillance / Observation Only?

- Stage 1A
- Stage 1A after RPLND pN0
- Stage 1B for T2 only
- Stage 1B after RPLND pN0
- 1S post chemo complete response markers neg
- IIA post chemo mass <1cm with markers neg

Sturgeon JF Eur Urol 2011
Zuniga BJU Int 2009

Surveillance / Observation

- 25% to 30% of patients with normal serum tumor markers relapse during surveillance. 15% of T1 and 50% of patients with T2 to T4 tumors will relapse.
- <10% of relapses on surveillance for NSGCT occur more than 2 years after orchiectomy
- Presence of Vascular invasion or embryonal carcinoma or absence of yolk sac elements is associated with risk of occult nodal disease
- Relapse rates: Vascular invasion 50% and 15-20% without it.
- Retroperitoneum is site of relapse in 2/3rd of patients,
- Lungs or markers alone in about 1/3rd and lower in other visceral sites.

de Wit R J Clin Oncol 2006
Daugaard G APMIS 2003
Read et al JCO 1992

Prospective trials of Surveillance in Stage 1

Author	No of Patients	Progression rate(%)	Death from disease	RP Progression rate(%)
Freedman et al	259	32	3	55
Jacobsen et al	83	28	nil	65
Peckhman et al	132	27	1	60
Read et al	396	25	5	61
Sogani et al	102	25	3	72
Sharir et al	170	75	1	65

Gunderson Tepper, 3rd edition

Chemo vs Surveillance in early stage disease

- 2 cycles of BEP vs surveillance in stage I. The 2-year recurrence-free survival was 98% in both arms.
- Long-term toxicity was assessed pre- and post-treatment with renal function, lung function, semen analysis, and audiometry.
- No major, clinically significant changes were observed. This demonstrates that the major toxic effects associated with BEP chemotherapy (renal, lung, hearing, fertility) were mild or absent following two cycles.

Macullen Annals of Oncology 2012

So Surveillance?

Benefits	Drawbacks
Excellent cancer cure rate	Requires frequent follow-up CT scans, with associated long-term risks
No treatment-related toxicity	Some patients may experience anxiety related to risk of recurrence
Excellent salvage rate	
Avoids overtreatment for the majority of patients	

SURGERY

- Radical Orchiedectomy
  - Done by inguinal incision to prevent alteration of lymphatic drainage pattern of the testicle by scrotal wall violation. Ligation of vas deferens and testicular vessels at internal inguinal ring, so no need of inguinal canal exploration if RPLND planned (therapy or staging).
  - Post Orchiectomy Serum Marker Status decides Staging and usually done after 3 weeks of Surgery
- Retroperitoneal Lymph node Dissection (RPLND)
  - Stage 1A, Stage 1B (recommended within 4 weeks of a CT scan and within 7 to 10 days of repeat serum marker testing to ensure accurate presurgical staging)
  - IIA,IIB upfront in marker negative or post-chemo marker negative
  - Post-chemo metastatic NSGCT with residual RP mass & marker neg
- Surgery for Residual Retroperitoneal Mass

- Bilateral infrahilar RPLND has replaced suprahilar dissection and is now the standard.

- Suprahilar dissection is done for residual hilar or suprahilar masses following chemotherapy for advanced-stage NSGCT.

- A bilateral infrahilar RPLND includes the precaval, retrocaval, paracaval, interaortocaval, retroaortic, preaortic, para-aortic, and common iliac lymph nodes bilaterally.

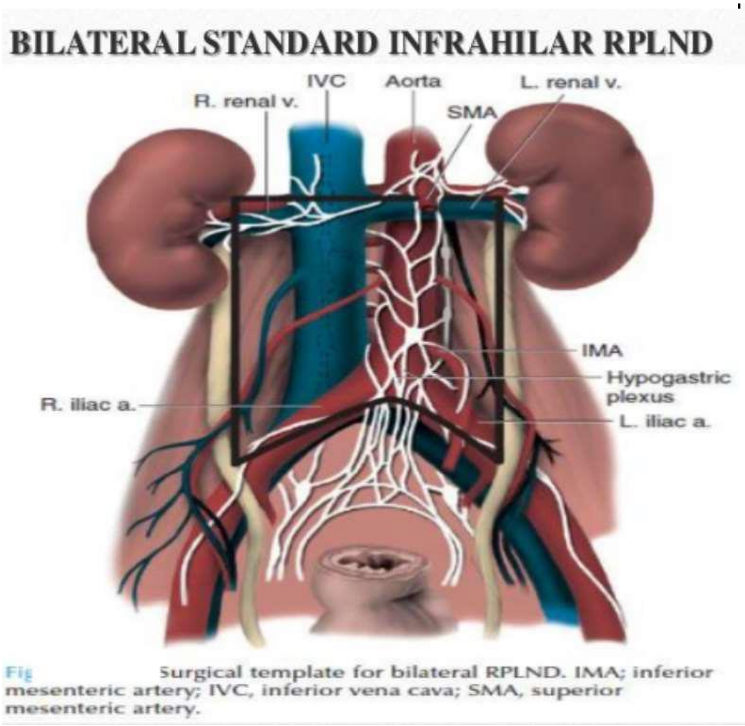
Chang SS J Urol 2002

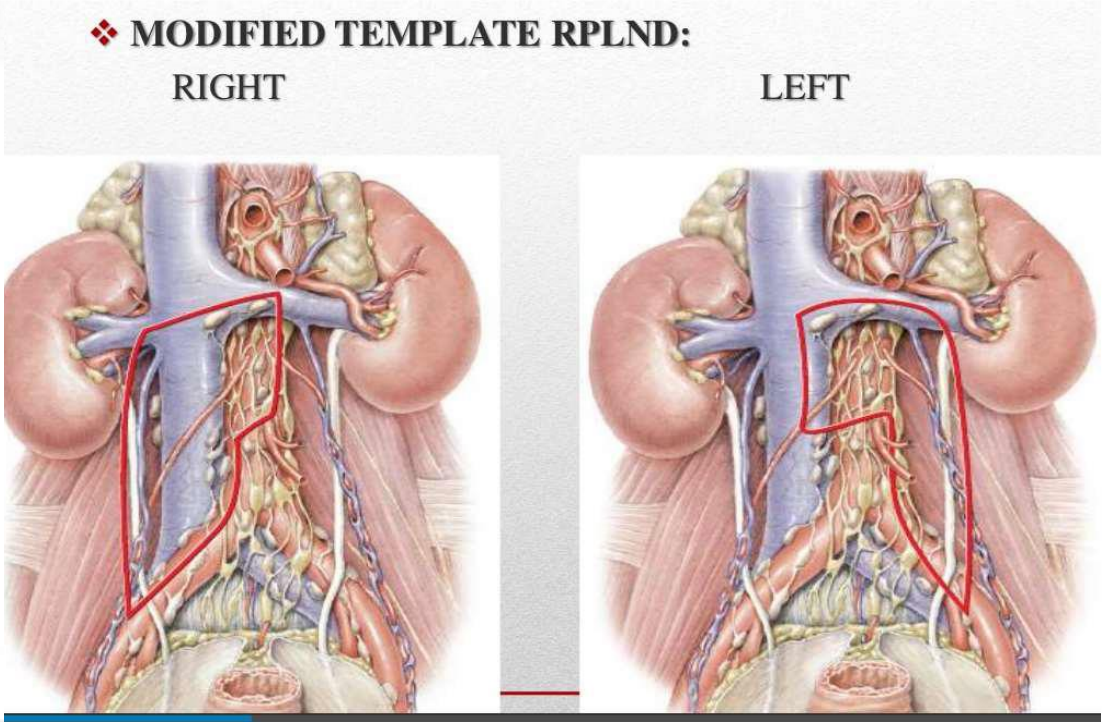
- Modified RPLND templates minimizes contralateral dissection, reducing trauma to the hypogastric plexus and contralateral postganglionic sympathetic fibers.

- Preservation of antegrade ejaculation with this approach ranges from 50% to 80%.

- Nerve sparing RPLNDs:
  - For right-sided tumors, the inter-aortocaval nodes and paracaval nodes are removed, with preservation of the left sympathetic chain.
  - For left-sided tumors, the para-aortic and inter-aortocaval nodes are removed and the right autonomic chain is preserved.

Chang SS J Urol 2002





Stage	IA, IB	IIA
pN0	Surveillance	Surveillance
pN1	Surveillance (preferred) vs. BEP-2Cycles	Surveillance (preferred) vs. BEP-2Cycles
pN2	BEP- 2Cycles	BEP- 2Cycles
pN3	BEP- 3Cycles	BEP- 3Cycles

Post RPNLD Stage wise management

Surgery for Residual Retroperitoneal Mass

- Post chemo residual masses with normal serum markers
- Should be done 4 to 6 weeks after chemo
- On histology
  - 50% show necrosis
  - 35% are mature teratoma
  - 15 % have malignant disease

Krege et al 2008 Eur Ural

Complications of Surgery

- Minor complications include
  - Lymphocele (30-40%)
  - Atelectasis (25-30%)
  - Wound infection (10%)
  - Prolonged ileus.
- Long-term morbidity with a standard bilateral RPLND retrograde ejaculation (50-60%) and subsequent infertility secondary to sympathetic nerve fiber damage.
- Mortality rate of less than 1%
- Major complications rare: hemorrhage, ureteral injury, bowel obstruction, pulmonary embolus, and wound dehiscence.

Shienfeld urology 2007

Indications for Chemotherapy in NSGCTs

- Stage IA ,IB; IIA,IIB; III
- Stage I,II post RPLND with pN1-pN3
- All stages marker positive
- Relapse
- Metastatic disease

Chemotherapy according risk group:

- For Good Risk Stage IIA-S1, IIB, IIC, IIIA: BEP for 3 cycles
  - If CR: Surveillance vs. RPLND
  - If Partial response (residual mass with normal AFP & hCG levels) : surgical resection and HPE; if necrosis or teratoma, then observe; if others then 2nd line chemo.
- For Intermediate & Poor Risk IIIB & IIIC: BEP 4 Cycles
  - If CR: Surveillance vs. RPLND
  - If Partial response (residual mass with normal AFP & hCG levels) : as in good risk group.

PRIMARY CHEMO REGIMES IN CHEMO NAÏVE NSGCTs

EP
Etoposide 100 mg/m² IV on Days 1–5
Cisplatin 20 mg/m² IV on Days 1–5
Repeat every 21 days[1]

BEP
Etoposide 100 mg/m² IV on Days 1–5
Cisplatin 20 mg/m² 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]

VIP
Etoposide 75 mg/m² IV on Days 1–5
Mesna 120 mg/m² slow IV Push before ifosfamide on Day 1, then
Mesna 1200 mg/m² IV Continuous Infusion on Days 1–5
Ifosfamide 1200 mg/m² on Days 1–5
Cisplatin 20 mg/m² IV on Days 1–5
Repeat every 21 days[3]

2ND LINE THERAPY FOR PROGRESSIVE / METASTATIC DISEASE

- Second line chemo can be conventional dose and high dose Chemo followed by ASCT
- After 2nd line CT if no complete response then disease is usually incurable
- Except if there is solitary site of metastasis which can be surgically removed

Lorch JCO 2010

Favourable factors	Unfavourable Factors
Testicular primary site	Incomplete response
Prior complete response	High level of tumor markers
Low serum tumour markers	Extra testicular tumour
Low volume disease	

Conventional-Dose Chemotherapy Regimens

VeIP

Vinblastine 0.11 mg/kg IV Push on Days 1–2
Mesna 400 mg/m² IV every 8 hours on Days 1–5
Ifosfamide 1200 mg/m² IV on Days 1–5
Cisplatin 20 mg/m² IV on Days 1–5
Repeat every 21 days[1]

TIP

Paclitaxel 250 mg/m² IV on Day 1
Ifosfamide 1500 mg/m² IV on Days 2–5
Mesna 500 mg/m² IV before ifosfamide, and then 4 and 8 hours after each ifosfamide dose on Days 2–5
Cisplatin 25 mg/m² IV on Days 2–5
Repeat every 21 days[2]

High-Dose Chemotherapy Regimens

Carboplatin 700 mg/m² (body surface area) IV
Etoposide 750 mg/m² IV
Administer 5, 4, and 3 days before peripheral blood stem cell infusion for 2 cycles[3]

Paclitaxel 200 mg/m² IV over 24 hours on Day 1
Ifosfamide 2000 mg/m² 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/m² IV Days 1–3
Administer with peripheral blood stem cell support at 14- to 21-day intervals for 3 cycles[4]

Palliative Chemotherapy

- For patients with persistent or recurrent disease

- Chemo can be
  - Gem+Carbo
  - Pacli+Carbo
  - Gem+ Pacli +/- Carbo
  - Oral Etoposide daily

Mulherin JCO 2011
Pectasides Ann Oncol 2004

Treatment Outcomes

- Stage I NSGCT 5-year OS of about 99% (exceeds 95%).
  - Surveillance has 30% relapse rate
  - RPLND has 10% relapse rate
- Stage II NSGCT, the 5-year OS is around 98% (exceeds 95%).
- For stage IIA disease
  - Chemotherapy (<5% relapse rate)
  - RPLND plus chemotherapy <5% relapse rate.
- Stage IIB or IIC disease, if chemotherapy is given, about 5% relapse rate.
- Stage III disease after chemotherapy: 20-25% relapse rate

Stephenson AJ BJU 2009

Risk Group wise Prognosis:

- The good-prognosis group (60% of cases) has an approximately 86% 5 year OS.
- The intermediate prognosis group (26% of cases) has an approximately 80% 5 year OS.
- In the poor-prognosis group (14% of cases), the 5 year OS is around 50%

Huyghe Cancer 2004

FOLLOW UP SCHEDULES

Table 5 Clinical Stage IA, NSGCT: Active Surveillance

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	Every 4–6 mo	Every 6–12 mo	Annually	---	---
Chest x-ray[2]	At mo 4 and12	Annually	Annually	Annually	Annually

Table 6 Clinical Stage IB, NSGCT: Active Surveillance

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	Every 4 mo	Every 4–6 mo	Every 6 mo	Annually	---
Chest x-ray[2]	Every 2 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Annually

FOLLOW UP SCHEDULES

Table 7 Clinical Stage IB NSGCT: Treated with 1–2 Cycles of Adjuvant BEP Chemotherapy

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 3 mo	Every 3 mo	Every 6 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	Annually	Annually	---	---	---
Chest x-ray[2]	Every 6–12 mo	Annually	---	---	---

Clinical Stage II-III NSGCT: Surveillance After Complete Response to Chemotherapy ± Post-chemotherapy RPLND

	Year (at month intervals)				
	1	2	3	4	5
H&P and marker[1]	Every 2 mo	Every 3 mo	Every 6 mo	Every 6 mo	Every 6 mo
Abdominal/ Pelvic CT[3]	Every 6 mo	Annually	---	---	---
Chest x-ray[2,4]	Every 6 mo	Every 6 mo	Annually[5]	Annually[5]	---

FOLLOW UP SCHEDULES

Pathologic Stage IIA/B NSGCT: Post-Primary RPLND and Treated with Adjuvant Chemotherapy

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 6 mo	Every 6 mo	Annually	Annually	Annually
Abdominal/ Pelvic CT	After RPLND	As clinically indicated			
Chest x-ray[2]	Every 6 mo	Annually	Annually	Annually	Annually

Pathologic Stage IIA/B NSGCT: Post-Primary RPLND and NOT Treated with Adjuvant Chemotherapy[1]

	Year (at month intervals)				
	1	2	3	4	5
H&P and markers[1]	Every 2 mo	Every 3 mo	Every 4 mo	Every 6 mo	Annually
Abdominal/ Pelvic CT	At 3–4 mo[7]	As clinically indicated			
Chest x-ray[2]	Every 2–4 mo	Every 3–6 mo	Annually	Annually	Annually

RECENT DEVELOPMENTS

- For stage I NSGCT, results from SWENOTECA study show that adjuvant therapy can be safely reduced to just one course of BEP, resulting in a reduction in relapse rate of 90-95%.
- The proper extent of PCS resection and the need for PC-RPLND in patients achieving complete remission remains controversial.
- Current European and Canadian guidelines favor observation for patients achieving complete radiographic remission post chemo, whereas in the NCCN guidelines either immediate PC-RPLND or observation are recommended.
- Modified unilateral PC-RPLND (either right or left) may be safe in select patients with low volume retroperitoneal disease (less than 5 cm), restricted to the primary landing zone of the affected testicle (based on lymphatic mapping studies of primary RPLND)

Ehrlich Y et al. Advances in the treatment of testicular cancer. Transl Androl Urol 2015;4(3):381-390.

TAKE HOME MESSAGE

- Stage IA, IB (T2 only):
  - Surveillance,
  - Nerve-sparing RPLND.
- Stage IB:
  - Nerve-sparing RPLND, or
  - Primary chemotherapy: BEP for 2 cycles, or
  - Surveillance (cT2 or post RPNLD with pN0)
- Stage IS: 3 cycles of BEP
- Stage IIA with Normal Markers
  - Nerve-sparing RPLND (Preferred), or
  - BEP 3 Cycles.
- For Good Risk Stage IIA-S1, IIB, IIC, IIIA: BEP 3 Cycles
- For Intermediate & Poor Risk IIIB & IIIC: BEP 4 Cycles

- After primary Chemo,
  - Residual mass of 1 cm or greater : Nerve-sparing RPLND
  - Residual mass <1cm: Surveillance vs. RPLND

- After primary RPLND,
  - pN0: Surveillance
  - pN1: Surveillance (preferred) vs. BEP- 2Cycles
  - pN2: BEP- 2Cycles
  - pN3: BEP- 3Cycles

- In case of Brain Mets or Acute cord compression or SVCO due to metastatic disease: Palliative Radiotherapy

Thank you