Management of Non Seminomatous Testicular Tumours

Dr. Ashutosh Mukherji
Professor and Head
Department of Radiation Oncology,
Mahamana Pandit Madanmohan Malviya Cancer Centre
And Homi Bhabha Cancer Hospital,
(A Unit of Tata Memorial Centre), Varanasi
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
- Juvenile granulosa cell tumour

Children >6 mths
- YST
- Teratoma
- Sex cord-stromal tumours

Young men
- GCT – seminomatous
- Sex cord-stromal tumours

Older men
- 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

<table>
<thead>
<tr>
<th>Seminomas</th>
<th>Non-seminomatous germ cell tumours</th>
<th>Teratoma</th>
<th>Sex cord stromal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodules of homogenous white or tan tissue</td>
<td>Zones of haemorrhage or necrosis</td>
<td>Cystic&lt;br&gt;Tooth&lt;br&gt;Cartilage</td>
<td>Yellow or tan</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>Group</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>S (Serum Tumor Markers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>pTis</td>
<td>N0</td>
<td>M0</td>
<td>S0</td>
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<tr>
<td>Stage I</td>
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<td>Stage IIA</td>
<td>pT1</td>
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<td>S0</td>
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<td>Stage IIB</td>
<td>pT2</td>
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<td>S0</td>
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<td></td>
<td>PT3</td>
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<td>M0</td>
<td>S0</td>
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<td></td>
<td>PT4</td>
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<td>S0</td>
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<td>S0</td>
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<td></td>
<td>Any pT/TX</td>
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<td>M0</td>
<td>S1</td>
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<td>M0</td>
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<td>Any N</td>
<td>M1</td>
<td>SX</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Any pT/TX</td>
<td>Any N</td>
<td>M1a</td>
<td>S0</td>
</tr>
<tr>
<td></td>
<td>Any pT/TX</td>
<td>Any N</td>
<td>M1a</td>
<td>S1</td>
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<tr>
<td>Stage IIIB</td>
<td>Any pT/TX</td>
<td>N1-3</td>
<td>M0</td>
<td>S2</td>
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<tr>
<td></td>
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<td>Any N</td>
<td>M1a</td>
<td>S3</td>
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<tr>
<td></td>
<td>Any pT/Tx</td>
<td>Any N</td>
<td>M1b</td>
<td>Any S</td>
</tr>
</tbody>
</table>

#### Serum Tumor Markers (S)

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

*N* indicates the upper limit of normal for the LDH assay.
<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Noneosinoma</th>
<th>Seminoma</th>
</tr>
</thead>
</table>
| 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        | Medialstinal 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 |


NCCN Guidelines Version 2.2.2015
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

<table>
<thead>
<tr>
<th>Author</th>
<th>No of Patients</th>
<th>Progression rate(%)</th>
<th>Death from disease</th>
<th>RP Progression rate(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedman et al</td>
<td>259</td>
<td>32</td>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>Jacobsen et al</td>
<td>83</td>
<td>28</td>
<td>nil</td>
<td>65</td>
</tr>
<tr>
<td>Peckhman et al</td>
<td>132</td>
<td>27</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>Read et al</td>
<td>396</td>
<td>25</td>
<td>5</td>
<td>61</td>
</tr>
<tr>
<td>Sogani et al</td>
<td>102</td>
<td>25</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>Sharir et al</td>
<td>170</td>
<td>75</td>
<td>1</td>
<td>65</td>
</tr>
</tbody>
</table>
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.
So Surveillance?

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent cancer cure rate</td>
<td>Requires frequent follow-up CT scans, with associated long-term risks</td>
</tr>
<tr>
<td>No treatment-related toxicity</td>
<td>Some patients may experience anxiety related to risk of recurrence</td>
</tr>
<tr>
<td>Excellent salvage rate</td>
<td></td>
</tr>
<tr>
<td>Avoids overtreatment for the majority of patients</td>
<td></td>
</tr>
</tbody>
</table>
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 Orchietomy 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.
• 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.
<table>
<thead>
<tr>
<th>Stage</th>
<th>IA, IB</th>
<th>IIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>Surveillance</td>
<td>Surveillance</td>
</tr>
<tr>
<td>pN1</td>
<td>Surveillance (preferred) vs. BEP-2Cycles</td>
<td>Surveillance (preferred) vs. BEP-2Cycles</td>
</tr>
<tr>
<td>pN2</td>
<td>BEP- 2Cycles</td>
<td>BEP- 2Cycles</td>
</tr>
<tr>
<td>pN3</td>
<td>BEP- 3Cycles</td>
<td>BEP- 3Cycles</td>
</tr>
</tbody>
</table>

**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.
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.
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
<table>
<thead>
<tr>
<th>Favourable factors</th>
<th>Unfavourable Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular primary site</td>
<td>Incomplete response</td>
</tr>
<tr>
<td>Prior complete response</td>
<td>High level of tumor markers</td>
</tr>
<tr>
<td>Low serum tumour markers</td>
<td>Extra testicular tumour</td>
</tr>
<tr>
<td>Low volume disease</td>
<td></td>
</tr>
</tbody>
</table>

**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 days¹

**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 days²

**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 cycles³

**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 cycles⁴
Palliative Chemotherapy

• For patients with persistent or recurrent disease

• Chemo can be
  – Gem+Carbo
  – Pacli+Carbo
  – Gem+ Pacli +/- Carbo
  – Oral Etoposide daily
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%
### FOLLOW UP SCHEDULES

#### Table 5 Clinical Stage IA, NSGCT: Active Surveillance

<table>
<thead>
<tr>
<th></th>
<th>Year (at month intervals)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>H&amp;P and markers</strong>¹</td>
<td>Every 2 mo</td>
</tr>
<tr>
<td><strong>Abdominal/Pelvic CT</strong></td>
<td>Every 4–6 mo</td>
</tr>
<tr>
<td><strong>Chest x-ray</strong>²</td>
<td>At mo 4 and 12</td>
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#### Table 6 Clinical Stage IB, NSGCT: Active Surveillance

<table>
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</tr>
<tr>
<td><strong>H&amp;P and markers</strong>¹</td>
<td>Every 2 mo</td>
</tr>
<tr>
<td><strong>Abdominal/Pelvic CT</strong></td>
<td>Every 4 mo</td>
</tr>
<tr>
<td><strong>Chest x-ray</strong>²</td>
<td>Every 2 mo</td>
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### FOLLOW UP SCHEDULES

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

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<tr>
<td><strong>Abdominal/ Pelvic CT</strong></td>
<td>Annually</td>
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<td><strong>Chest x-ray(^2)</strong></td>
<td>Every 6–12 mo</td>
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</table>

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

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</tr>
<tr>
<td><strong>H&amp;P and marker(^1)</strong></td>
<td>Every 2 mo</td>
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<tr>
<td><strong>Abdominal/ Pelvic CT(^3)</strong></td>
<td>Every 6 mo</td>
</tr>
<tr>
<td><strong>Chest x-ray(^2,4)</strong></td>
<td>Every 6 mo</td>
</tr>
</tbody>
</table>

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\(^1\) Hemato-Pathological Evaluation.\n
\(^2\) Chest x-ray for potential complications.\n
\(^3\) Abdominal/ Pelvic CT to detect residual disease.\n
\(^4\) After RPLND.\n
\(^5\) Annually if negative imaging.\n
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30
### FOLLOW UP SCHEDULES

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

<table>
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<th>Year (at month intervals)</th>
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<td>4</td>
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<tr>
<td>H&amp;P and markers¹</td>
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<td>Every 6 mo</td>
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<td>Annually</td>
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<tr>
<td>Abdominal/</td>
<td>After RPLND</td>
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<td>Pelvic CT</td>
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<td>Chest x-ray²</td>
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**Pathologic Stage IIA/B NSGCT: Post-Primary RPLND and NOT Treated with Adjuvant Chemotherapy¹**

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<thead>
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<th>Year (at month intervals)</th>
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<td>5</td>
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<tr>
<td>H&amp;P and markers¹</td>
<td>Every 2 mo</td>
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<tr>
<td>Abdominal/</td>
<td>At 3–4 mo⁷</td>
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<td>Pelvic CT</td>
<td>As clinically indicated</td>
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<tr>
<td>Chest x-ray²</td>
<td>Every 2–4 mo</td>
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¹ For more information onOND Treated with Adjuvant Chemotherapy, please consult the relevant section of the treatment guidelines.
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)

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