TESTIS NEOPLASMS

ONCOLOGY - ADULT

BACKGROUND

The vast majority are classified as **germ cell tumors** (**95%**), while the remaining are predominately **sex cord/stromal tumors** (**mainly Leydig cell and Sertoli cell tumors**)[1]

Germ cell tumors (GCT) are further designated as **seminoma** or **non-seminoma germ cell tumors** (**NSGCT**) and represent the most common malignancy seen in men ages 20-40[1]

The incidence in the United States is 6.4/100,000 men resulting in approximately 9,610 cases in 2020[1]

BACKGROUND

- The most common presentation is **localized seminoma, which represents approximately 50% of the cases**, and only 10-30% of men will present with metastatic disease.[1]
- Risk factors for testicular cancer include:
  - Cryptorchidism (RR 4-6)
  - Family or personal history of testicular cancer (RR 2-12)
  - Intra-tubular germ cell neoplasia (ITGCN)
    - 50% of men with ITGCN will develop a GCT within 5 years

Seminoma	
Classic	Most common GCT, peak incidence 35-40 years of age, 15% contain syncytiotrophoblasts (resulting in bHCG production), arise from ITGCN
Spermatocytic	Only 1% of GCT, peak incidence 50-60 years of age, essentially benign tumor cured with orchiectomy alone, does not arise from ITGCN. In 2016, the WHO renamed "spermatocytic seminoma" to "spermatocytic tumour" and classified it within the non-GCNIS (germ cell neoplasia in situ) related tumors
NSGCT	
Embryonal Carcinoma	Poorly differentiated, able to differentiate into other NSGCT, peak incidence 25-35 years of age, aggressive tumor with high rate of metastasis
Yolk Sac	Pure tumors are rare, most common GCT in children/infants, present in 40% of mixed GCTs, generally produce AFP (never produce bHCG), Schiller-Duval bodies are classic pathologic finding
Choriocarcinoma	Rare, aggressive type of GCT (1% pure, 10% mixed tumors), peak incidence 20-30 years of age, early hematogenous spread (including brain), high bHCG common, no AFP production
Teratoma	Contain well or incompletely differentiated cell layers of endoderm, mesoderm, or ectoderm, pure teratomas do not produce AFP or bHCG, pure teratomas rarely seen in adults (more common in pediatric population), approximately half of mixed GCT contain teratomatous elements, chemoresistant, morbidity related to local growth and malignant transformation

EVALUATION

A painless testicular mass is the most common presentation of testicular cancer[1]

Other presenting symptoms can be related to metastatic disease: abdominal mass, back pain, supraclavicular mass, shortness of breath, and hemoptysis

Men with a testicular mass, or suspected mass, should undergo a **scrotal ultrasound as the initial diagnostic study**

Obtain serum tumor markers (STM)

SERUM TUMOR MARKERS

Alpha-fetoprotein (AFP)

- **Half-life 5-7 days**, elevated in 50-80% of NSGCT, EC and yolk sac tumor produce AFP, seminoma and choriocarcinoma do not, can be elevated in patients with liver disease, hepatocellular carcinoma, stomach/pancreas/biliary duct/lung cancers.

Beta-human chorionic gonadotropin (bHCG)

- **Half-life 24-36 hours**, elevated in 20-60% of NSGCT and 15% of seminomas, produced by EC/choriocarcinoma/seminoma, can be elevated in liver/biliary/pancreas/stomach as well as lung/breast/kidney/bladder cancers, can be elevated secondary to marijuana use.

Lactate Dehydrogenase (LDH)

- LDH-1 is the most common isoenzyme elevated in GCT, **half-life 24 hours**, non-specific marker of GCT, measure of disease burden, utilized by some clinicians for prognostication at the time of diagnosis.

INITIAL TREATMENT

A radical inguinal orchiectomy is the standard treatment of the primary tumor if testis cancer is suspected. This involves removal of the testicle and spermatic cord to the level of the internal inguinal ring through an inguinal incision

A trans-scrotal orchiectomy or biopsy <u>should not</u> be performed

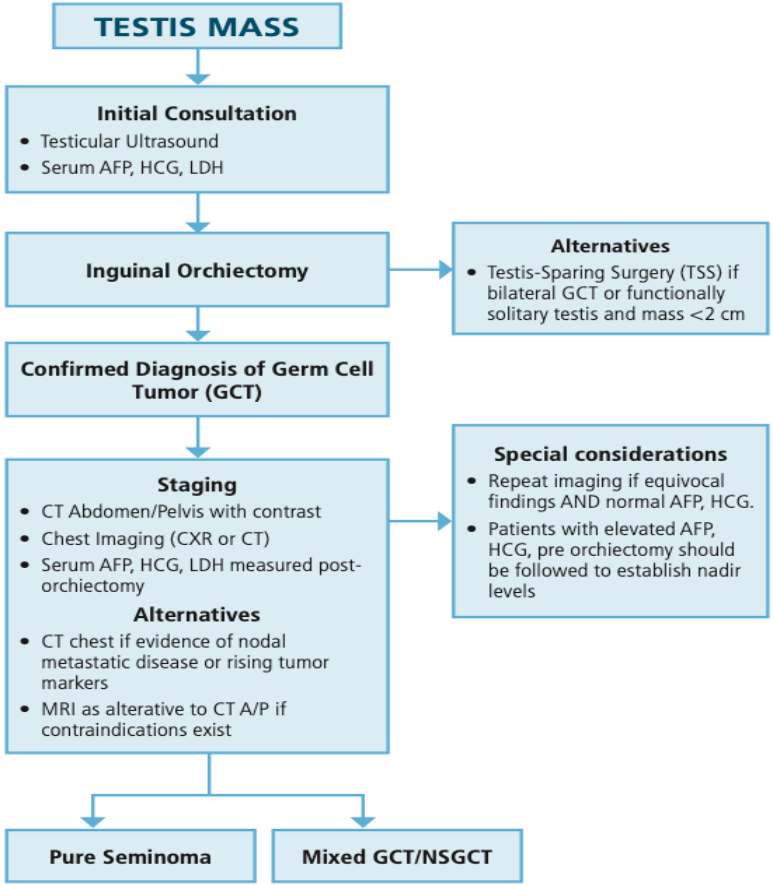
Testis sparing surgery can be considered in a small tumor in a solitary testis, when small bilateral tumors exist, or increased suspicion of a benign tumor

INITIAL TREATMENT

Once a testicular cancer has been diagnosed, complete staging should be performed with computed tomography (CT) of the chest/abdomen/pelvis with oral and intravenous contrast

Alternatively, a chest radiograph can be obtained as the initial staging in patients with a low risk of thoracic metastasis such as when there are normal post-orchiectomy STM and no abdominal/pelvic metastases

DIAGNOSIS AND TREATMENT OF EARLY STAGE TESTICULAR CANCER: AUA GUIDELINE ALGORITHM



STAGING

Metastatic spread of GCTs typically follows a predictable pattern based on the lymphatic drainage of the testis (excluding choriocarcinoma). For the **left testis, the primary drainage is the para-aortic lymph nodes.** The **primary drainage for the right testicle is the infrarenal inter-aortocaval lymph nodes, followed by paracaval and para-aortic regions**

Drainage of the retroperitoneal lymphatics occurs in a right to left direction allowing for frequent contralateral metastases from right side tumors, but this is an uncommon occurrence for left sided tumors.

Given this predictable route of spread, **the retroperitoneum serves as the initial site of metastasis in 70-80% of patients**[1]

STAGING

Primary tumor pathology, staging imaging studies, and post-orchiectomy STM form the basis for clinical staging in testicular cancer[2]

It is important to note there is a difference in clinical and pathologic staging of lymph nodes, where the latter also includes the number of involved nodes and the presence of extranodal extension in addition to the size criteria[2]

STAGING

- Patients with advanced GCTs are further risk stratified using the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification, which provides prognosis and guides the choice of chemotherapy regimen for patients with advanced disease

- The 2017 AJCC TNM staging for testicular cancer and IGCCCG classification are seen in the following slides[2,47]

STAGING

Primary Tumor (T)	
pTx	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis	Intratubular germ cell neoplasia
pT1	Tumor limited to the testis and epididymis without lymphovascular invasion, may invade tunica albuginea but not tunica vaginalis
pT2	Tumor limited to the testis and epididymis with lymphovascular invasion or tumor involving the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without lymphovascular invasion
pT4	Tumor invades the scrotum with or without lymphovascular invasion
Regional Lymph Nodes (Clinical) (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis within 1-5 lymph nodes all nodes masses less than 2cm in size
N2	Metastasis within a lymph node greater than 2cm but not greater than 5cm in size, or more the 5 lymph nodes involved, none greater than 5cm and none demonstrating extranodal extension of tumor
N3	Metastasis within one or more lymph nodes greater than 5cm in size
Distant Metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Distant metastasis at site other than nonregional lymph nodes or lung
Serum Tumor Markers (S)	
Sx	Tumor markers not available or performed
S0	Tumor markers within normal limits
S1	LDH <1.5 x normal, hCG<5000 IU/L, AFP <1000 ng/ml
S2	LDH 1.5-10 x normal, hCG 5000-50000 IU/L, AFP 1000-10000 ng/ml
S3	LDH >10 x normal, hCG>50000 IU/L, AFP >10000 ng/ml

AFP-alpha-fetoprotein, hCG-human chorionic gonadotropin, LDH-lactate dehydrogenase | From AJCC Cancer Staging[4]

STAGING

- AJCC STAGING

Stage Grouping				
Stage	**T**	**N**	**M**	**S**
Stage I	pT1-4	N0	M0	SX
IA	pT1	N0	M0	S0
IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
IS	Any pT	N0	M0	S1-3
Stage II	Any pT	N1-3	M0	SX
IIA	Any pT	N1	M0	S0-1
IIB	Any pT	N2	M0	S0-1
IIC	Any pT	N3	M0	S0-1
Stage III	Any pT	Any N	M1	SX
IIIA	Any pT	Any N	M1a	S0-1
IIIB	Any pT	N1-3	M0	S2
	Any pT	Any N	M1a	S2
IIIC	Any pT	N1-3	M0	S3
	Any pT	Any N	M1a	S3
	Any pT	Any N	M1b	Any S

STAGING

- IGCCCG

Good Prognosis	
Non-seminoma	**Seminoma**
1. Testicular/retroperitoneal primary 2. No nonpulmonary visceral metastases 3. Markers: AFP <1000 ng/ml and hCG <5000 IU/L and LDH <1.5 x normal	1. Any primary site 2. No non-pulmonary visceral metastases 3. Markers: Normal AFP and Any hCG and Any LDH
Intermediate Prognosis	
Non-seminoma	**Seminoma**
1. Testicular/retroperitoneal primary 2. No non-pulmonary visceral metastases 3. Markers: AFP 1000-10000 ng/ml and/or hCG 5000-50000 IU/L and/or LDH 1.5-10 x normal	1. Any primary site 2. Non-pulmonary visceral metastases 3. Markers: Normal AFP and Any hCG and Any LDH
Poor Prognosis	
Non-seminoma	**Seminoma**
1. Mediastinal primary 2. Non-pulmonary visceral metastases 3. Markers: AFP >10000 ng/ml and/or hCG >50000 IU/L and/or LDH >10 x normal	No seminoma patients are poor prognosis

MANAGEMENT OF STAGE I SEMINOMA

- For patients with **pure seminoma stages IA and IB**, treatment options following orchiectomy include:
  - (i) Surveillance (recommended)
  - (ii) Radiotherapy
  - (iii) Chemotherapy with carboplatin (1 or 2 cycles)
- More than **80 percent of patients with stage I seminoma are cured with orchiectomy alone**, and the disease specific survival for stage I disease is 99% irrespective of the management strategy used[3]

MANAGEMENT OF STAGE I SEMINOMA: SURVEILLANCE

- The safety of active surveillance has been consistently demonstrated in a number of studies. In the Swedish Norwegian testicular cancer study group (**SWENOTECA**)
  - **13% of patients with clinical stage I seminoma relapsed following surveillance.**[9] No factors predicting relapse were identified in these patients and **the overall survival was 98% in the surveillance group**

- An analysis of 5,561 clinical stage I seminoma patients from 17 trials showed the **highest risk of recurrence was within the first 2 years** which decreases thereafter.[7] Relapses after 5 years are relatively uncommon, but have occurred more than 9 years after orchiectomy.[8] The most common site of relapse is the retroperitoneal lymph nodes.

MANAGEMENT OF STAGE I SEMINOMA: SURVEILLANCE

- **Surveillance Schedule For Stage I Seminoma[6]**

Year	1	2	3	4	5
History and physical exam	Every 3-6 mo	Every 6-12 mo	Every 6-12 mo	Every 12 mo	Every 12 mo
Beta-HCG, AFP, and LDH	optional	optional	optional	optional	
Abdominal/pelvic CT	At 3, 6, 12 mo	Every 6-12 mo	Every 6-12 mo	Every 12-24 mo	Every 12-24 mo
Chest x-ray	As clinically indicated				

MANAGEMENT OF STAGE I SEMINOMA: RADIOTHERAPY

- **Radiation therapy (RT) alone prevents relapse in more than 96%** of patients with clinical stage I seminoma
- Current NCCN Guidelines recommend the **PA-strip field for stage IA and IB seminoma**[6]
- **Dosing for clinical stage I disease is 20 Gy given in 10 fractions.**
- Toxicity of RT includes GI complications (5%), leukopenia (5-15%), and oligospermia (8%)[3]
- Current EAU guidelines do not recommend RT for adjuvant therapy (21, or new EAU ref)

MANAGEMENT OF STAGE I SEMINOMA: CHEMOTHERAPY

- Single agent **carboplatin** is standard of care chemotherapy for stage I seminoma[6]

- Multiple studies have also looked at the relapse rate with either 1 or 2 cycles of carboplatin. In an analysis of 837 patients, those who had received either 1 or 2 cycles of carboplatin, relapse rates were 4.4% vs. 3%, respectively[13]

MANAGEMENT OF STAGE I SEMINOMA: CHEMOTHERAPY

- NCCN recommends either 1 or 2 cycles of carboplatin (AUC=7 x 1 or 2 cycles) for adjuvant therapy in stage I seminoma

- Carboplatin is associated with short-term thrombocytopenia (4-12%) and GI complications (8%).[16] Platinum-based chemotherapy has been associated with late toxicity including increased risk of cancer and heart disease.

MANAGEMENT OF STAGE I NSGCT

- **Approximately 70% will be cured with radical orchiectomy alone.** The management options for these patients include:[6]
  - (i) Surveillance
  - (ii) Retroperitoneal lymph node dissection (RPLND)
  - (iii) Cisplatin-based chemotherapy.
- The risk of recurrence is approximately 30% for men undergoing surveillance, **treatment at the time of recurrence is almost always curative,** although at a potentially higher burden of treatment.

MANAGEMENT OF STAGE I NSGCT

- **THE MOST IMPORTANT FACTORS USED TO PREDICT OCCULT METASTASES ARE THE PRESENCE OF LYMPHOVASCULAR INVASION (LVI) AND EMBRYONAL PREDOMINANCE WITHIN THE PRIMARY TUMOR**[17]
  - MEN WITH NONE OF THESE FACTORS HAVE AN OCCULT METASTASES RATE OF 10-14%. THOSE CONSIDERED HIGHER RISK HAVE ONE OR MORE OF THESE FACTORS AND CONSTITUTE BETWEEN 10-30% OF MEN WITH STAGE I NSGCT.
- IN SEVERAL STUDIES, THE PRESENCE OF LVI ALONE OR LVI WITH EMBRYONAL CARCINOMA PREDOMINANCE IS ASSOCIATED WITH A 40-55% RELAPSE RATE[17]

MANAGEMENT OF STAGE I NSGCT-SURVEILLANCE

- The main advantage of surveillance is sparing the morbidity of treatment for the majority of men with a stage I NSGCT.
- Patients at low risk of relapse are the ideal candidates for this strategy
- Surveillance protocols are quite rigorous, especially during the first 2 years, and compliance is critical. Non-compliance has been reported in 35-80% of patients and represents a major obstacle to this approach in stage I patients.[1]

MANAGEMENT OF STAGE I **NSGCT**-SURVEILLANCE

- A recent study with over 1,100 patients on surveillance for Stage I NSGCT demonstrated the following:[20]
  - An overall recurrence rate of 19% (44% LVI+, 14% LVI-)
  - A median time to relapse of 6 months
  - The overwhelming majority of relapses (95%) occurred within 2 years, with less than 1% occurring after 3 years
  - 90% were IGCCCG good risk recurrences

MANAGEMENT OF STAGE I NSGCT-SURVEILLANCE

Surveillance Schedule For Stage I NSGCT[6]

For Clinical Stage IA NSGCT

Year	1	2	3	4	5
History and physical exam	Every 2 mo	Every 3 mo	Every 4-6 mo	Every 6 mo	Every 12 mo
Beta-HCG, AFP, and LDH	Every2 mo	Every 3 mo	Every 4-6 mo	Every 6 mo	Every 12 mo
Chest x-ray	At 4 and 12 mo	Every 12 mo	Every 12 mo	Every 12 mo	Every 12 mo
Abdominal CT	Every 4-6 mo	Every 6-12 mo	Every 12 mo	As clinically indicated	As clinically indicated

For Clinical Stage IB NSGCT

Year	1	2	3	4	5
History and physical exam	Every 2mo	Every 3mo	Every 4-6mo	Every 6mo	Every 12mo
Beta-HCG, AFP, and LDH	Every 2mo	Every 3mo	Every 4-6mo	Every 6mo	Every 12mo
Chest x-ray	Every 4mo	Every 4-6mo	Every 4-6mo	Every 12mo	As clincaly indicated
Abdominal CT	Every 4mo	Every 4-6mo	Every 6mo	Every 12mo	As clinically indicated

AUA Surveillance Schedule

Table 3. *Clinical stage I NSGCT active surveillance follow-up*

	Year 1	Year 2	Year 3	Year 4	Year 5	> Year 5
History, physical and tumor markers	Every 2–3 months	Every 2–4 months	Every 4–6 months	Every 6–12 months	Every 6–12 months	If clinically indicated
Chest x-ray and CT abdomen ± pelvis	Every 3–6 months	Every 4–12 months	Once		Once	If clinically indicated

MANAGEMENT OF STAGE I NSGCT-CHEMOTHERAPY

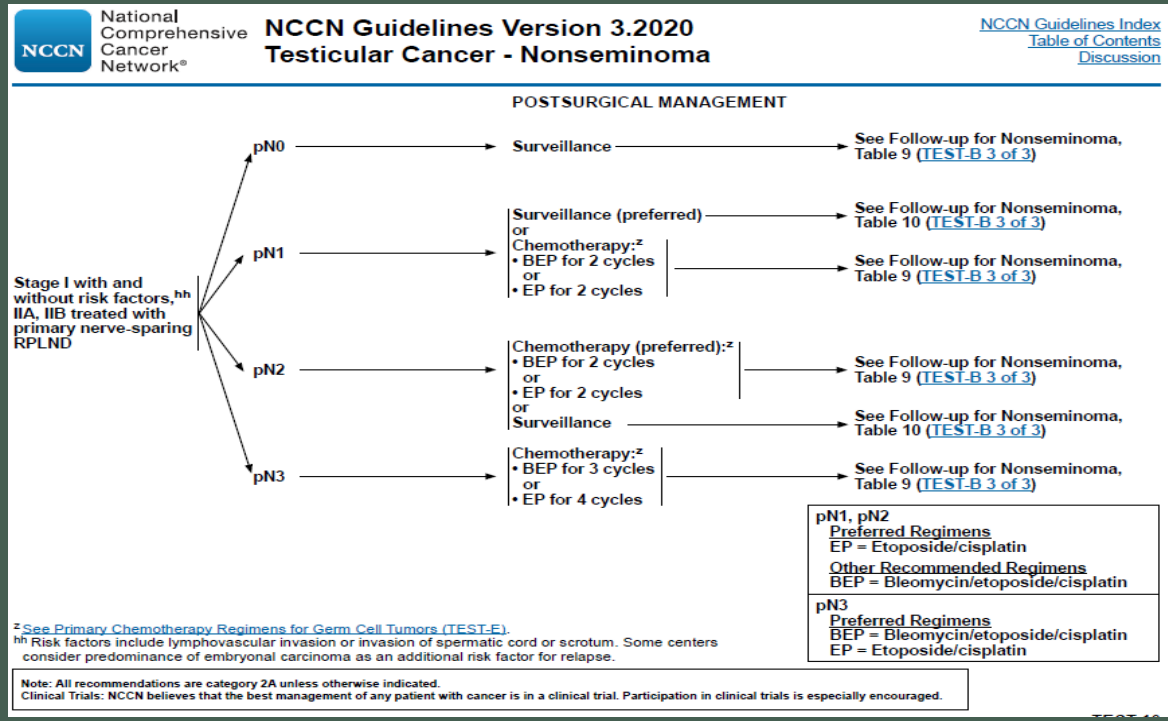
- Bleomycin, etoposide, and cisplatin (BEP) is the standard regimen used
- The use of 1 cycles is currently recommended by the NCCN and EAU due to a relapse rate less than 5%[6]
- This is supported by a publication from the SWENOTECA group reported an updated experience with a single cycle of BEP for stage I patients with good results[26]
  - With a median follow-up of 7.9 years, there was 5 year relapse rate of 3.2% in patients with LVI and 1.6% for patients without LVI. All recurrences were IGCCCG good risk and there was 100% 5 year CSS. The administration of up to two courses of platinum-based chemotherapy may lessen concerns of acute and delayed side effects of treatment (including a lowered risk of bleomycin-induced pulmonary toxicity), however long term follow up is needed.

MANAGEMENT OF STAGE I NSGCT-RPLND

- For men with high-risk pathologic features or for those who are unable to comply with a surveillance schedule, RPLND offers an appropriate choice for adjuvant treatment for several reasons:
  - (I) RPLND provides **accurate pathologic staging**
  - (II) RPLND in experienced hands is associated with **low short and long-term morbidity**
  - (III) RPLND **minimizes the risk of relapse due to chemoresistant GCT and teratoma**
  - (IV) Because the risk of retroperitoneal relapse is rare in those with pathologically confirmed stage I or II disease, RPLND provides for a simplified follow-up regimen, limited to tumor markers and chest imaging. Relapse in any site after a negative RPLND is uncommon and is generally curable with chemotherapy.

MANAGEMENT OF STAGE I NSGCT-RPLND

- PRIOR TO RPLND PATIENTS SHOULD HAVE CT A/P WITHIN 4 WEEKS OF SURGERY AND REPEAT STM WITHIN 7-10 DAYS
- RECOMMENDATIONS FOR ADJUVANT THERAPY FOLLOWING PRIMARY RPLND:[6]



SURGICAL CONSIDERATIONS-RPLND

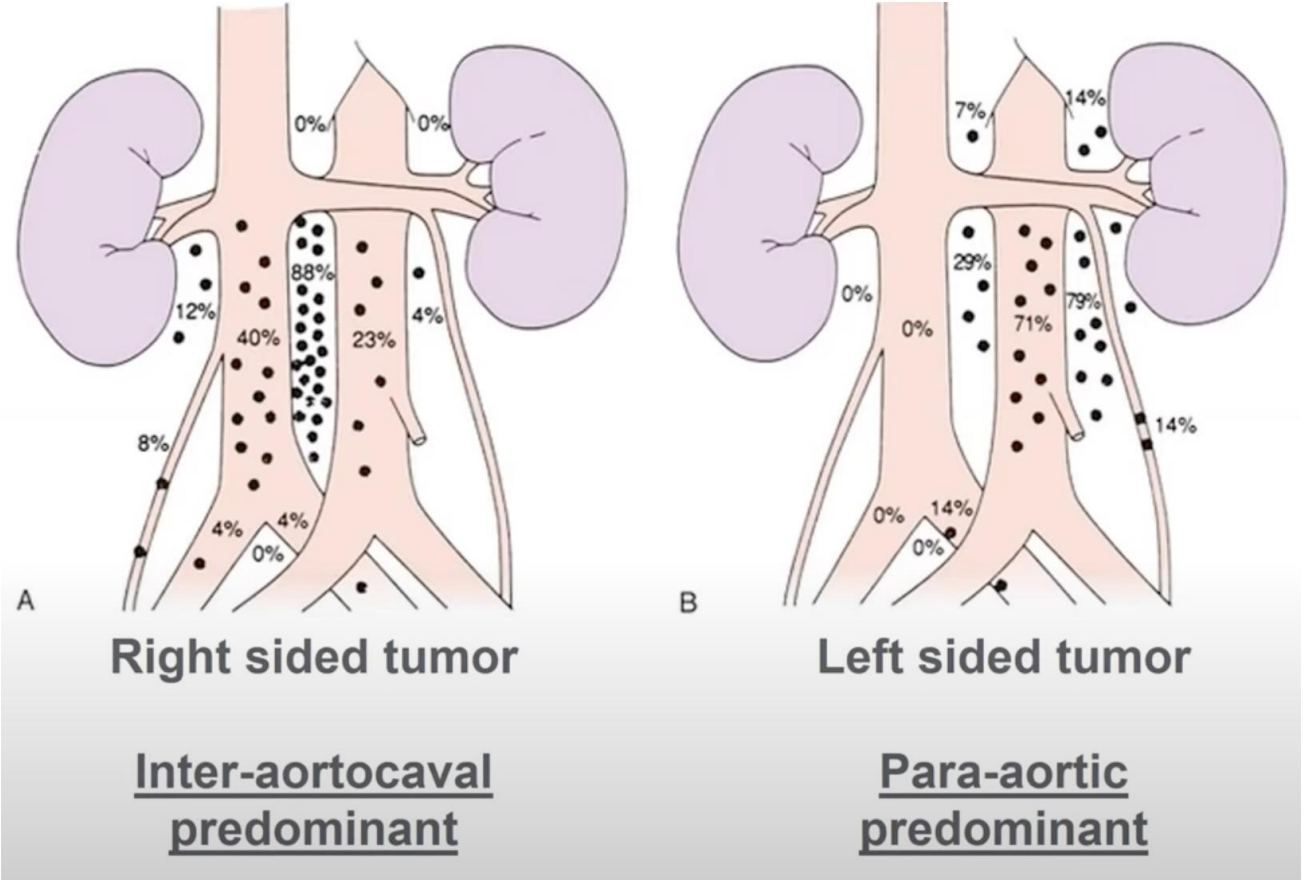
- Contralateral nodal involvement is more common in right-sided tumors – following the right to left lymphatic drainage.
- It is important to consider the neuroanatomy of the retroperitoneum when performing a RPLND as injury to these structures results in anejaculation.
  - The sympathetic trunks are bilateral, paravertebral chains that give rise to the postganglionic fibers. **These fibers course posterior to the vena cava and anterior to the aorta and coalesce at the superior hypogastric plexus, which lies just caudal to the IMA.**

SURGICAL CONSIDERATIONS-RPLND

- A **FULL BILATERAL TEMPLATE EVOLVED TO INCLUDE ONLY THE AREA FROM THE RENAL HILUM TO THE BIFURCATION OF THE COMMON ILIAC VESSELS CAUDALLY, WITH THE URETERS AS THE LATERAL BOARDERS.**
- MODIFIED TEMPLATES WERE DEVELOPED TO DECREASE MORBIDITY[22,23]
  - A RIGHT-SIDED TEMPLATE INCLUDES LYMPHATIC TISSUE FROM THE RIGHT URETER AND PARACAVAL REGIONS ALONG WITH INTERAORTOCAVAL AND THE PRE- AND PARA-AORTIC REGIONS ABOVE THE IMA.
  - LEFT-SIDED TEMPLATES REQUIRE DISSECTION OF ALL PARA-AORTIC LYMPHATIC TISSUE MEDIAL TO THE LEFT URETER AS WELL AS INTERAORTOCAVAL AND PRE-AORTIC LYMPHATIC TISSUE ABOVE THE IMA

SURGICAL CONSIDERATIONS-RPLND

- The next technical advancement in RPLND was the development of prospective nerve-sparing techniques, which allowed for a full bilateral dissection with preservation of antegrade ejaculation[24]
- Modified templates and nerve sparing techniques, will maintain ejaculatory function in the vast majority of patients
- The **split-and-roll technique** with control of lumbar vessels should be performed to allow complete circumferential dissection of the great vessels.
- RPLND is traditionally performed via an open transabdominal approach
  - Alternatives: extraperitoneal, laparoscopic, robotic approaches[25,50-52]



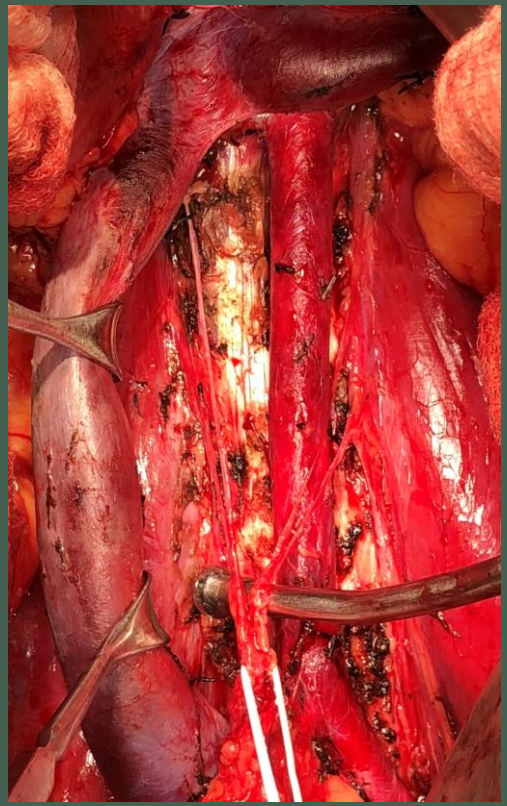
Right sided tumor

Inter-aortocaval predominant

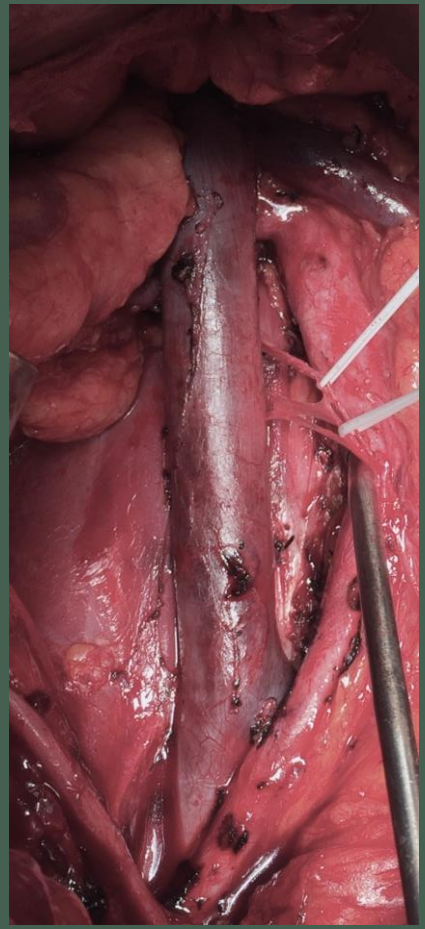
Left sided tumor

Para-aortic predominant

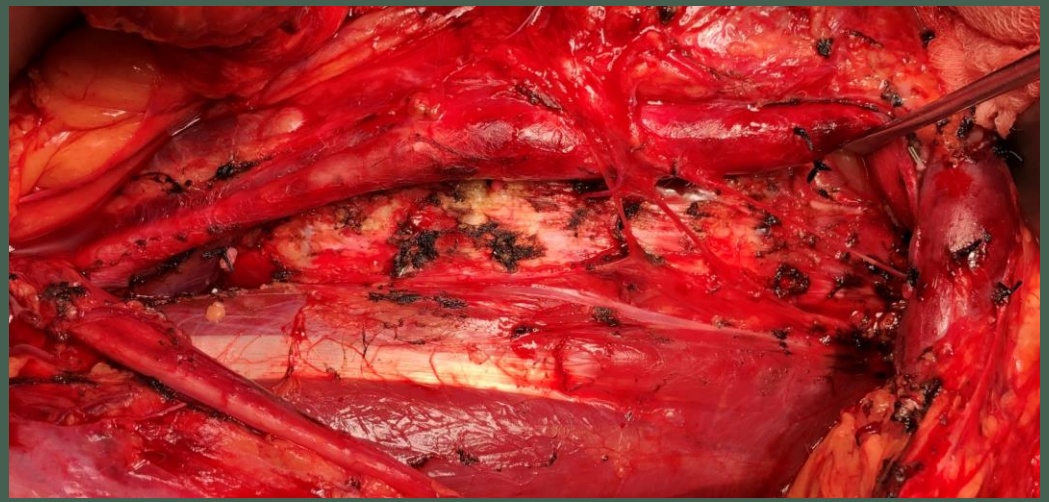
FULL BILATERAL NERVE SPARING TEMPLATE



RIGHT SIDED NERVE SPARING TEMPLATE



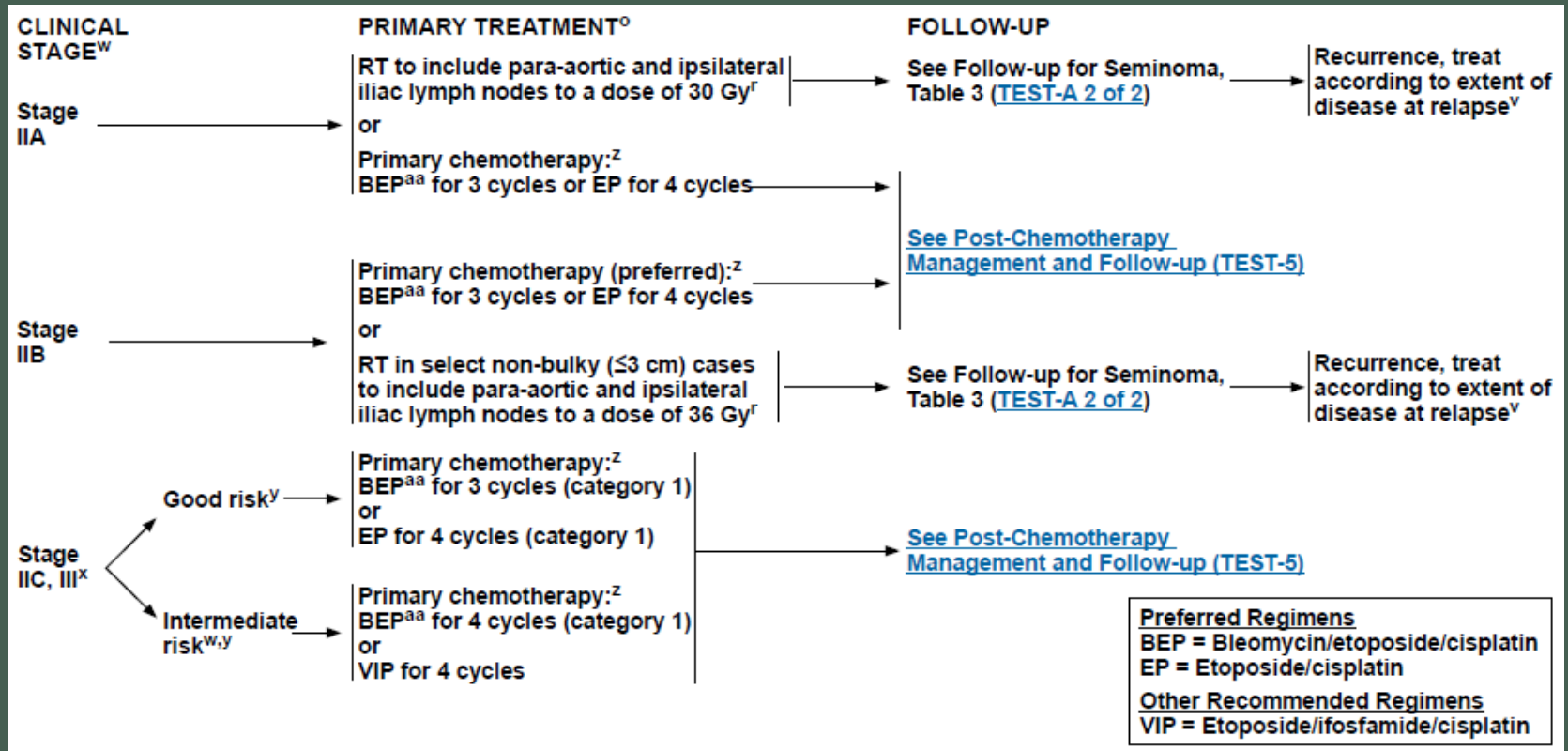
LEFT SIDED NERVE SPARING TEMPLATE



MANAGEMENT OF STAGE IIA AND IIB PURE SEMINOMA

- **Radiation therapy (RT) is used in the treatment of Stage IIA and IIB pure seminoma**[6,14,15,27,28]
- The primary difference in the radiation field used for stage II versus I is the inclusion of the ipsilateral iliac lymph nodes in a **"dog-leg" field.**
- The cumulative dose for IIA disease is **30 Gy** and **36 Gy** for IIB disease. **Overall survival is as high as 100% with RT.**[6,14]
- In patients with **bulky lymphadenopathy (> 3 cm), chemotherapy is preferred to RT.** Both the NCCN and EAU guidelines recommend 4 courses of EP or 3 cycles of BEP[6,14,15]

MANAGEMENT OF STAGE IIA, IIB, IIC PURE SEMINOMA



[o] Discuss sperm banking prior to chemotherapy or radiation treatment.
[r] See Principles of Radiotherapy for Pure Testicular Seminoma (TEST-C).
[v] Patients should not be treated based upon an elevated LDH alone.
[w] Intermediate risk in seminoma is based on metastases to organs other than the
[x] All stage IIC and stage III seminomas are considered good-risk disease except for

MANAGEMENT OF STAGE IIC AND III PURE SEMINOMA

- The treatment for IIC seminoma patients is chemotherapy with 3 cycles of BEP or 4 cycles of EP[3,6,15,29,30,31]
- **Stage III seminoma is treated with chemotherapy determined by IGCCCG risk classification**
  - **Good risk: EP x4 cycles or BEP x3 cycles**
  - **Intermediate risk: BEP x4 cycles**
- **Following first line therapy for advanced seminoma there will be a post-chemotherapy mass in approximately 60-80% of patients**[32]
  - Pathology of masses 90% fibrosis and 10% have residual viable tumor
  - Rarely teratoma

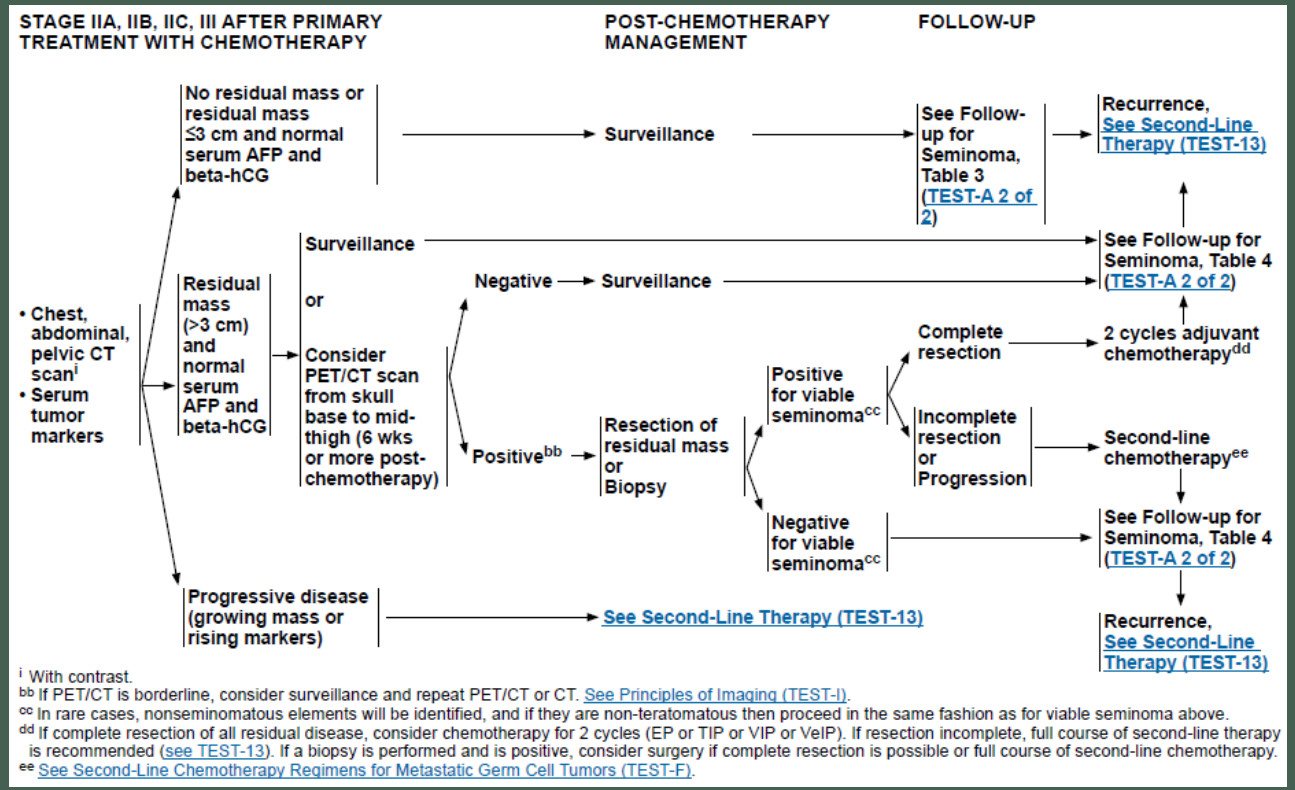
MANAGEMENT OF POST CHEMOTHERAPY SEMINOMA

- MANAGEMENT OF POST CHEMOTHERAPY SEMINOMA MASS BASED ON SIZE AND **PET IMAGING**[6]
- **IT WAS DEMONSTRATED THAT THE PRESENCE OF VIABLE TUMOR WAS 3% VS. 27% FOR MASSES < 3 VS. ≥ 3 CM, RESPECTIVELY.**[33] THESE CHARACTERISTICS OF POST-CHEMOTHERAPY SEMINOMA HAVE LED TO A DIFFERENT MANAGEMENT STRATEGY COMPARED TO NSGCT.

MANAGEMENT OF POST-CHEMOTHERAPY SEMINOMA

- NCCN guidelines recommend surveillance of masses ≤ 3 cm, while masses > 3 cm should be further evaluated with a **2-^{18}fluoro-deoxy-D-glucose positron emission tomography (PET) scan** or undergo surveillance.
- If floridly positive then an RPLND or biopsy should be performed.[6]
- In 2018, the NCCN guidelines added the option to simply observe masses >3cm as an alternative to PET imaging.
- PET scans should be performed at least 6 weeks after the completion of chemotherapy.

MANAGEMENT OF PURE SEMINOMA POST-CHEMOTHERAPY MASSES



[i] With contrast.
[bb] If PET/CT is borderline, consider surveillance and repeat PET/CT or CT. See Principles of Imaging (TEST-I).
[cc] In rare cases, nonseminomatous elements will be identified, and if they are non-teratomatous then proceed in the same fashion as for viable seminoma above.
[dd] If complete resection of all residual disease, consider chemotherapy for 2 cycles (EP or TIP or VIP or VeIP). If resection incomplete, full course of second-line therapy is recommended (see TEST-13). If a biopsy is performed and is positive, consider surgery if complete resection is possible or full course of second-line chemotherapy.
[ee] See Second-Line Chemotherapy Regimens for Metastatic Germ Cell Tumors (TEST-F).

MANAGEMENT OF STAGE IIA NSGCT

STAGE IIA WITH NORMAL MARKERS, PRIMARY RPLND IS AN APPROPRIATE TREATMENT OPTION.[6,5,34,35]

- STAGE IIA NSGCT CAN BE TREATED WITH PRIMARY CHEMOTHERAPY CONSISTING OF 4 CYCLES OF EP OR 3 CYCLES OF BEP
- THE NCCN GUIDELINES RECOMMEND ALL **PATIENTS WITH ELEVATED AFP OR HCG LEVELS FOLLOWING ORCHIECTOMY SHOULD UNDERGO PRIMARY CHEMOTHERAPY**
- IF RPLND IS UNDERTAKEN, PRINCIPLES OF NERVE-SPARING RPLND SHOULD BE FOLLOWED, BUT **CANCER CONTROL SHOULD NEVER BE COMPROMISED TO PRESERVE EJACULATORY FUNCTION.**

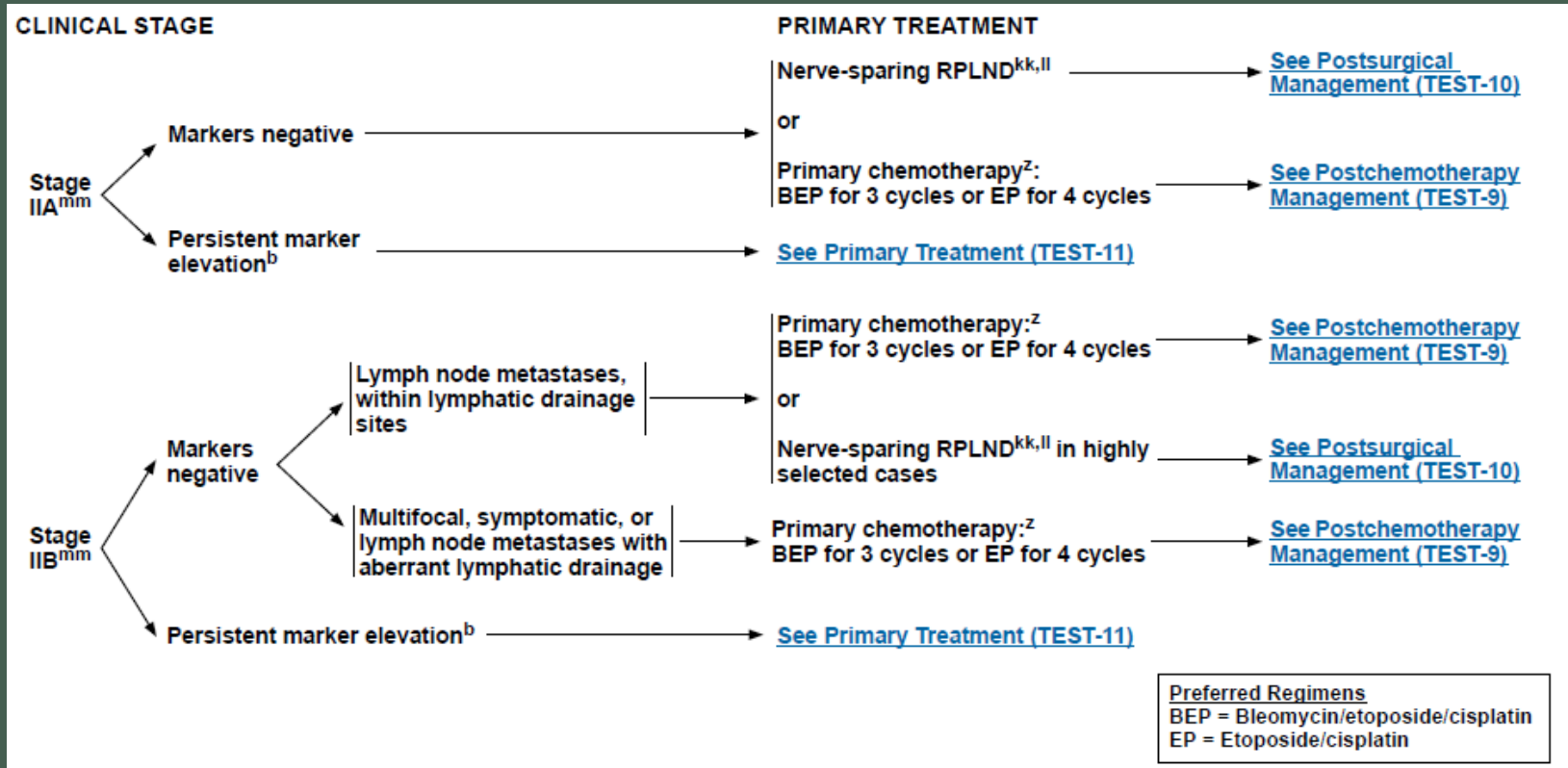
MANAGEMENT OF STAGE IIA NSGCT

- RPLND is curative for pN0 disease and surveillance is recommended to avoid chemotherapy
- **For patients with pN1 disease following RPLND, cure rates are as high as 90%**[6,21,34,35]
  - For pN1 adjuvant chemotherapy with 2 cycles of EP or BEP is an option; however, if an adequate, complete RPLND was performed and no concerns of surgical compromise exist, surveillance is preferred for pN1
- While surveillance for **pN2** is an option in very select cases, **chemotherapy is preferred with EP or BEP for 2 cycles** due to the ~50% risk of relapse[21]
- **Full induction chemotherapy is recommended for pN3 disease** – 4 cycles of EP or 3 cycles of BEP[6,14,15]

MANAGEMENT OF STAGE IIB NSGCT

- Primary chemotherapy with 4 cycles of EP or 3 cycles of BEP may be used for IIB disease
- In select Stage IIB cases where the abdominal imaging reveals a solitary lesion in the primary landing zone and markers have normalized, a RPLND is an option for primary treatment.[6,15] **If primary RPLND is chosen for IIB disease, adjuvant therapy is dictated by pathologic nodal staging**
- Both treatment approaches result in a cure rate which approaches 98%[6]

PRIMARY MANAGEMENT OF STAGE IIA-IIB NSGCT



[b] Mildly elevated, non-rising AFP levels may not indicate presence of germ cell tumor. Decisions to treat should not be based on AFP values <20 ng/mL. Further workup

MANAGEMENT OF STAGE IIC AND III NSGCT

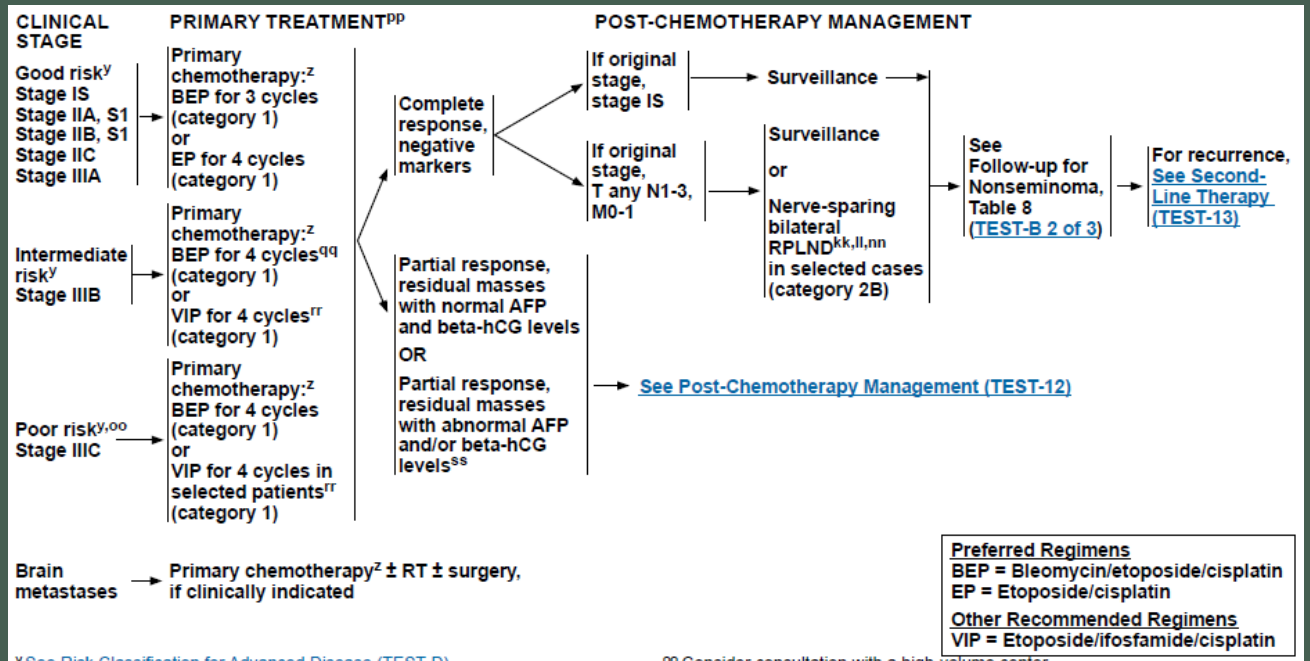
- **Primary chemotherapy is based on IGCCCG classification**

- **Good risk:** 4 cycles of EP or 3 cycles of BEP
- **Intermediate risk:** 4 cycles of BEP (preferred) or 4 cycles VIP
- **Poor risk:** Patients should be considered for a clinical trial if available. Standard therapy is 4 cycles of BEP. If bleomycin is not able to be used, then 4 cycles of VIP (etoposide, ifosfamide, cisplatin) can be used.[6,14,15]

MANAGEMENT OF STAGE IIC AND III NSGCT

- **CHEMOTHERAPY SIDE EFFECTS:** FATIGUE, ALOPECIA, NAUSEA AND VOMITING (PROPHYLACTIC ANTIEMETICS ADMINISTERED), MYELOSUPPRESSION, AND ASSOCIATED RISK OF INFECTION, NEPHROTOXICITY, PERIPHERAL NEUROPATHY, OTOTOXICITY, AS WELL AS RAYNAUD PHENOMENON AND PULMONARY TOXICITY (BASELINE AND SURVEILLANCE PFTS REQUIRED) ASSOCIATED WITH BLEOMYCIN, ALTHOUGH CLINICALLY SIGNIFICANT PULMONARY TOXICITY IS RARE.

MANAGEMENT OF STAGE IIC, IS, S1, IIIC NSGCT



[y] See Risk Classification for Advanced Disease (TEST-D).
[z] See Primary Chemotherapy Regimens for Germ Cell Tumors (TEST-E).
[kk] RPLND is recommended within 4 weeks of CT scan and 7–10 days of marker-measurement.
[ll] See Principles of Surgery for Germ Cell Tumors (TEST-H).
[nn] Referral to high-volume centers should be considered for surgical resection of masses post-chemotherapy.
[oo] Consider consultation with a high-volume center.
[pp] To assess response after treatment, CT with contrast of chest/abdomen/pelvis and any other sites of disease is recommended.
[qq] If intermediate risk is based on LDH 1.5–3 times the upper limit of normal, then BEP for 3 cycles can be considered.
[rr] Patients who may not tolerate bleomycin.
[ss] Recommend referral to a high-volume center.

OUTCOMES ADVANCED GCT'S

Risk Groups For Seminoma			
Risk Group	**Features**	**5-yr OS**	**5-yr DFS**
Good **90%**	No organ metastases other than lung (- NPVM)	86%	82%
Intermediate **10%**	+NPVM	72%	70%

Risk Categories for Non-seminoma			
Risk Group	**Features**	**5-year Survival**	**5-year NED**
Good **60%**	Meet all of the following: HCG<5,000; AFP<1,000; LDH<1.5xULN; primary site not the mediastinum, no NPVM.	90%	88%
Intermediate **25%**	Good-risk except ≥1 of following: HCG: 5,000-50,000 AFP: 1,000-10,000 LDH: 1.5xULN-10xULN	80%	75%
Poor **15%**	Any of the following: 1° mediastinal site, +NPVMs, HCG>50,000; AFP>10,000; or LDH>10xULN	40%	50%

NPVM: non-pulmonary visceral matastases (IGCCCG, JCO, 1997[47])

MANAGEMENT NON-RP NSGCT

- **Post-chemotherapy masses in the lung, mediastinum, and neck should be resected as these sites may harbor viable tumor or teratoma.**
- The pathology between the retroperitoneum and these metastatic sites are often discordant (30-45%) and there is no reliable method to predict extra-retroperitoneal pathology
  - **The presence of fibrosis in the retroperitoneum is most predictive of fibrosis in the chest; yet ~20% of these lesions will be either viable tumor or teratoma.**[1]
- Post-chemotherapy liver masses will have discordant pathology in 50% of the cases.
  - Fibrosis in the retroperitoneum was most predictive of fibrosis in the liver (~95%). Consideration for simultaneous liver resection should be made for these patients.[42]

NSGCT: RECURRENCE AFTER CHEMOTHERAPY

- Relapse following chemotherapy for NSGCT is designated as **early or late relapse**
  - defined by recurrence before or after 2 years respectively from completing initial therapy.
- Patients relapsing within 2 years should receive second-line/salvage therapy
  - An exception to this situation is patients with normalized or declining STM and growing retroperitoneal masses, called **growing teratoma syndrome**. These patients should undergo RPLND with resection of gross disease.
- **Late relapses are rare, ~3%, and mainly occur in the retroperitoneum, 50-70%.[1] These relapses tend to be chemo resistant and are often managed surgically.**

NSGCT: SECOND LINE CHEMOTHERAPY

- A high proportion of patients who recur after standard chemotherapy will remain curable with second- and third-line treatment strategies
- The most commonly used salvage regimens include: **paclitaxel, ifosfamide, cisplatin (TIP); and vinblastine, ifosfamide, cisplatin (VeIP).** [6,15,43,44]
  - High-dose chemotherapy with autologous stem cell support with preparative regimens such as carboplatin and etoposide have also demonstrated promising outcomes[45,46,47]
  - There is an actively accruing randomized phase III trial comparing TICE (paclitaxel, ifosfamide, carboplatin, etoposide) plus stem cell transplant versus TIP (TIGER trial, NCT02375204)
- Post-chemotherapy surgery remains a necessary component in patients who respond to salvage therapy

SEX CORD STROMAL TUMORS

- This group of tumors arise from Leydig, Sertoli, and Granulosa cells
- Low incidence leading to a lack of robust data on management
- Median age at diagnosis is 45 (zuninga et al)
- Presentation: palpable testis mass, virilization, gynecomastia, loss of hair, testicular atrophy (dilworth et al, risk et al)
- **Radical orchiectomy** is standard first line treatment
- **Radiation and chemotherapy have limited efficacy and role for adjuvant therapy is not well defined**
- RPLND has been reported, but routine use has not been defined
- 5yr survival: Leydig cell 91%, Sertoli cell 77% (banerji et al)
- There is poor survival for metastatic disease (<2 yrs)

SURVIVORSHIP

- The high rate of cure for GCTs, the young age at diagnosis and the multimodality management necessitate that survivorship issues including late effects of treatment become an integral part of the care plan
- Patients with GCTs are at an increased risk for cardiovascular disease, secondary malignancies, infertility, hypogonadism as well as other late effects of treatment including hearing loss, kidney dysfunction, lung toxicity, peripheral neuropathy, anxiety disorder and depression
- Long term follow up should focus on monitoring for these late effects of cancer and its treatment.
- All patients should be strongly encouraged to bank sperm prior to initiating treatment