

Testis Neoplasms

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1. Epidemiology

Testicular neoplasms are relatively uncommon tumors although they represent the most common tumor in young men (age 20-40). 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). Germ cell tumors (GCT) are further designated as **seminoma or non-seminoma germ cell tumors (NSGCT)**.

The annual incidence in the United States is 6.4/100,000 men resulting in an estimated 9,910 cases in 2022 (American Cancer Society 2022). However, with a multidisciplinary treatment approach including cisplatin-based chemotherapy, surgery and radiation, testis cancer results in only 460 deaths annually.¹

Incidence rates for testicular cancer have been steadily rising for the past few decades.^{2,3} The incidence of testicular cancer is highest among non-Hispanic Whites and lowest among African-Americans, while the incidence for Asian and Hispanic men falls in between.⁴ Interestingly, the incidence in non-Hispanic Whites seems to have slowed since 2002 whereas the incidence in other ethnic groups continues to rise. Potential risk factors that explain this rise include in-utero exposures and tobacco/marijuana use.^{5,6} Mortality rates have inversely declined during this time except in the Hispanic men where rates have steadily increased.

During the past few decades, there also has been a stage migration as more men over time are presenting with localized disease presumably due to increased awareness and self-detection. The most common histology of testicular germ cell tumor at presentation is **pure seminoma**. Most of these patients present with **localized disease** (only 10-30% of patients with seminoma initially present with metastatic disease). Patients presenting with non-seminomatous germ cell tumors tend to have more advanced disease at diagnosis.

Risk factors for testicular cancer include cryptorchidism, intra-tubular germ cell neoplasia (ITGCN), and family or personal history of testicular cancer. Cryptorchidism remains a

powerful factor with a relative risk (RR) of 4-6, but this decreases to 2-3 with pre-pubertal orchidopexy.⁴ It is felt that **most GCTs arise from ITGCN** and its presence is a major risk factor as **50% of men with ITGCN will develop a GCT within 5 years.**⁴ **Family history is associated with a RR 2-12 depending on the affected family member.** In a mostly homogenous population of Nordic countries, the lifetime cumulative risk of GCT in a brother of a patient with testis cancer was observed to be 2.3% which is a four-fold increase in risk compared to the general population.⁷ Despite this strong familial influence, no dominant single gene alteration has been identified in testicular cancer and the genetic basis for the disease likely results from numerous minor gene alterations.^{8,9} Genome wide association studies have identified common susceptibility loci that increase risk of GCT development, accounting for 44% of observed disease heritability.¹⁰

There are several distinct histologic subtypes of GCT. **Seminoma, the most common histology**, is divided into **classic seminoma and spermatocytic seminoma**. In 2016, the WHO renamed “spermatocytic seminoma” as “**spermatocytic tumor**” and classified it within the **non-GCNIS (germ cell neoplasia in situ) related tumors.**¹¹

The remaining ~50% of testis tumors are **NSGCTs** which are comprised of the following histologic categories: **embryonal carcinoma (EC), yolk sac tumors (endodermal sinus tumors), choriocarcinoma, teratoma, and mixed GCT** (combination of multiple non-seminomatous elements and may include seminoma as well). The salient characteristics of each tumor type are summarized in **Table 1**.

Bilateral testicular germ cell tumors occur in 2.5% of patients, the majority of which occur metachronously (1.8% overall). The median time to occurrence of the second tumor is approximately 6 years (range 0.5-28 years) highlighting the **importance of long-term surveillance of the remaining testis**. The **second tumor histology is discordant in 42% of cases** and generally presents at a **similar stage** as the first tumor.¹²

Table 1. Histologic Classification and Characteristics of Germ Cell Tumors

Seminoma	Most common GCT, Peak incidence 35-40 years of age 5% contain syncytiotrophoblasts (resulting in bHCG production) Arise from ITGCN No AFP production
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 (endodermal sinus tumor)	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	Less common, very 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, and/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, radiation-resistant Morbidity related to local growth ("Growing Teratoma Syndrome") and potential for malignant transformation

2. Presentation & Evaluation

A painless testicular mass is the most common presentation of testicular cancer. However, some men will present with testicular swelling, discomfort, or pain. 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**. Current ultrasound technology allows detection of masses as small as 2-3mm. Heterogeneous lesions are more likely NSGCTs, as seminomas tend to appear more homogeneous.⁴ The classic finding is a solid, hypoechogenic hypervascular parenchymal mass of the testis. There is **no role for CT, MRI, or other advanced imaging of the testis** (e.g. PET CT) at presentation.

There is conflicting evidence regarding the association between testicular microlithiasis and risk of testicular cancer. Microlithiasis are defined as small, clustered calcifications sporadically distributed throughout the testicular parenchyma and may exist in 0.5-10% of adolescents/men.¹³ The association with testicular cancer may be related to the presence or absence of other testicular symptoms such as infertility, atrophy or history of contralateral germ cell tumor. A small retrospective, single-institution study of men with contralateral germ cell tumors demonstrated that microlithiasis in the normal testicle was significantly associated with risk of germ cell neoplasia in-situ in that testicle (OR 28.6: 4.8 – 170.4).¹⁴ Other retrospective studies of symptomatic patients have confirmed this strong association.^{15,16} This data has been used to suggest that symptomatic men with microlithiasis may be at higher risk of developing testicular cancer; however, the implications of this finding on cancer surveillance beyond routine testicular self-examination is unknown. Further, a prospective cohort study of men undergoing a screening testicular ultrasound demonstrated the rate of asymptomatic microlithiasis was 5.6%. With 5-years of follow-up, only 1 patient with microlithiasis developed a testicular germ cell tumor thus advocating that intense screening for or surveillance of men with microlithiasis is not warranted.¹⁷ Thus, the most uniformly agreed upon screening regimen for testicular cancer is routine self-examination regardless of the presence or absence of microlithiasis.

2.1 Tumor Markers

Tumor markers should be obtained at the time of diagnosis, **prior to orchectomy** or other therapy.

2.1.1 Alpha-Fetoprotein (AFP)

The **half-life of AFP is 5-7 days** and it is elevated in 50-80% of NSGCT. **Embryonal carcinoma and yolk sac tumors produce AFP**, seminoma and choriocarcinoma do not. AFP may also be elevated in patients with liver disease, hepatocellular carcinoma, and stomach/pancreas/biliary duct/lung cancers. Mildly elevated AFP may not represent germ cell tumor, thus **the decision to treat a patient should not be made for an AFP level < 20.**¹⁸

2.1.2 Beta-Human Chorionic Gonadotropin (bHCG)

The **half-life of bHCG is 24-36 hours** and it is elevated in 20-60% of NSGCT and 15% of seminomas. **bHCG is elevated in embryonal carcinoma/choriocarcinoma/seminoma.** Elevations may also be observed in liver, biliary, pancreas, stomach, lung, breast, kidney, and bladder cancers as well as secondary to marijuana use. **Significant hypogonadism may also cause low level elevation of HCG and these patients can be challenged with testosterone injections which normalize their HCG levels.** False elevations of HCG may be related to heterophile antibody interference in the HCG immunoassay.

2.1.3 Lactate Dehydrogenase (LDH)

LDH-1 is the most common isoenzyme elevated in GCT, which is a non-specific marker of GCT, generally used as a **surrogate for disease burden**, and is utilized by some clinicians for prognostication at the time of diagnosis. The **half-life of LDH is 24 hours**. Patients should not be treated due to elevated LDH alone.

2.1.4 MicroRNA

MicroRNA (miR) are small noncoding RNAs involved in epigenetic gene regulation. A cluster of microRNAs are expressed in GCT tissue and also measurable in the blood. Circulating miR-371a-3p is the promising blood-based biomarker with improved sensitivity and specificity over current STMs that reliably detects all macroscopic GCT histologies, except for teratoma.¹⁹ miR-371a-3p holds promise in the following clinical scenarios: 1) patients with inconclusive testicular masses, 2) surveillance after orchiectomy for early detection of relapse, 3) response monitoring during chemotherapy, 4) management of post-chemotherapy residual masses, 5) surveillance after curative intent. Two large ongoing clinical trials (AGCT 1531 and SWOG 1823) will further our understanding of the performance characteristics of miR-371a-3p. Standardization, reproducibility, and thresholding must be optimized before miR-371a-3p can be recommended for clinical use.

One particularly useful characteristic of miR is the **short half-life of <24 hours**, although the decay can be prolonged with bulky metastatic disease. **Additionally, when compared with traditional testicular cancer serum tumor markers, miR has markedly improved sensitivity and specificity.**

One significant drawback to miR is the **inability of miR-371a-3p to detect teratoma**, though this is an area of ongoing investigation.²⁰

3. 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 should not be performed.** Biopsy (percutaneous) should only be performed if there is high suspicion for an alternate diagnosis (e.g., lymphoma in the setting of bilateral synchronous tumors).

Historically, testis-sparing surgery (partial orchiectomy) was only considered in the case of a small tumor in a solitary testis, small bilateral tumors, or increased suspicion of a benign

tumor.²¹ However, some single center experiences are exploring partial orchiectomy with small solitary tumors even with a normal contralateral tumor.²² Of the 77 patients undergoing a partial orchiectomy at Princess Margaret Hospital, 39 (50%) were performed for a small lesion with a normal contralateral testis. While palpable lesions did recur in a small proportion of patients, these were successfully salvaged with radical orchiectomy. There were 3 deaths in the series of which the partial orchiectomy was felt to be non-contributory. Conversely, a recent systematic review and patient-specific meta-analysis reporting on 285 patients who underwent a partial orchiectomy presented evidence favoring the historical approach of only performing partial orchiectomy for small tumors in a solitary testicle. ²³ The authors reported an incidence of hypogonadism of 27% which increased to 40% if postoperative radiotherapy is utilized. Furthermore, the incidence of infertility was 18% and much higher with postoperative radiation.

Benign histology is encountered more commonly in small testis lesions and testis-sparing surgery may be considered for small masses certainly 1cm or less. When testis-sparing surgery is performed, intraoperative frozen section can reliably distinguish between benign and malignant lesions in the vast majority of cases. Biopsies of the adjacent testicular parenchyma should be performed to rule out the presence of germ cell neoplasia in-situ (GCNIS). For patients with GCNIS, adjuvant radiotherapy to the residual testis using doses of at least 20 Gy is usually sufficient to prevent the development of a GCT while preserving Leydig cell function (and thereby testicular androgen production). However, most patients will be rendered infertile following radiation therapy particularly when there is only a solitary testis. Post-operative radiation in the presence of GCNIS on biopsy reduces the risk of local recurrence from as high as 50% down to 2%. ²³

Prior to definitive management, patients should be counseled about the **treatment-associated risks of hypogonadism and infertility** and should be offered **sperm banking**, when appropriate. In patients without a normal contralateral testis or with known subfertility, this should be considered **prior to orchiectomy**.²⁴ Additionally, prior to orchiectomy, placement of a testicular prosthesis at the time of surgery should be offered. Patient satisfaction with testicular prosthesis placement has been reported to be over 80% with a very low complication rate.²⁵

4. Staging

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

Alternatively, a chest radiograph can be obtained as the initial staging in patients with a low risk of thoracic metastasis such as in the case of clinical stage I seminoma when there are normal post-orchiectomy serum tumor markers (STM) and no abdominal/pelvic metastases. Brain imaging should only be performed as clinically indicated. **PET-CT is NOT indicated in the initial staging of testis cancer.**

Metastatic spread of GCTs typically follows a predictable pattern based on the lymphatic drainage of the testis. 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 contralateral metastases from right side tumors, but this is an uncommon occurrence for left-sided tumors.² Clinical staging is extremely important and given this predictable route of spread, **the retroperitoneum serves as the initial site of metastasis in 70-80% of patients.**²¹ Importantly, despite advances in CT technology, **approximately 30% of patients are clinically understaged by CT** and harbor occult metastatic disease in the retroperitoneum (when using a cutoff of 1cm for an abnormal lymph node).²¹

Finally, clinical staging, risk stratification, and treatment relies on **post-orchiectomy serum tumor markers (STM)**, generally performed several weeks following orchiectomy (determined by the initial levels and the appropriate T1/2 time intervals). **Primary tumor pathology, staging imaging studies, and post-orchiectomy STM form the basis for clinical staging in testicular cancer.** The 8th edition of the AJCC TNM staging for testicular cancer are presented in **Table 2a** and **Table 2b**.²⁶ 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. The initial diagnosis, evaluation, and staging is summarized in **Figure 1**.

The 8th edition of the AJCC TNM staging was released in 2017. There are some notable changes made to the new edition from the prior 7th edition (published in 2010).²⁶

- 1) **Germ cell neoplasia in situ** has been adopted, abbreviated **Tis**.
- 2) **The T staging for seminoma was split into two, pT1a and pT1b based on a size cut-off of 3 cm.**
- 3) The following are classified as **pT2** tumors: **hilar soft tissue invasion, LVI in spermatic cord without parenchymal invasion, and epididymal invasion.**
- 4) **Discontinuous involvement of the spermatic cord with LVI is classified as M1.** However, the 2018 NCCN guideline committee recommended that the classification of stage I disease as per the 7th edition of the AJCC TNM staging (**tumor limited to the testis and epididymis without lymphovascular invasion, may invade tunica albuginea but not tunica vaginalis**) should continue to be used for clinical decision-making based on validated clinical variables for recurrence and the 8th edition should be used for documentation purposes only.¹⁸

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 (**Table 3**). This consensus group divides patients into good, intermediate, and poor risk disease based on a combination of imaging findings, serum tumor marker elevation levels, and histology (of note, there is no “Poor risk” category for pure seminoma). These risk factors were revalidated in a contemporary cohort of patients with NSGCT treated with chemotherapy, which also identified older age and lung metastasis as negative risk factors for progression-free survival (PFS). IGCCCG risk criteria were also recently revalidated in contemporary patients with advanced seminoma, which found that patients with LDH

more than 2.5x upper limit of normal had elevated risk compared to those with lower LDH.^{27,28}

TABLE 2a. AJCC TNM Staging Classification of Testicular Tumors. 8th ed, 2017²⁶

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 than 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 Staging²⁹

Table 2b. TMN Staging of Testicular Tumors: 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

AFP-alpha-fetoprotein, hCG-human chorionic gonadotropin, LDH-lactate dehydrogenase |
From AJCC Cancer Staging²⁹

Table 3. International Germ Cell Cancer Collaborative Group (IGCCCG) Risk Classification for Advanced GCT

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

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

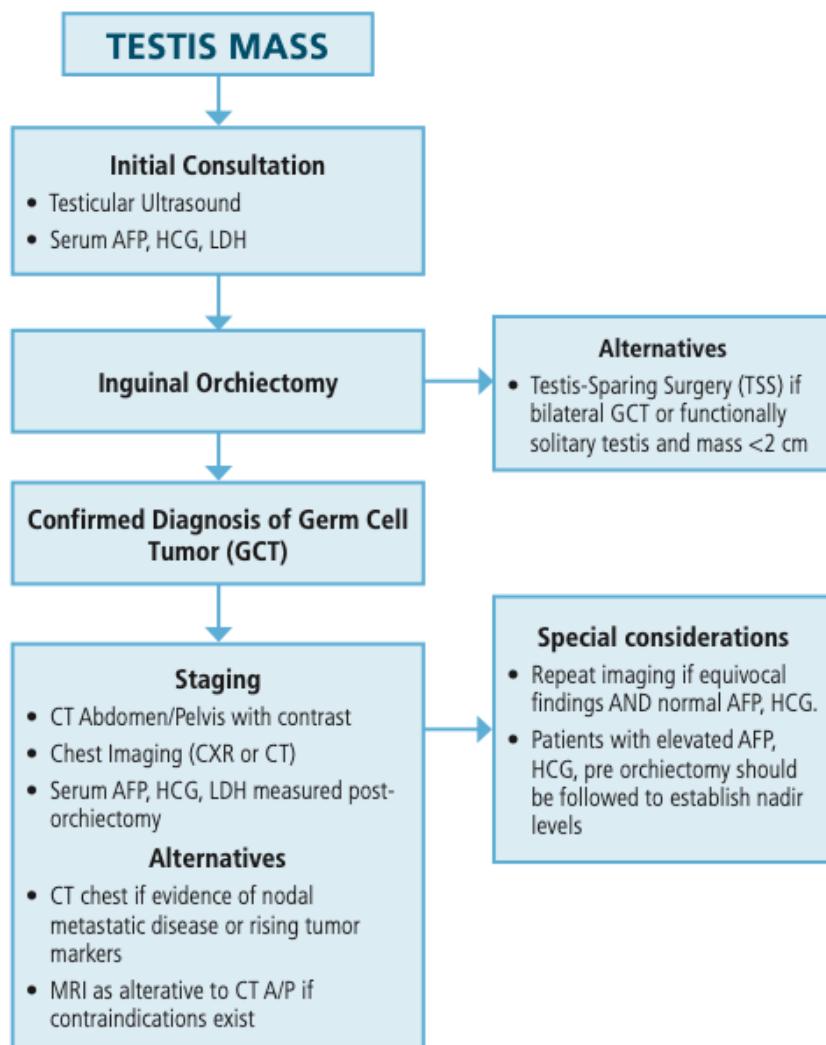


Figure 1. Diagnosis and Treatment of Early Stage Testicular Cancer: AUA Guideline

See AUA Testis Cancer Guideline³⁰

5. Management of Stage I Seminoma

For patients with Stage IA and IB pure seminoma, treatment options following radical orchiectomy include (i) Surveillance (preferred) (ii) Retroperitoneal Radiotherapy (iii) Chemotherapy with carboplatin (1 or 2 cycles). **More than 80% of patients with stage I seminoma are cured with orchiectomy alone, therefore surveillance is the preferred approach**, and the disease specific survival for stage I disease is 99% irrespective of the management strategy used.³¹

5.1 Surveillance for Stage IA and IB Seminoma

Because of the high cure rates achieved by orchiectomy for **stage I seminoma, surveillance is**

recommended as the preferred treatment strategy in order to limit overtreatment and the subsequent morbidity associated with radiation and chemotherapy, while allowing for successful salvage therapy in those who relapse. Surveillance requires close adherence to the observation protocol including interval clinical assessments and imaging and this approach should be considered when a patient is deemed reliable.

Assessing a patient's risk of occult metastases is important when counseling men with stage I disease. In an analysis of over 600 patients, rete testis invasion and tumors ≥ 4 cm were identified as risk factors for predicting relapse. For patients with 0, 1, or 2 of these risk factors the recurrence rates were 12%, 16%, and 32%, respectively. Although a risk-adapted approach to the use of surveillance in stage I seminoma may be considered, these factors have not been validated in multivariate analysis, leading **the National Comprehensive Cancer Network (NCCN) to recommend against a risk-adapted approach and supporting surveillance as the preferred strategy for all stage I patients.^{18,32,33}** The **AUA Guideline on the Diagnosis and Treatment of Early Stage Testicular Cancer** similarly strongly recommends surveillance as the preferred strategy for stage I seminoma.²⁴

Conversely, the EAU extensively discusses a risk-adapted approach for stage 1 seminoma patients, incorporating the risk factors of size and rete testis invasion. The EAU takes a slightly more aggressive approach, proposing either surveillance or adjuvant carboplatin if such risk factors for relapse are present. Further, the EUA discourages adjuvant radiation.³⁴

The safety of active surveillance has been consistently demonstrated. In the Swedish Norwegian testicular cancer study group (SWENOTECA), **13% of patients with clinical stage I seminoma relapsed following surveillance.**³⁵ No factors predicting relapse were identified in these patients and **the overall survival was 98% in the surveillance group.** In a systematic review of 14 studies involving over 2000 men, Groll and colleagues identified relapse in 17% of men managed with surveillance, with a **seminoma-related mortality rate of 0.3%.**³⁶ A 2017 publication evaluated outcomes of surveillance versus primary radiotherapy for patients with stage I seminoma at high risk for recurrence based on tumor size ≥ 6 cm.³⁷ This was a retrospective study of the large Danish Testicular Cancer Database. The 10-year risk of recurrence was 2.8% vs 32% for RT vs surveillance, respectively. In this high-risk group, therapy was avoided in 68% of patients without increasing the need for greater than one line of therapy being required (5.8% vs. 3.4%) and there was no difference in OS. This lends further support to surveillance in a non-risk adjusted manner in stage I seminoma.³⁷

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.³⁸ Relapses after 5 years are relatively uncommon, but have occurred more than 9 years after orchiectomy.³⁹ **The most common site of relapse is the retroperitoneal lymph nodes.** Recurrence patterns were retrospectively evaluated in over 1,300 clinical stage I seminoma patients initially followed with surveillance, demonstrating **an overall recurrence rate of 13%, with 92% of recurrences occurring within 3 years, of which 99% were IGCCCG good risk.**⁴⁰ Accordingly, the NCCN has proposed widely accepted surveillance schedules for a stage IA and IB seminoma and the new AUA Guidelines

advocate for a similar surveillance **schedule**. (**Table 4A** and **Table 4B**).¹⁸ Notably, interval CT is not recommended in either guideline statement after 5 years from radical orchiectomy for seminoma unless there is a clinical indication.

Concerns related to radiation exposure and risk of secondary malignancy related to interval imaging in the recommended seminoma surveillance protocols exist. A large randomized, phase III, noninferiority trial sponsored by the Medical Research Council (MRC), (TRISST) Trial of Imaging and Schedule in Seminoma Testis (TRISST) evaluated the optimal imaging modality and frequency.^{41,42} Stage I seminoma patients were evaluated with either 7 CTs or MRIs (at 6, 12, 18, 24, 36, 48, and 60 months) or 3 CTs or MRIs (at 6, 18, and 36 months) with 669 men randomized to the 4 arms: 7 CTs over 5 years, 7 MRIs over 5 years, 3 CTs over 3 years, or 3 MRIs over 3 years. There was no difference in 5 –year DFS or OS or >stage IIC relapse leading to the conclusion that reduced schedule MRI was non-inferior.

Table 4A. Surveillance Schedule For Stage I Seminoma (NCCN guidelines)

Year	1	2	3	4	5
History and physical exam	Every 3-6 mo	Every 6 mo	Every 6-12 mo	Every 12 mo	Every 12 mo
Beta-HCG, AFP, and LDH	optional	optional	optional	optional	
Abdominal/pelvic CT (with or without contrast is acceptable)	At 3, 6, 12 mo	Every 6 mo	Every 6-12 mo	Every 12-24 mo	Every 12-24 mo
Chest x-ray	As clinically indicated				

Table 4B. Surveillance Schedule For Stage I Seminoma (AUA Guidelines)

	Years 1-2	Years 3-5	< Year 5
History and physical CT abdomen ± pelvis	Every 4-6 months	Every 6-12 months	If clinically indicated

* Routine surveillance imaging of the chest and serum tumor marker assessment can be obtained as clinically indicated

5.2 Radiation Therapy for Stage IA, IB Seminoma

For men with stage I seminoma who desire treatment or are unable to adhere to a surveillance schedule, radiotherapy or single agent chemotherapy with carboplatin are reasonable alternatives, with distinct advantages and disadvantages to each approach.

5.2.1 Fields and Dosing

Radiation therapy (RT) alone prevents relapse in more than 96% of patients with clinical stage I seminoma. Radiotherapy is initiated once the orchectomy incision has fully healed.

Classically, RT has been delivered to the bilateral para-aortic nodes and ipsilateral pelvic lymph nodes in a "dog leg" field. This approach includes all ipsilateral regional nodes at risk for occult metastatic disease. RT to the inguinal orchectomy scar or ipsilateral scrotal contents is used only if scrotal violation or tumor spillage occurred during the orchectomy.

Para-aortic (PA) strip protocols were developed to decrease treatment-related morbidity while maintaining similar efficacy to the "dog leg" RT field. Current NCCN and AUA Guidelines recommend the PA-strip field for stage IA and IB seminoma.^{18,24} Fields should not include the mediastinum due to the low risk of relapse in this location. Seminoma requires a low therapeutic dose due to its extreme radiosensitivity. Dosing for clinical stage I disease is 20 Gy or 25.5 Gy given in 10 fractions. Anti-emetics may be used if needed. A scrotal shield should be used in all patients to minimize radiation to the remaining testicle.

Stage IS seminoma is rare. The NCCN guidelines advocate for repeated serum tumor marker measurement and assessment of chest, abdominal, and pelvic CT with contrast to scan for evaluable disease. These patients are generally treated with 20 Gy to the para-aortic nodes with or without coverage of the ipsilateral ilioinguinal nodes if only low volume retroperitoneal disease is observed. Of note, in the case of an elevated AFP after orchectomy for pure seminoma, patients should be treated according to NSGCT algorithms.

5.2.2 Post-Radiotherapy Outcomes

Favorable long-term outcomes in patients with clinical stage I seminoma treated with adjuvant RT are illustrated by a combined analysis of three randomized phase III trials involving 2466 patients treated between 1989-2001.⁴³ The Medical Research Council Testicular Tumor Working Group TE10 trial randomly assigned 478 men with stage I seminoma to 30Gy para-aortic strip vs. para-aortic plus ipsilateral iliac lymph node RT following inguinal orchectomy. Short-term side effects and the incidence of azoospermia were significantly decreased using para-aortic strip compared with a dog-leg RT field (11% vs 35%). With a median follow-up of over 10 years, there were 10 relapses in the para-aortic strip group (4 pelvic relapses) and 9 in the dog-leg RT group (no pelvic relapses). There was only one death due to seminoma in the trial. All relapses were successfully treated with

chemotherapy.⁴³

The TE18 (EORTC 30942) trial compared a standard radiation dose of 30 Gy in 15 fractions to 20 Gy in 10 fractions. With a median follow-up of 7 years, the relapse-free rates at 5 years were 95% and 97% for the 30 and 20 Gy groups, respectively.⁴³ While men receiving the higher dose had significantly more lethargy (20% vs 5%) and inability to work (46% vs 28% percent) at four weeks, these differences disappeared by 12 weeks. **This study also raised concerns about the risk of secondary malignancy associated with RT.**

Based on the available data from clinical trials, **patients with stage IA, IB, or IS seminoma electing adjuvant RT should have 20 Gy to the para-aortic region. Toxicity of RT includes GI complications (5%), leukopenia (5-15%), and oligospermia (8%).³¹** Currently the EAU guidelines do not recommend RT as an option for adjuvant therapy for stage I pure seminoma.⁴⁴

5.3 Chemotherapy for Stage IA and IB Seminoma

Cisplatin-based combination chemotherapy is the standard treatment for advanced testicular GCTs, including both seminomas and NSGCTs. This led to the evaluation of chemotherapy as an adjuvant option in men with stage I seminoma. **Single-agent carboplatin** (rather than cisplatin-based) regimens have been used to **decrease toxicity**.

The efficacy of adjuvant carboplatin for stage I seminoma was evaluated in a phase III trial (EORTC 30982). Men with stage I seminoma were randomized to adjuvant RT (20-30 Gy) or a single dose of carboplatin (AUC=7 x 1 cycle). **At a median of 6.5 years, relapse-free rates were similar between carboplatin and RT (95% vs. 96%, respectively).**⁴³ There were no deaths due to seminoma.

Multiple studies have also looked at the relapse rate with either 1 or 2 cycles of carboplatin. In an analysis of 837 patients relapse rates among those who had received either 1 or 2 cycles of carboplatin were 4.4% vs. 3%, respectively.⁴⁵ Largely due to the results of EORTC 30982, the EAU recommends 1 cycle of carboplatin in the adjuvant setting while acknowledging that 2 cycles does further reduce recurrence rates to the 1-3% range.^{44,46} Given this available data, **the NCCN recommends either 1 or 2 cycles of carboplatin (AUC=7 x 1 or 2 cycles) as an option for adjuvant therapy in stage I seminoma.**

Carboplatin is associated with short-term thrombocytopenia (4-12%) and GI complications (8%).⁴⁷

Platinum chemotherapy is also associated with late toxicity including increased risk of second malignancies, heart disease, metabolic syndrome, chronic kidney disease and neurotoxicity .

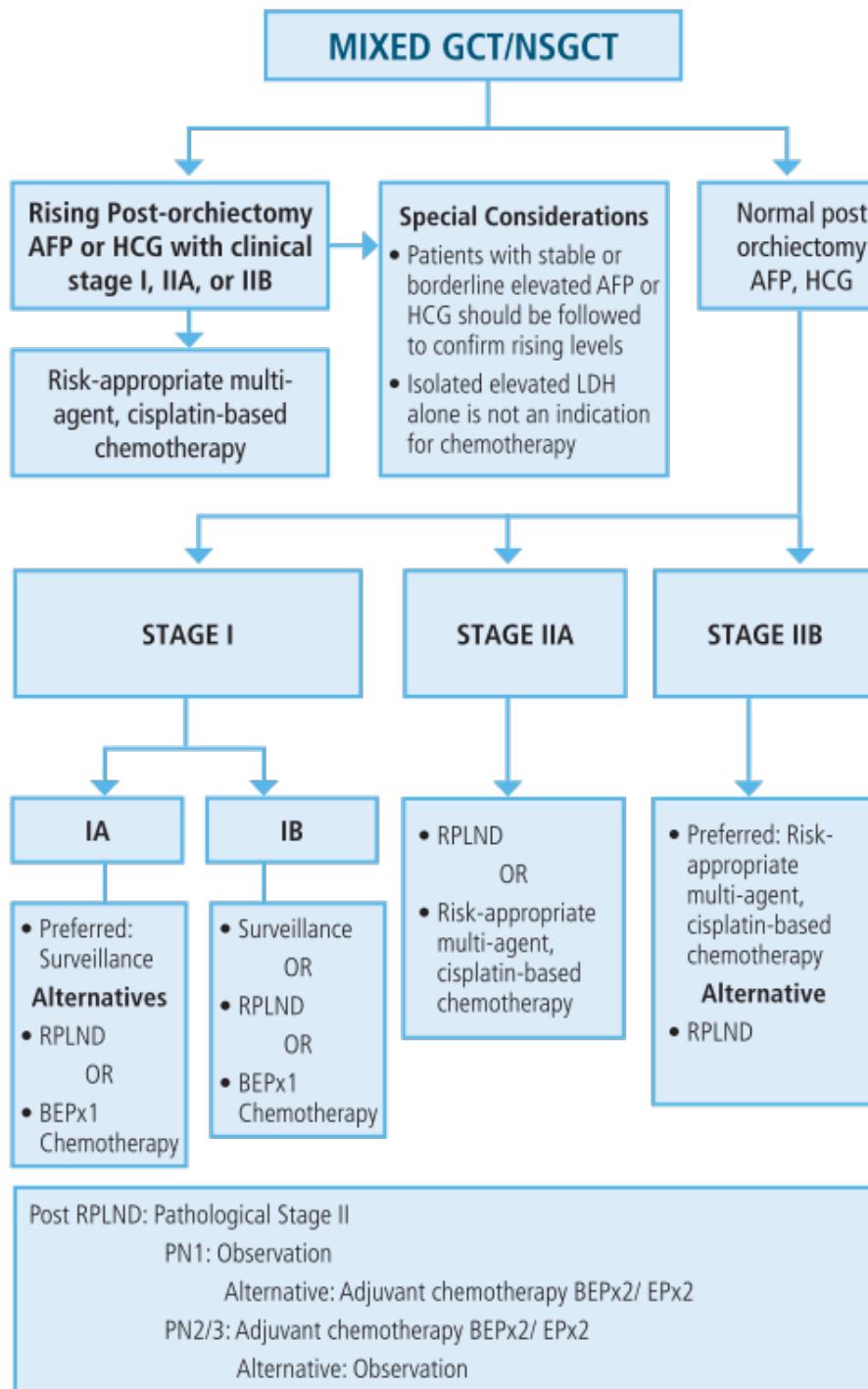
Table 5: Summary of guideline recommendations for Stage IA and IB seminoma

		AUA Guidelines	NCCN Guidelines	EAU guidelines
State IA Seminoma				
	Surveillance	*	*	*
	Radiation Therapy	#	#	%
	Single cycle Carboplatin	#	#	#
Stage IB Seminoma				
	Surveillance	*	*	*
	Radiation Therapy	#	#	%
	Single cycle Carboplatin	#	#	#
* Preferred options # Alternative option % Discouraged option				

6. Management of Stage I Non-Seminomatous Germ Cell Tumors

For men with stage I NSGCTs, approximately 70% will be cured with radical orchectomy alone. The management options for these patients include (i) Surveillance, which is the preferred option, (ii) RPLND, and (iii) cisplatin-based chemotherapy. The AUA Guideline includes a treatment algorithm (Figure 2).

6.1 Risk Stratification



*IGCCCG good risk chemotherapy BEPx3 or EPx4.
Intermediate or poor risk BEPx4.

Figure 2: AUA Guideline Mixed GCT/NSGCT Treatment Algorithm

All cases of NSGCT should be clinically staged at diagnosis with CT imaging and post-orchiectomy STM as per above. **Any persistent elevation of tumor markers following radical orchiectomy indicates metastatic disease, mandating systemic chemotherapy.**

Up to 30% of men with clinical stage I NSGCTs will harbor micrometastatic disease. Adjuvant treatment following orchiectomy can reduce the risk of relapse but represents overtreatment in approximately 70% of patients. **Although the risk of recurrence is approximately 30% for men undergoing surveillance, treatment at the time of recurrence is almost always curative,** albeit at a potentially higher treatment burden.

Attempts have been made to identify men with clinical stage I NSGCTs at high risk of relapse following orchiectomy. **The most important factors used to predict occult metastases are:**

1. **The presence of lymphovascular invasion (LVI)**
2. **Embryonal carcinoma predominance in the primary tumor**

At least one of these variables occurs in 10-30% of men.⁴⁸ Men with no risk factors have an occult metastases rate of 10-14%. **The presence of LVI alone or LVI with embryonal carcinoma predominance is associated with a 40-55% relapse rate in historical series.**⁴⁴ Recently, a retrospective series demonstrated relapse rates and median time-to-relapse of 25%/8.5 months, 41%/6.8 months and 78%/3.8 months for no risk factors, either LVI or embryonal carcinoma predominance, or both LVI and EC predominance, respectively.⁴⁹

Table 6: Summary of guideline recommendations for Stage IA and IB nonseminoma

		AUA Guidelines	NCCN Guidelines	EAU guidelines
Stage IA NSGCT				
	Surveillance	*	*	*
	RPLND	#, @	#	%@
	BEPx1	#	#	#
Stage IB NSGCT				
	Surveillance	*	*	#
	RPLND	*	*	%@
	BEPx1	*\$	*	*
* Preferred options # Alternative option % Discouraged option @ RPLND advised if secondary somatic malignancy in the primary \$ 1-2 cycles of BEP are options				

6.2 Surveillance for Stage I Non-Seminomatous Germ Cell Tumors: Protocols and Outcomes

The **main advantage of surveillance is avoidance of treatment-associated morbidity** in the majority of men with stage I NSGCT.

Patients at low risk of relapse are the ideal candidates for this strategy. Most surveillance protocols involve frequent imaging and clinical assessments, 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.**⁴

The British Columbia Cancer Agency and the Oregon Testis Cancer Program placed 223 unselected men on surveillance and reported a **26% risk of relapse.**⁵⁰ **Most relapses occurred within 2 years (88%) while only 3% of all patients relapsed beyond 2 years.** Of those who relapsed, all achieved long-term remission following chemotherapy with or without retroperitoneal lymph node dissection (RPLND) which was only required in 8%. **Disease-specific survival was 100% after a median follow-up of 52 months.**

The Swedish and Norwegian Testicular Cancer Project (SWENOTECA) Management Program identified 745 men between 1998-2005 who were treated prospectively for clinical stage I NSGCT.⁵¹ Surveillance was recommended for men without LVI (n=491). At a median follow-up of 4.7 years **relapse rates were 12%, 1.3%, and 0% among men who underwent surveillance, 1 cycle, or 2 cycles of BEP chemotherapy, respectively.** The **overall mortality rate was 1%, and none of these deaths were due to testicular cancer.** Another recent study with over 1,100 patients on surveillance for Stage I NSGCT demonstrated an overall recurrence rate of 19% (44% LVI+, 14% LVI-, remainder unknown), with a median time to relapse of 6 months.⁴⁰ The overwhelming majority of relapses (95%) occurred within 2 years, with less than 1% occurring after 3 years and 90% of patients relapsed with IGCCCG good risk disease. **These outcomes led the authors to suggest less intensive surveillance schedules for clinical stage I patients.**

Although studies have demonstrated variable adherence to surveillance protocols, >98% of relapses continue to be salvageable.⁴⁴ There is no consensus on the optimum surveillance schedule and no one schedule has been shown to be superior to another. The NCCN and AUA Guideline surveillance protocols are included below (Table 7A and Table 7B).^{18,24}

Table 7A. Surveillance Schedule For Stage I NSGCT (NCCN)

Year	1	2	3	4	5
For Clinical Stage IA NSGCT					
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	Every 2 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 ± pelvic CT	Every 4-6 mo	Every 6-12 mo	Every 12 mo	As clinically indicated	As clinically indicated
For Clinical Stage IB NSGCT					
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	Every 2 mo	Every 3 mo	Every 4-6 mo	Every 6 mo	Every 12 mo
Chest x-ray	Every 4 mo	Every 4-6 mo	Every 6 mo	Every 12 mo	As clinically indicated
Abdominal ± pelvic CT	Every 4 mo	Every 4-6 mo	Every 6 mo	Every 12 mo	As clinically indicated

Table 7B.
Surveillance
Follow-up for
Clinical
Stage I
NSGCT - AUA
Guidelines

	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	Once	If clinically indicated

6.3 Retroperitoneal Lymph Node Dissection (RPLND)

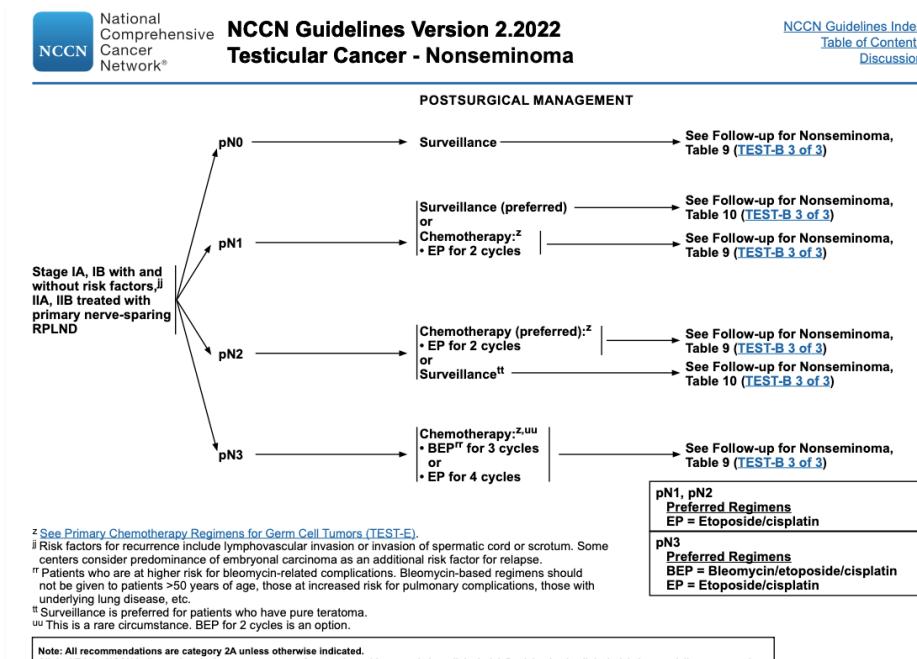


Figure 3: NSGCT Post-RPLND Management According to pN Stage

For men with high-risk pathologic features or for those who are unable to comply with a surveillance schedule, primary RPLND offers an appropriate choice for adjuvant treatment .

RPLND provides several advantages over surveillance or adjuvant chemotherapy in clinical stage I NSGCT

- i. RPLND provides **accurate pathologic staging**
- ii. RPLND in experienced hands is associated with **low risk of short and long-term morbidity**
- iii. RPLND **minimizes the risk of relapse due to chemoresistant GCT and teratoma.**

Contemporary series demonstrate that upwards of 80% of patients found to have pathologic stage II active germ cell cancer are cured with surgery alone. Thus, with RPLND, patients can avoid chemotherapy and chemotherapy-associated long-term adverse side effects.

As the risk of retroperitoneal relapse after RPLND 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 only. **Relapse in any site after a negative RPLND is uncommon and is generally curable with chemotherapy .**

These advantages make **RPLND the most commonly used option in the United States for stage I patients who elect adjuvant therapy over surveillance.¹⁸**

Conversely, a **risk-adapted approach** is presented in the **EAU guidelines** as follows:

- **Low risk stage I NSGCT:** surveillance recommended

- **High risk stage I NSGCT (LVI present):** adjuvant chemotherapy with bleomycin, etoposide and cisplatin (BEP) for one cycle is recommended.^{44,46}

There is a considerable discrepancy in the management of Stage I NSGCT between the European and American guidelines. Both guidelines recommend surveillance as the preferred option for patients with Stage 1A disease. The AUA suggests that RPLND or one cycle of BEP are options for stage 1A patients unwilling to undergo surveillance or at high risk of noncompliance. The EAU promotes adjuvant chemotherapy in this patient population. The AUA has a direct statement recommending RPLND for patients with stage 1 disease with transformed elements in the primary, which is recently included in the EAU guidelines. For stage IB disease, both guidelines recommend surveillance, adjuvant chemotherapy or RPLND. In the EAU guidelines, nerve-sparing RPLND is only recommended for patients that are unwilling to undergo surveillance and have contraindications to adjuvant chemotherapy. Broadly, primary RPLND is discouraged in the EAU guidelines while it is presented as a comparable alternative to adjuvant chemotherapy in the AUA guidelines. The reluctance to promote RPLND as a balanced alternative to adjuvant chemotherapy in the European guidelines is based on the results of the study from Albers et al. comparing primary RPLND and adjuvant chemotherapy for high risk disease, where patients treated with chemotherapy had significantly lower recurrence rates. ⁵²

Per the **NCCN guidelines**, for stage I NSGCT patients who do not accept surveillance or primary RPLND, **one cycle of Bleomycin, Etoposide and Cisplatin (BEP) is recommended.**¹⁸ The German Testicular Cancer Study Group compared one cycle of BEP to RPLND in stage I NSGCT patients and found a 2-year recurrence-free survival rate of >99% with BEP and 92% with RPLND.⁵³ Although this study has been criticized for a high relapse rate in the RPLND group, it does support BEP as an option for adjuvant treatment.

NS-RPLND is recommended within 4 weeks of a CT scan and with 7-10 day of serum tumor markers. Approximately **30% of patients undergoing RPLND for Stage I disease are upstaged to pathologic Stage II** (e.g. have active NSGCT identified in the nodal specimens). In patients with **negative pathology after primary PRLND (pN0), approximately 10% will experience distant relapse most often found in the chest.**

The use of adjuvant chemotherapy after primary RPLND is based on the degree of nodal involvement. If the nodes are not involved with tumor (pN0) no chemotherapy is given. **Surveillance is recommended for pathologic N1 disease** based on a low risk of recurrence (~10-20%). **Chemotherapy is preferred for N2 and N3 disease** based on higher recurrence rates (~50-70%). Following grossly complete resection, with normal post-RPLND STM, recommended regimens include either EP or BEP for 2 cycles for pN1 or pN2 disease; or 4 cycles of EP or 3 cycles of BEP for pN3 disease.⁵⁴ The management of pathologic stage II disease after primary RPLND is outlined in **Figure 3.**¹⁸ Recent data suggest that relapse rates for patients with pN2 and pN3 disease may be closer to ~20%, similar to pN1 patients, and that adjuvant treatment may be overtreatment in a significant proportion of patients.⁵⁵

6.3.1 Surgical Considerations

The principles underlying the surgical treatment of testicular GCT are based upon stereotypic patterns of metastatic spread. The spermatic cord contains lymphatic channels that ascend into the retroperitoneal lymph node chains.

- The **interaortocaval and paracaval nodes**, at the level of the second lumbar vertebral body, are typically the first echelon of lymph nodes draining the **right testis**.
- The first lymph nodes draining the **left testis** are typically located in the **para-aortic** region in an area bounded by the renal vein superiorly, the aorta medially, the ureter laterally, and the origin of the inferior mesenteric artery (IMA) inferiorly.

Secondary lymphatic spread may occur in a retrograde fashion to the common and external iliac nodes, or cephalad via the cisterna chyli and thoracic duct to the supraclavicular nodes. Contralateral nodal involvement is more common in right-sided tumors due to lymphatic drainage from right to left.

Also included in the RPLND is resection of the ipsilateral gonadal vessels and proximal intraabdominal vas deferens to the level of the internal ring.²⁴

In selected patients, a nerve-sparing (NS-)RPLND may be performed to reduce the risk of retrograde ejaculation. The relevant neuroanatomy includes the bilateral paravertebral sympathetic trunks which give rise to the postganglionic fibers that **course posterior to the inferior vena cava and anterior to the aorta and coalesce at the superior hypogastric plexus, caudal to the IMA**.

Historically, a suprahilar bilateral RPLND template was standard. Over time, **a full bilateral template evolved to include the area between the renal hilum to the bifurcation of the common iliac vessels caudally, with the ureters as the lateral boarders**. Due to the morbidity of this dissection (mainly retrograde ejaculation), modified templates were developed to facilitate nerve-sparing. There have been several minor variations reported regarding modified RPLND templates, but in general, **for a modified right-sided modified, the lymphatic tissue medial to the right ureter, lateral and posterior to the inferior vena cava, in the interaortocaval and the pre- and para-aortic regions above the IMA is removed. Left-sided templates require dissection of all para-aortic lymphatic tissue medial to the left ureter as well as the interaortocaval and pre-aortic lymphatic tissue above the IMA.**

A retrospective study of 364 patients with clinical stage I NSGCT undergoing a full bilateral RPLND, demonstrated a risk of extra-template disease in 1-5% if modified templates were used.⁵⁶ This finding led these authors and others to advocate for a full bilateral, nerve sparing RPNLD by an experienced surgeon for all stage I patients undergoing adjuvant surgery.^{4,56} In contrast, a contemporary series of 257 patients undergoing modified unilateral templates confirmed a minimal risk of contralateral recurrence of 1.6% with nearly 5 years of follow-up.⁵⁷ To this end, although the oncologic efficacy of modified templates has been demonstrated by several authors, other groups have expressed concerns over potential extra-template disease and recommend that all patients receive a bilateral template resection.^{56,58}

In contemporary practice, **nerve-sparing techniques in which the L1-4 nerves are dissected out** from the nodal packets allow for a full bilateral dissection with preservation of antegrade ejaculation. Both the use of modified templates and nerve-sparing techniques have been demonstrated to **maintain ejaculatory function in the majority of patients.** The **split-and-roll technique** with control of lumbar vessels is performed to allow complete circumferential dissection of the great vessels.

The Surgical Considerations listed in the 2019 AUA Guideline on Testis Cancer²⁴ are as follows:

Primary RPLND should be performed with curative intent in all patients. RPLND should be performed with adherence to the following anatomical principles, regardless of the intent to administer adjuvant chemotherapy. These principles are applied to both open and minimally invasive approaches. (Moderate Recommendation; Evidence Level: Grade B).

- Primary RPLND should be performed with curative intent in all patients. RPLND should be performed with adherence to the following anatomical principles, regardless of the intent to administer adjuvant chemotherapy. These principles are applied to both open and minimally invasive approaches. (Moderate Recommendation; Evidence Level: Grade B). Figures 4 and 5 demonstrate bilateral dissections with appropriately selected patients for nerve-sparing techniques
- A full bilateral template dissection should be performed in patients with suspicious lymph nodes based on CT imaging or intraoperative assessment and in those with somatic-type malignancy in the primary tumor.
- A full bilateral template or modified template dissection may be performed in patients with clinically negative lymph nodes.
- A right modified template dissection may omit the para-aortic lymph nodes below the inferior mesenteric artery. Omission of para-aortic lymph nodes above the inferior mesenteric artery is controversial.
- A left modified template dissection may omit paracaval, precaval, and retrocaval lymph nodes. Omission of interaortocaval lymph nodes is controversial.
- Nerve-sparing should be offered in select patients desiring preservation of ejaculatory function.
- Nerve-sparing attempts should not compromise the quality of the lymph node dissection.
- A complete retroaortic and/or retrocaval lymph node dissection with division of lumbar vessels should be performed when within the planned template.
- The ipsilateral gonadal vessels should be removed in all patients.
- The cephalad extent of the dissection is the crus of the diaphragm to the level of the renal arteries. The caudad extent of disease is the crossing of the ureter over the ipsilateral common iliac artery.





Figure 4: Nerve sparing RPLND (para-aortic dissection)

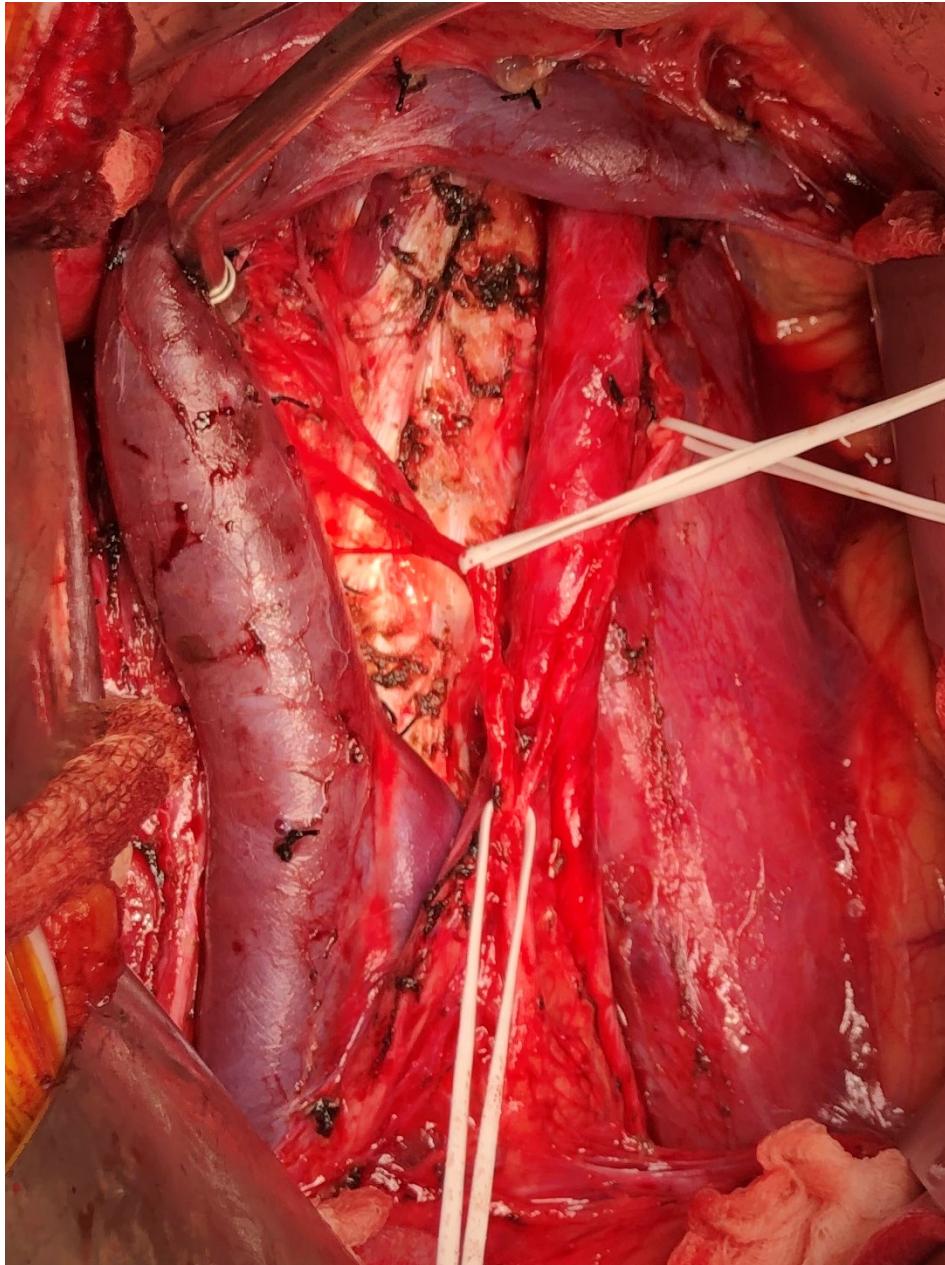


Figure 5: Bilateral nerve-sparing RPLND

Photograph courtesy of Clint Cary, MD

6.3.2 Emerging Techniques

While open RPLND is traditionally performed transperitoneally, requiring either evisceration onto the chest or bilateral bowel mobilization and packing, a **midline extraperitoneal approach** was described in 2017.⁵⁹ This approach avoids entry into peritoneal cavity with the objective of minimizing bowel manipulation in an attempt to further decrease morbidity. In an initial series of 68 patients, in both primary and post-chemotherapy settings, the authors reported favorable outcomes.

Laparoscopic RPLND (L-RPNLD) is an emerging technique that may reduce morbidity compared to

open RPLND. Cancer control rates appear to be similar in retrospective studies with limited follow-up, although there are no randomized trials comparing the two procedures and some differences exist in the utilization of post-RPLND chemotherapy among L-RPNLD series.⁶⁰ Several observational series have demonstrated the feasibility of this approach in expert hands and report benefits with respect to blood loss and decreased length of stay. Longer-term outcomes in larger cohorts, particularly without liberal use of adjuvant chemotherapy for pN1 disease, are required to fully evaluate oncologic efficacy.

As has been seen in other areas of genitourinary cancer surgery, the feasibility of a **robotic-assisted laparoscopic approach to RPLND** has also been demonstrated by experienced surgeons, with proponents advocating that this technology addresses some of the technical challenges of traditional laparoscopic approaches, with favorable preliminary outcomes, including low perioperative complications rates, nodal yields of approximately 25, and reported LOS of 1-2 days.^{61,62} However, these series represent highly selected patients in the setting of high volume surgeons, and longer term oncologic outcomes remain to be demonstrated. Another recent report noted that robotic-assisted RPLND was associated with adverse outcomes including aberrant in-field and out-of-field recurrence patterns.⁶³

6.4 Adjuvant Chemotherapy

For men with stage I NSGCT who select adjuvant chemotherapy, one cycle of a cisplatin-based regimen, usually bleomycin, etoposide, and cisplatin (BEP), is the standard of care.¹⁸ This approach is associated with a relapse rate of <5%.

Studies initially used two cycles of adjuvant BEP but long-term follow-up has demonstrated increasing treatment-related morbidity and mortality with additional chemotherapy doses.^{64,65} Use of one cycle of adjuvant BEP is also supported by a publication from the SWENOTECA group: Among stage I NSGCT patients with a median follow-up of 7.9 years after a single cycle of BEP, researchers observed a 5-year relapse rate of 3.2% in patients with LVI and 1.6% for patients without LVI.⁶⁶ All recurrences were IGCCCG good risk and the 5-year CSS was 100%. The 111 study from the United Kingdom assessed 1 cycle of BEP in single-arm Phase III trial including high risk patients and similarly reported acceptable rates of malignant recurrence at 1.3%.⁶⁷ Reduction from one to two cycles of BEP reduces acute and delayed side effects of treatment (including a decreased risk of bleomycin-induced pulmonary toxicity). Given the overall low recurrence rates with one cycle and similar cancer-specific survival between one and two cycles of BEP with less long-term toxicity, the most recent update to the EAU guidelines similarly recommends 1 cycle of BEP.^{44,46} A recent report by the Global Germ-Cell Cancer Group characterized 51 patients who relapsed after adjuvant BEP, demonstrating that 37% of patients relapsed after >2 years (a substantially higher rate than stage 1 NSGCT patients in general) with late relapse associated with inferior survival. The 5-year progression-free survival and overall survival of relapsed patients was 67% and 81%, respectively.⁶⁸

7. Management of Stage II, III Pure Seminoma and NSGCT

Stage II disease is characterized as either N+ with/without S1 disease (**Table 2b**). Stage III disease is characterized by advanced disease consisting of M1a/b and/or N+ with \geq S2 disease. The established guidelines for these advanced cases have been published in the NCCN Guidelines as well as the European Association of Urology (EAU) Guidelines.^{18,44,46} The management of advanced stage GCTs is dependent on the histology type (i.e. seminoma or non-seminoma) as well as the risk stratification of the IGCCCG (**Table 3**).

7.1 Management of Stage IIA and IIB Pure Seminoma

See **Figure 7**

Radiation therapy (RT) is the mainstay of treatment of Stage IIA pure seminoma.^{18,44,46,69,70}

Chemotherapy is the preferred treatment for stage IIB disease, although select non-bulky IIB pure seminoma can be managed with RT. The primary difference in the radiation field used for stage II versus I disease is the inclusion of the ipsilateral iliac lymph nodes in a “dog-leg” field. The cumulative dose for IIA disease is **30 Gy** while the dose is slightly higher at **36 Gy** for IIB disease.

5-year overall survival approaches 100% with RT for IIA/IIB disease, although the recurrence risk is substantially higher in IIB disease.^{18,71}

In most patients IIB disease, especially those with **bulky lymphadenopathy (> 3 cm)**, **chemotherapy is preferred to RT**, with both the NCCN and EAU guidelines recommending **4 courses of EP or 3 cycles of BEP.**^{18,46,71} Again, **5-year overall survival approaches 100% with chemotherapy.**⁷² However, survivorship studies have demonstrated that radiation and chemotherapy are associated with the potential for significant long-term treatment related morbidity including the risk of secondary cancers and cardiovascular disease.^{73,74} Thus, three recent Phase II trials have investigated treatment alternatives in this cohort. Results of these trials have been presented in abstract form and the full manuscripts are anxiously anticipated.

There has been interest in the role of primary RPLND for stage II seminoma given the predictable lymphatic drainage patterns of GCTs and therapeutic benefit of surgery in NSGCT. First, PRIMETEST is a Phase II single center study completed in Germany investigating the role of unilateral primary RPLND (open or robotic) in 33 men with CS IIA/IIB Seminoma. Of note, this study included patients who previously received carboplatinum for adjuvant therapy for CS I disease and subsequently developed progression. In a recently updated analysis, relapse rates were 31% resulting in a RFS of 69% with a median time to recurrence of 6 months. Of the 10 men who recurred, in-field and contralateral retroperitoneal recurrences were observed in 3 and 4 patients, respectively. Overall survival was 100% as all patients were salvaged with chemotherapy.⁷⁵ Second, the SEMS trial enrolled 55 patients with CS IIA Seminoma from 12 U.S. and Canadian centers. Men underwent a modified template open RPLND for lymphadenopathy (1-2 nodes) measuring less than 3 cm. The primary endpoint was 2-year RFS. The authors reported a recurrence rate of 22% and a 2-year RFS of 81% with a median time to recurrence of 8 months. Eight of twelve recurrences occurred in the retroperitoneum (in-field and contralateral). Overall survival was 100% as all patients with recurrent disease were salvaged with either repeat surgery or chemotherapy.⁷⁶ For both surgical

studies, complications were infrequent with Clavian-Dindo \geq III complications occurring in 11% and 3.6% of men in PRIMETEST and SEMS, respectively.

The Phase II SAKK 01/10 trial investigated the combination of carboplatin and involved-node radiotherapy in men with IIA/IIB Seminoma to de-escalate treatment (compared to BEP x3 or EP x4 and/or dog-leg whole field radiotherapy) and thus potentially minimize treatment related morbidity. One-hundred and twenty patients were given a single dose of carboplatin (AUC 7) followed by either 30 Gy for IIA or 36 Gy for IIB disease targeted at the involved lymph nodes only, at 20 centers throughout Germany and Switzerland. The primary outcome was 3-year PFS which was 93.7% (90%CI 88.5-99.6) with a median time to recurrence of 16.7 months. All men who recurred were salvaged with chemotherapy. With a median follow-up of 4.5 years, there were no reported long-term side effects, and the 4 secondary cancers diagnosed were all thought to be outside of the radiotherapy field.⁷⁷

A few notable points differentiating these studies should be considered while we await the final manuscripts. First, for the surgical studies, the inclusion criteria (mass size and past chemotherapy inclusion), surgical approach and template varied considerably between PRIMETEST and SEMS which may account for some of the discrepancy in RFS reported between the studies. The exact patient who may benefit most from an upfront surgical approach is yet to be known; however, it is likely to be a patient with lower volume disease < 3 cm, who are not previously pretreated who undergo an open, bilateral template RPLND by an experienced surgeon. The need to expand the surgical template in primary RPLND for stage II seminoma is supported by the contralateral RP recurrences in PRIMETEST and SEMS (not reported) and a recently presented large single-institution cohort study.⁷⁸ Second, the results of SAKK 01/10, while statistically negative, are impressive with regards to oncological efficacy and may be comparable to current standard therapies. Only 5.6% recurred in this trial and all recurrences were salvaged with chemotherapy, yet the burden for cure (XRT and induction chemotherapy) in those men with regard to long-term toxicity exceeds that of men who recur after RPLND (surgery and induction chemotherapy). Moreover, long term follow-up data for is not mature enough to comment on the goal of reducing long-term morbidity of whole-field radiotherapy or multiagent chemotherapy with this new regimen. Perhaps this may be an ideal option in the future for men with larger volume IIB disease where oncological outcomes with surgery alone may be deficient. Finally, the surgical studies, like primary RPLND for CS II NSGCT, report a non-inconsequential pN0 rate ranging of 9 and 20% for PRIMETEST and SEMS, respectively. This highlights the limitations of current imaging and management decisions based on the size criteria of retroperitoneal lymph nodes. More accurate staging studies are needed. Perhaps with further investigation and wide-spread availability, mi-RNA may help providers select those patients without active disease in their enlarged lymph nodes thus allowing for less invasive management/surveillance.

7.2 Management of Stage IIC and III Seminoma

See **Figure 7**

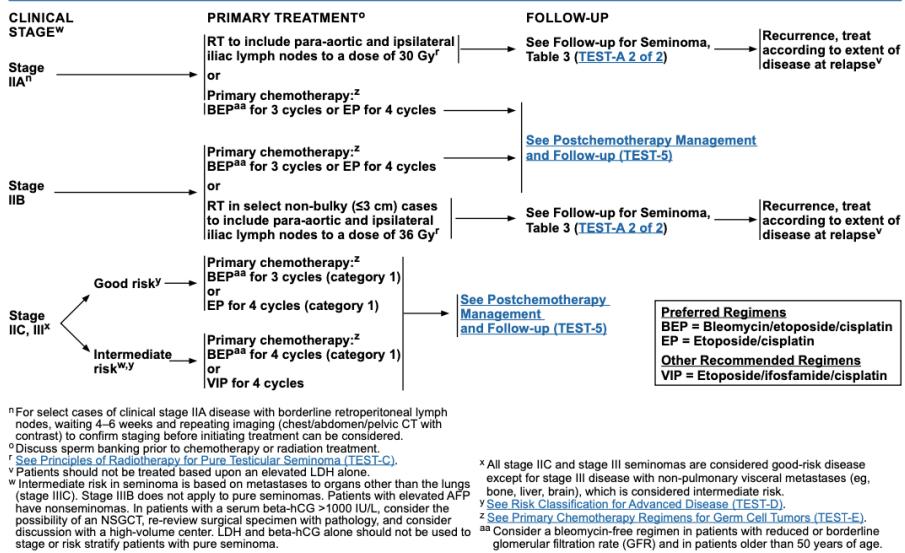


Figure 6: treatment of stage IIA, IIB, IIC, III Pure Seminoma

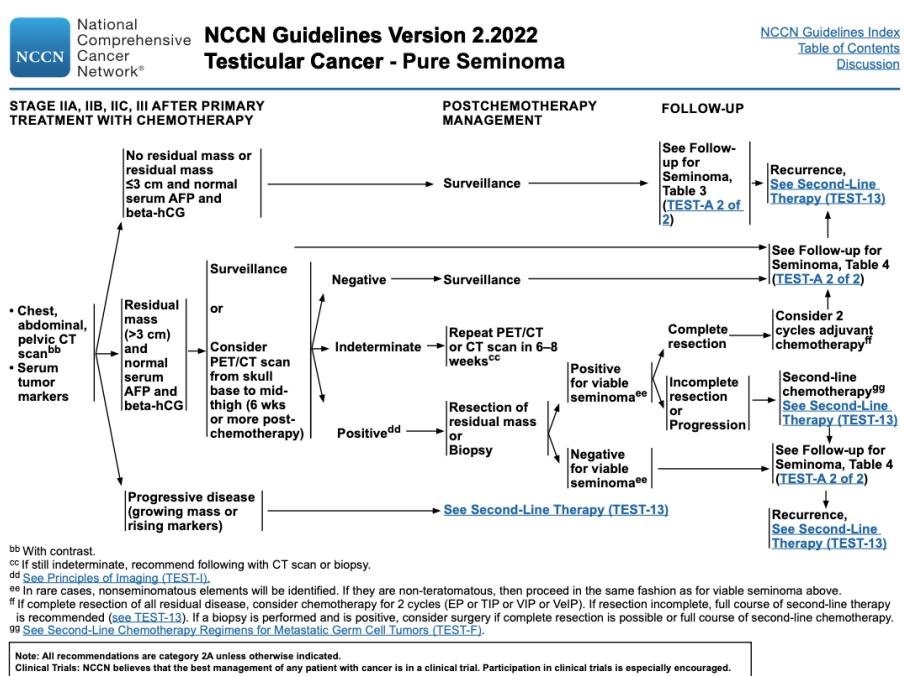


Figure 7: Treatment Strategy for post chemotherapy Stage IIA, IIB, IIC and III Pure Seminoma

7.2.1 Management of Stage IIC Seminoma

All stage IIC seminomas are good risk disease and therefore **the standard treatment is chemotherapy with 3 cycles of BEP or 4 cycles of EP**.^{31,18,46,79,80,81}

7.2.2 Management of Stage III Seminoma

Stage III seminomas are considered advanced GCTs and managed with primary chemotherapy

based on IGCCCG risk stratification. See section **7.4 Management of Advanced GCTs**

7.2.3 Management of Post-Chemotherapy Mass in Patients with Seminoma

Following first-line therapy for advanced seminoma, a post-chemotherapy mass persists in approximately 60-80% of patients.⁸² Pathology of these masses reveal 90% of patients have fibrosis and 10% have residual viable tumor. Due to the significant desmoplastic reaction related to treated seminoma, post-chemotherapy (PC) RPLND is technically challenging and in some cases not feasible.

Unlike NSGCT, the size of a residual post-chemotherapy mass is predictive of viable tumor. **In series of 104 patients, it was demonstrated that the presence of viable tumor was 3% vs 27% for masses < 3 vs ≥ 3 cm, respectively.⁸³** These characteristics of post-chemotherapy seminoma have led to a different management strategy compared to NSGCT. **The NCCN guidelines recommend surveillance of masses ≤ 3 cm, while masses > 3 cm can either be observed or be further evaluated with a 2-¹⁸fluoro-deoxy-2-D-glucose positron emission tomography (PET) scan performed at least 6 weeks after completion of chemotherapy. For FDG-avid masses, resection or biopsy is recommended or alternatively, PET/CT could be repeated in 8-12 weeks to assess for changes or persistence of FDG-avidity.** If the final pathology demonstrates viable tumor, 2 additional cycles of chemotherapy should be considered. In the case of incomplete resection of viable tumor, then 4 cycles of second-line chemotherapy is recommended.¹⁸ Many post-chemotherapy PET/CT scans show indeterminate FDG-avidity and in this case, repeat PET/CT or CT is recommended in 6-8 weeks.

The use of PET scans in the post-chemotherapy setting is based on the SEMPET study by De Santis and colleagues demonstrating a positive and negative predictive value of 100% and 96% respectively, in masses > 3 cm.⁸² It is important to note that **PET scans need to be performed at least 6 weeks post-chemotherapy** to avoid a false positive result. In contrast to the SEMPET study, more recently a large retrospective study demonstrated a post predictive value of only 23% of PET/CT for viable tumor in residual lesions after chemotherapy for advanced seminoma, calling into question the use of PET for clinical decision-making based in this setting.⁸⁴ Starting in 2018, the NCCN guidelines differed from past editions in the use of PET scan in the setting of post-chemotherapy masses >3cm, **permitting either further evaluation with PET CT with resection as indicated vs. surveillance.** The management of post-chemotherapy seminoma is depicted in Figure 7. The recommended follow-up schedule for seminoma after chemotherapy is presented in **Table 8a** and **Table 8b.**¹⁸

**Table 8a. Surveillance Schedule For Post-Chemotherapy/Radiotherapy Seminoma
(stage IIA , non-bulky stage IIB)**

Year	1	2	3	4	5
History and physical exam	3 mo	6 mo	6 mo	6 mo	6 mo
Chest x-ray	6 mo	6 mo	–	–	–
Abdominal/pelvic CT	At 3 mo, then 9 or 12 mo	12 mo	12 mo	As clinically indicated	As clinically indicated

Table 8b. Surveillance Schedule For Post-Chemotherapy Seminoma (bulky-stage IIB, stage IIC, stage III)

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

7.3 Management of Stage IIA/B NSGCT

See Figure 8

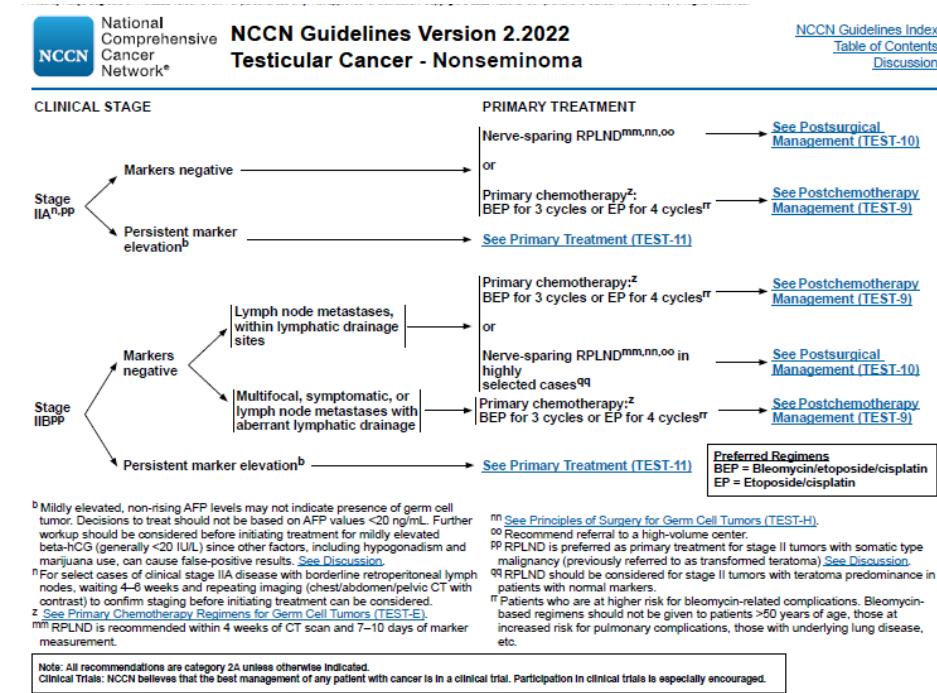


Figure 8: Management of Stage IIA and IIB NSGCT

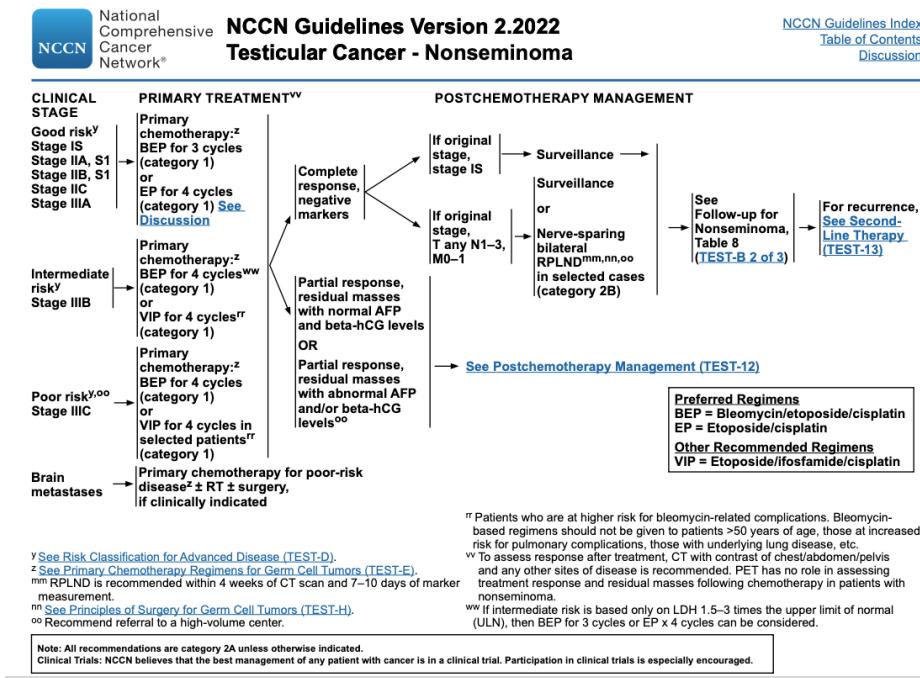


Figure 9: Primary chemotherapy for NSGCT.

7.3.1 Stage IIA NSGCT

Stage IIA can be treated with **primary chemotherapy consisting of 4 cycles of EP or 3 cycles of BEP**, however, for patients with **Stage IIA NSGCT with normal STM**, **primary RPLND** is an appropriate treatment option.^{18,46,85,86} As noted, all patients with elevated AFP or HCG levels

following orchiectomy should undergo primary chemotherapy.^{87,88}

Short interval reimaging with STMS and axial imaging of the chest, abdomen and pelvis should be considered in patients with a small retroperitoneal mass and negative markers following orchiectomy, since some proportion of these patients will have pN0 disease (or involution of nodes) and some people may develop overt metastases, and thus not benefit from locoregional treatment.

If primary RPLND is undertaken, principles of nerve-sparing RPLND should be followed if feasible, but **cancer control should never be compromised to preserve ejaculatory function**. Patients who have not previously undergone sperm-banking should be encouraged to do so prior to surgery. With appropriate surgical resection, 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%.**^{18,54,85,86}

- For pN1 disease, 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.⁵⁴
- **Chemotherapy with 4 cycles of EP or 3 cycles of BEP is recommended for pN3 disease given the nearly 100% relapse rate.**^{18,44,46}

As mentioned previously, recent data suggest that relapse rates for patients with pN2 and pN3 disease may be closer to ~20%, similar to pN1 patients, and that adjuvant treatment may be overtreatment in a significant proportion of patients.⁵⁵ Decision-making for adjuvant therapy should be made in multidisciplinary teams with expertise in GCT management. The rationale for primary RPLND in stage IIA NSGCT is 1) avoidance of chemotherapy in patients who are found to have pN0 disease, 2) resection of chemotherapy resistant teratoma, 3) cure rates that approach 85% with surgery alone, 4) surgical techniques that preserve antegrade ejaculation, 5) potentially avoiding post chemotherapy surgery. Conversely, upfront RPLND may not be widely available, and a proportion of patients will relapse after surgery.

7.3.2 Stage IIB NSGCT

Primary chemotherapy with 4 cycles of EP or 3 cycles of BEP may be used for IIB disease.

Following chemotherapy, post-chemotherapy RPLND (PC-RPLND) is recommended for any residual masses > 1cm on subsequent imaging in the setting of negative STM.

In select Stage IIB cases where the abdominal imaging reveals a solitary lesion in the primary landing zone and markers have normalized, RPLND is an option for primary treatment.^{18,46} **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%.¹⁸ The potential benefit of primary RPLND in these cases is the decreased overall amount of exposure to the chemotherapy and any associated long-term complications.

7.3.3 Stage IIC and III NSGCT

See **Figure 9**

Primary chemotherapy for IGCCCG good risk disease (3 cycles of BEP or 4 cycles of EP) is used for the management of patients with stage IIC (nodes greater than 5 cm) and IIIA NSGCT. Stage IIIB and IIIC NSGCT are treated with either 4 cycles of BEP or 4 cycles of VIP.

7.4 Management of Advanced GCTs

Treatment of advanced GCTs is based on the IGCCCG risk stratification (**Table 3**). The mainstay of treatment is **risk-stratified primary cisplatin-based chemotherapy**. Carboplatin is inferior to cisplatin for advanced GCTs. **There is no poor risk seminoma**. Contemporary outcomes for patients with advanced GCTs are summarized in **Table 9** based on a 2021 revalidation of the IGCCCG risk stratification in patients with seminoma and non-seminoma. **The IGCCCG has also recently produced a web-based calculator based on this updated analysis to estimate progression-free survival of patients with non-seminoma treated with first-line chemotherapy** (<https://www.eortc.org/IGCCCG-Update>). New risk factors were also validated including age and pulmonary metastases for non-seminoma, and LDH>2.5xULN for seminoma.^{27,28}

Side effects associated with chemotherapy may include fatigue, alopecia, nausea and vomiting (prophylactic antiemetics administered), myelosuppression and associated risk of infection and bleeding, nephrotoxicity, peripheral neuropathy, ototoxicity, venous thromboembolism, as well as Raynaud phenomenon and pulmonary toxicity (**baseline and surveillance pulmonary function tests are recommended**) associated with bleomycin, although clinically significant pulmonary toxicity is rare. Long-term chemotherapy-associated adverse events are increasingly recognized and include cardiotoxicity, metabolic syndrome, and secondary malignancy.

7.4.1 Good Risk GCT

The goal of treatment for these patients is to minimize toxicity yet maximize response. The two regimens include **4 cycles of EP or 3 cycles of BEP**.^{18,44,46}

7.4.2 Intermediate Risk GCT

The standard regimen is **4 cycles of BEP, or 4 cycles of VIP** (etoposide, ifosfamide, cisplatin) for patients who may not tolerate bleomycin.^{18,44,46}

7.4.3 Poor Risk GCT

Patients should be considered for a **clinical trial** if available, given poor outcomes in this patient population. The standard regimen used is 4 cycles of BEP. If bleomycin is not able to be used, then 4 cycles of VIP can be used.^{18,44,46}

Table 9. Distribution and Treatment Outcomes of Advanced GCTs

Risk Group	Features	5-yr OS	5-yr PFS
Risk Groups For Seminoma			
Good 90%	No organ metastases other than lung (-NPVM)	95%	89%
Intermediate 10%	+NPVM	88%	79%
Risk Group	Features	5-year Survival	5-year PFS
Risk Categories for Non-seminoma			
Good 60%	Meet all of the following: HCG<5,000; AFP<1,000; LDH<1.5xULN; primary site not the mediastinum, no NPVM.	92%	89%
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	48%	41%
NPVM: non-pulmonary visceral metastases ^{27,28}			

7.5 Post-Chemotherapy Management of NSGCT

Following chemotherapy for NSGCT, any evidence of radiographic disease (> 1 cm on axial imaging) in the setting of negative tumor markers should be resected.^{18,44,46,89,90,91} PC-RPLND is required in this setting since there are no reliable clinical or radiographic methods to predict retroperitoneal pathology. PET scanning has no value in the setting of NSGCT since teratoma is often not FDG-PET avid and therefore cannot be distinguished from fibrosis. Historically following PC-RPLND for NSGCT, the final pathology demonstrates fibrosis (~45%), teratoma (~45%), and viable tumor (~10%). At the time of PC-RPLND, if fibrosis or teratoma is found, then no further therapy is required, and patients are recommended to initiate guideline-recommended surveillance. If residual viable tumor is identified, observation, adjuvant chemotherapy with two cycles of conventional chemotherapy, or salvage chemotherapy may be employed.¹⁸ These decisions are difficult and should be made in the context of multi-disciplinary teams at high-volume centers, taking into account residual volume of viable GCT, completeness of resection, and post-surgical tumor markers.⁹²

If there is an incomplete response with persistently elevated markers and residual radiographic disease, second-line chemotherapy should be utilized. PC-RPLND should be performed in patients following salvage chemotherapy with normal markers. Rates of viable tumor in the retroperitoneum are much higher in the post-salvage setting (~50%) with necrosis and teratoma seen in ~20-25% each.^{4,93} A surveillance schedule for PC NSGCT patients is presented in **Table 10.**

Table 10. Surveillance Schedule For Post-Chemotherapy NSGCT+/- RPLND

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

7.6 Post-Chemotherapy Retroperitoneal Lymph Node Dissection

PC-RPNLD is frequently a technically more challenging operation than primary RPLND. This may be related to the size of the retroperitoneal mass, desmoplastic reaction around the great vessels, and potential need for reconstruction or the need for resection of adjacent organs. As such, **PC-RPLND should be undertaken by experienced surgeons**. Patients should be counselled that nerve-sparing may not be feasible or oncologically sound. While the surgical principles are similar to those for primary RPNLD, for large masses within the upper retroperitoneum, a thoracoabdominal incision may be needed for appropriate exposure. Another complicating factor in the care of these patients is **prior exposure to bleomycin and the potential resulting pulmonary toxicity which should be discussed with the anesthesia team**. This requires careful perioperative care by **avoiding high oxygen concentrations and conservative fluid replacement, favoring colloids over crystalloids**.

Major complications occur in up to 18% of patients undergoing PC-RPLND (compared to 8% for primary RPNLD).⁴ Potential complications include **chylous ascites** (2-3%), **renovascular injury** (2-3%), and **small bowel obstruction** (2-3%). The need for subsequent nephrectomy during PC-RPLND can be as high as 15% with the strongest predictors being a retroperitoneal mass greater than 10 cm and left-sided primary tumor.⁹⁴

7.7 Resection of Non-Retroperitoneal Metastatic NSGCT

While the retroperitoneum represents the most common site of metastases, GCTs can metastasize to the lung, liver, neck, mediastinum, bone and brain. Management of these masses is complex and requires multidisciplinary teams. Generally, if markers are confirmed to be rising, salvage chemotherapy is recommended. If markers are normal, surgical resection should be considered (i.e., for teratoma, malignant transformation, or chemotherapy-resistant disease). Even in the context of elevated/rising markers and non-retroperitoneal disease, surgical resection may provide durable control; these decisions should be made at experienced, high-volume centers.⁹⁵

The retroperitoneal and other metastatic sites may have **discordant pathology (15-45%)** and there is no reliable method to predict extra-retroperitoneal pathology. Below are site specific considerations.

Lung: 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.²¹ In the presence of high-volume pulmonary disease, resection of larger lesions should be prioritized since they are more likely to demonstrate teratoma or viable GCT, which may dictate management of other ipsilateral and contralateral lung lesions that are typically concordant.

Mediastinum: The location and burden of mediastinal disease dictate surgical approach. Lower, posterior mediastinal disease, such as retrocrural disease, can generally be managed by a urologic oncologists at the time of RPLND by splitting the diaphragmatic crus. Upper mediastinal disease is generally managed by thoracic surgeons.

Liver: Discordance between retroperitoneal and liver histologies is reportedly between 6 and 21%. The number, location, and size of liver metastases will largely dictate observation, biopsy, or surgical approach and timing of resection, which should be discussed in multidisciplinary teams.⁹⁶ If surgery is warranted, consideration for simultaneous liver resection should be made for these patients.⁹⁷

Neck: There is significant concordance between retroperitoneal and cervical pathology in germ cell tumor patients, approaching 75%.⁹⁸ Management of persistent post-chemotherapy cervical lymph nodes with resection is typically warranted. Radical, modified template, or mass excisions of the neck are all described and generally well tolerated either separately or concomitantly with resection of other sites.⁹⁹

Other sites: (Bone, brain): Surgical resection of other, less commonly involved non-retroperitoneal sites may be associated with significant morbidity and requires multidisciplinary input.

7.8 Recurrence following first-line chemotherapy for NSGCT

Relapse following chemotherapy for NSGCT is designated as **early or late relapse - defined by recurrence before or 2 years after completion of initial therapy**. Patients relapsing within 2 years should receive second-line/salvage chemotherapy. 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%.**⁴ These relapses tend to be chemo-resistant and are often managed surgically.

8. Second Line and Subsequent Therapy

Patients with disease relapse after first-line chemotherapy (within 2 years) and those who do not experience a durable complete response to first-line therapy should receive second-line therapy. **A high proportion of patients who recur after standard chemotherapy will remain curable with second- or third-line treatment strategies**. If tumor markers are elevated and persistently rising after primary chemotherapy, a full course of second-line chemotherapy should be completed. Options for second-line therapy include clinical trials (*preferred), conventional dose chemotherapy, or high-dose chemotherapy with stem cell rescue.

Second-line conventional dose chemotherapy regimens combine **cisplatin and ifosfamide with vinblastine or paclitaxel**.^{18,46,100,101} **The most commonly used salvage regimens include: paclitaxel, ifosfamide, cisplatin (TIP); and vinblastine, ifosfamide, cisplatin (VeIP). High-dose chemotherapy with autologous stem cell transplant with preparative regimens such as carboplatin and etoposide have also demonstrated efficacy.**^{102,103,104} There is an actively accruing randomized phase III trial comparing high dose chemotherapy with TICE (paclitaxel, ifosfamide, carboplatin, etoposide) plus stem cell transplant versus TIP (TIGER trial). Patients who respond completely to second- and third-line systemic therapy (e.g. no residual masses) may be followed with surveillance vs. PC-RPLND, while **post-chemotherapy surgery is indicated in patients with residual masses with negative STM**. Rarely, relapsed or refractory GCTs have microsatellite

instability or mismatch repair deficiency and **pembrolizumab** has recently been added to NCCN guidelines as a treatment option for these patients.¹⁰⁵

8.1 Salvage Surgery

PC-RPLND may be necessary and therapeutic in certain high-risk populations such as in salvage, desperation, or late relapse settings. A salvage PC-RPLND is often defined as an operation performed after salvage chemotherapy in a man with a persistent or growing residual disease and negative serum tumor markers. Surgery is indicated in this setting due to the increased risk of active cancer in the residual mass (~30-50%) when compared to PC-RPLND after first-line chemotherapy. Long-term OS in these patients, despite some level of platinum resistance and more aggressive biology, is 60-75%.

In some cases, surgical resection may be employed in patients with refractory GCTs e.g. in the case of **elevated or rising serum tumor markers as well as in cases of incomplete response to second-line chemotherapy and resectable metastases (“desperation” RPLND)**.¹⁸ There have been reports of durable responses in up to 50% with best results occurring in men with elevated AFP (opposed to bHCG), declining or slowly rising STM and disease confined to the retroperitoneum which can be completely excised^{46,106,107,108}

Late relapses are defined as relapses which occur >2 years after an initial complete response. As noted above, these recurrences are rare (~3%) and mostly recur within the retroperitoneum. Yolk sac tumor is the dominant histology of LR. Surgical excision, when localized, is the preferred management option due to the chemorefractory nature of the disease. Chemotherapy is reserved for widespread metastasis or unresectable disease. Overall survival after LR RPLND approaches 60% in select cases.¹⁰⁹

Surgery in any of these high-risk scenarios is best directed by a multidisciplinary approach and should only be performed by experienced surgeons in centers of excellence.¹¹⁰

8.2 Brain Metastases

Brain MRI with and without contrast should be considered in patients at diagnosis of GCTs if clinically indicated. This includes all patients with bHCG levels >5000, non-pulmonary visceral metastatic disease, extensive lung metastasis, or neurologic symptoms. For patients with NSGCT, brain MRI should also be performed at diagnosis for choriocarcinoma or AFP>10,000.

Prognosis is poor in patients with brain metastases. Treatment should include primary chemotherapy with or without RT or surgical resection.¹⁸ Prospective trials on management of patients with brain metastases are lacking, but cures are possible with a multimodality approach.¹¹¹

Brain MRI should be considered in patients with elevated or rising markers after primary or secondary chemotherapy to evaluate for occult brain metastases, since the brain is commonly the only site of progression for patients with poor risk NSGCT.¹¹²

9. Sex Cord Stromal Tumors

9.1 Epidemiology

This group of testicular tumors are derived from **Leydig, Sertoli, and Granulosa cells**. Together, they represent approximately **5% of testicular tumors**. Because of their low incidence, minimal data exists regarding the natural history of these tumors and therefore, recommended treatment for these tumors remains based on limited clinical experience. Due to the limited data on these tumors, this section will focus only on Leydig and Sertoli cells tumors.

Recent evidence has shown the median age for patients with sex cord stromal tumors was 45 compared with germ cell tumors at age 34.¹¹³ **Leydig cell tumors also have a bimodal age distribution with peaks between age 5-10 and then again later in adulthood.**¹¹⁴ Another striking difference between sex cord stromal tumor and germ cell tumors was the significant racial differences **with 17% of sex cord tumors found in non-Hispanic Blacks compared with 3% in germ-cell tumors.**¹¹³

Overall, Leydig cell tumors comprise 1% of testicular tumors, but are the single most common sex cord stromal tumor, occupying 75% of the diagnoses in this group. The second most common sex cord stromal tumor is Sertoli cell, although they are still quite rare, representing only 0.4-1.5% of testicular masses.¹¹⁵

9.2 Presentation and evaluation

Similar to GCTs, most patients with sex cord stromal tumors present with a palpable testicular mass. Prepubertal patients with **Leydig cell tumors often present with virilization while 20-40% of adults will present with feminizing signs including gynecomastia, loss of body hair, and testicular and prostatic atrophy**¹¹⁴ Sertoli cell tumors can also present with gynecomastia and typically present with **a painless scrotal mass.**¹¹⁶

Evaluation of patients with a scrotal mass involves history and physical exam, screening for endocrine related changes, as well as scrotal ultrasound as the initial diagnostic study. Testicular tumor markers (AFP, HCG, LDH) should be obtained also.

9.3 Initial Treatment

Radical inguinal orchiectomy is the standard treatment option for patients with suspected testicular tumors. When a sex cord stromal tumor is identified, metastatic staging workup is required with CT scans of the chest, abdomen, and pelvis.

Patients present with Stage I disease 93% of the time compared with 77% for germ-cell tumors.¹¹³ Unfortunately, 5-year overall survival for patients with Stage I disease is 91% for patients with Leydig cell tumors and 77% for Sertoli cell tumors which is significantly worse when compared with germ-cell tumors.¹¹⁷

9.4 Adjuvant Treatment

There are limited data available to guide adjuvant therapy decisions in patient with sex cord stromal tumors. The combination of low incidence as well as lack of agreed upon pathologic criteria defining

malignancy in these tumors leads to treatment decisions based upon limited data.¹¹⁸

Small series of patients who have undergone adjuvant therapy have been published. **Leydig cell tumors appear to be radio-resistant**¹¹⁹ while there may be some benefit in Sertoli cell tumors.¹²⁰ **Chemotherapy also appears to have limited efficacy.**¹¹⁶

Retroperitoneal lymphadenectomy (RPLND) has also been reported on a limited basis. For patients who have proven Stage I disease after RPLND there has been excellent survival with questionable utility in patients with Stage IIB and above.¹¹⁸

Numerous chemotherapy and hormonal agents have been used in patients with metastatic disease with limited benefit and **most patients die of disease within 2 years.**

10. Survivorship

See AUA Core Curriculum **Cancer 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.

All men receiving a diagnosis of GCT should be counseled regarding the increased risk of **subfertility** associated with definitive treatments and should be recommended to consider sperm-banking prior to definitive therapy. Overall, GCT is also associated with an increased risk of **hypogonadism** in 10-15% of patients, with an adjusted OR of 2.0, 4.8-7.9, and 3.5 following orchectomy, chemotherapy, and radiation therapy respectively. **Up to 15% of testis cancer patients may require testosterone supplementation following definitive therapy.**¹²¹

Long-term complications of therapy for patients with GCTs are dependent on the treatment modalities received and survivorship care plans should be individualized and comprehensive. Receipt of chemotherapy is associated with long-term **cardiovascular disease, metabolic syndrome, secondary malignancies, infertility, as well as other late effects of treatment including hearing loss, kidney dysfunction, and peripheral neuropathy.** Bleomycin can cause Raynaud's phenomenon and pulmonary toxicity. Particular attention needs to be paid to the risk of secondary malignancies as recent data suggests a 1.5-fold increase among patients treated for seminoma and 2.2-fold increase for patients treated for NSGCT. The impact of therapy was dose dependent and related to chemotherapy and/or radiotherapy, and no increased risk was seen in patients treated with surgery alone. ¹²² This highlights the importance of the appropriate use of surveillance and RPLND when possible and long term follow up should focus on monitoring for these late effects of cancer and its treatment. Additionally, many survivors of GCTs experience ongoing psychological distress, chronic fatigue, body image disturbance, anxiety, and depression.

Survivorship care plans should include counseling on the elevated recurrence risk and any need for cancer-specific follow-up. Additionally, patients should be screened for known risk factors such as hypertension, hyperlipidemia, and testosterone deficiency. A healthy lifestyle should be promoted including physical activity, avoidance of smoking, and minimization of noise exposure.

Videos

ROBOTIC RETROPERITONEAL LYMPH NODE DISSECTION FOR TESTICULAR CARCINOMA

Robotic Retroperitoneal Lymph Node Dissection for Stage 1 Non-Seminomatous Testicular Cancer: Technically Feasible with Left and Right Modified Templates

Open Retroperitoneal Lymph Node Dissection (split/roll technique)

Presentations

Testis Neoplasms Presentation 1

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