

Germ Cell Testicular Tumors—Contemporary Diagnosis, Staging and Management of Localized and Advanced disease



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Germ cell testicular tumors are the most commonly diagnosed cancer in young men, with cure rates exceeding 95%. Clinical stage 1 disease is the most common manifestation, with radical orchiectomy curing the majority of Clinical stage 1 patients, making active surveillance the treatment of choice, with a cancer specific survival nearing 100% and low relapse rates. However, in metastatic disease, chemotherapy, radiotherapy, and surgery are curative options. Chemotherapy remains the mainstay of therapy for advanced disease with surgical management of residual disease. Patients with advanced disease should be treated in high volume experienced academic centers with multidisciplinary teams. Research exploring refinement of diagnosis and treatment, and lowering treatment burden is underway. *UROLOGY* 125: 8–19, 2018. © 2018 Elsevier Inc.

The incidence of germ cell testicular tumors (GCTT) in the United States of America has been rising 0.8% per year over the last decade and is currently 5.7 per 100,000 men per year.¹ Approximately 1 of 250 men will be diagnosed with GCTT during their lifetime, most frequently aged 20–34, representing 0.5% of all new cancer cases. Treatment is most effective and overall mortality is low and has been stable from 2004 to 2013 at 0.3 per 100,000 men per year.¹ The 5-year survival for those with localized, regional, and distant metastatic GCTT is 99.2%, 96%, and 73%, respectively.² There has been stage migration with more patients presenting with clinical stage 1 (CS1) disease.³

Known GCTT risk-factors include a previous primary GCTT, cryptorchidism, family history, the premalignant stage of germ cell neoplasia in situ (GCNIS), race, geography, environmental exposure, and infertility.

GCTT constitute approximately 95% of all testicular tumors and histologically include seminoma and nonseminoma (52% and 48%, respectively) or a mixture. Mixed GCTT will always be managed as nonseminoma. Age of onset of the different histologies varies, as do the expected serum tumor marker (STM) levels ([Supplemental table 1](#)).

Bilateral GCTT occur (1%–5%), usually metachronously.⁴ Approximately 5% of GCTTs are extragonadal,⁵ usually midline and in the retroperitoneum, mediastinum, or cerebrum.

MATERIALS AND METHODS

We searched PubMed for available literature on testicular tumors and GCTT, focusing on incidence, diagnosis, pathology, staging, treatment, follow-up, and future research directions. Search terms included “testicular cancer,” and “germ cell testicular tumors”. References from review articles and guidelines were also assessed to develop a narrative review. No limits were set on publication date, but non-English language, nonhuman studies, editorials/letters, and case reports were excluded.

DIAGNOSIS

Signs and Symptoms

The most common presentation is a painless testicular mass with a differential diagnosis including hydrocele, varicocele, spermatocele, hematoma, and inguinal hernia.⁶ Pain occurs in 20% of patients due to intratumor hemorrhage or infarction and must be distinguished from painful epididymitis/orchitis and testicular torsion. Other uncommon presentations include gynecomastia (7%) or nipple tenderness. In advanced cases, weight loss, palpable masses, back or flank pain (11%)⁷ can occur with pulmonary, gastrointestinal, or neurologic symptoms.⁶

Imaging

Scrotal ultrasound is highly sensitive for detecting the usually hypoechoic vascular tumor ([Supplemental](#)

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Figure 1). Rarely, GCTT may present with wide spread metastasis with no detectable⁸ or “burned-out” primary tumor.

For staging, chest with abdominopelvic computed tomography (CT) are performed. CT scans are sensitive for macroscopic retroperitoneal lymph nodes (RLN) which are the most common initial site of metastases (Supplemental Figure 2). Bone scans, spinal or brain CT/MRI, and Positron emission tomography (PET) scans are rarely indicated.

Serum Tumor Markers

The STMs α -fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase are most useful in diagnosis and management (Supplemental table 1). Elevation of 1 or more markers is usually diagnostic. Approximately 10%-15% of seminomas secrete hCG, however, AFP is never secreted.⁹ STMs may be elevated at the time of radical orchiectomy (RO) and must be serially monitored until they normalize or reach a nadir baseline. The half-lives for AFP, hCG, and lactate dehydrogenase are 5-7, 1-3, and 4-4.5 days, respectively, requiring measurements for up to 4 weeks after RO or until normalization.

PATHOLOGY

Seminoma

Seminomas constitute 60% of GCTT and histologically 95% are classical type. These tumors contain large uniform cells with a “fried egg” appearance.¹⁰ Syncytiotrophoblasts are present in 10%-15%, accounting for the elevated hCG levels.

Spermatocytic seminoma is rare (<1%) and originates from more mature germ cells, with unique genetic and morphologic signatures. It typically presents in older men (mean age of 54 years) and cryptorchidism is not a risk-factor.¹¹ They have low malignant potential; and are usually cured by RO. Classic seminoma metastasizes via lymphatic spread to the RLN if lymphatic flow has not been altered by previous inguinal or scrotal surgery. Although rare, advanced seminoma can present with supra-diaphragmatic lymphadenopathy or visceral metastases in the lung, liver, brain, and other sites. Seminoma has a relatively favorable prognosis and only liver and brain metastasis have been associated with an adverse prognosis.¹²

Nonseminoma

These typically manifest at a younger age than seminoma, peaking at 20–24 years and contain various subtypes.

Embryonal carcinoma (EC): Usually smaller than seminomas with poor demarcation. Histologically, they are epithelial with clusters or sheets of cells that exhibit cytological atypia; and stain for OCT3/4, SOX2, NANOG, and SALL4. EC is an aggressive tumor associated with metastasis, even when STMs are normal. This is the most undifferentiated cell-type of nonseminoma, with a total potential capacity to differentiate to other cell types.

Yolk sac tumors (YST): Harbor a shiny surface and often display lower nuclear grade and are the most varied in appearance. YST tumors stain for SALL4, AFP, and GATA3. Although rare, they are more common in the mediastinal and pediatric GCTTs.¹³ Schiller-Duval bodies, which resemble endodermal sinuses, manifest in roughly half of cases. Cytoplasmic and extracellular eosinophilic hyaline globules are another characteristic present in 84% of cases. YST usually produce AFP but not hCG.

Choriocarcinoma: Exhibit hemorrhagic features with microscopic necrosis; composed of both syncytiotrophoblast and cytotrophoblast. This is a rare, aggressive tumor with highly elevated hCG and hematogenously disseminated disease; commonly classified as poor-risk at diagnosis.

Mature Teratoma: Well-differentiated or have incompletely differentiated elements of at least 2 of the 3 germ cell layers: endoderm, mesoderm, and ectoderm. There are solid with cystic areas and STMs are usually normal or AFP is mildly elevated. Approximately 47% of adult mixed GCTTs contain teratoma but pure teratomas are uncommon.¹⁴ They are histologically benign but are frequently found at metastatic sites and are chemoresistant. Teratomas have many genetic abnormalities, including aneuploidy, i (12p), and widely variable proliferative capacity; they may grow and involve surrounding structures to become unresectable¹⁵ (“Growing teratoma syndrome”).¹⁵ Rarely, teratoma may undergo a malignant somatic transformation to rhabdomyosarcoma, adenocarcinoma, or primitive neuroectodermal tumor, which are highly aggressive, chemoresistant, with poor prognosis.

STAGING

Patterns of Metastasis

Most GCTT (90%) which metastasize, do so lymphatically in a predictable pattern. Right-sided tumors spread to the precaval and interaortocaval lymph-nodes, while left-sided tumors spread to the para-aortic nodes. Location and node size are important for staging accuracy. The most common sites of spread are the RLN (75%), lungs (9%),⁸ followed by liver, brain, and bone.

Stage Groups and Relative Incidence

Clinical stage is assigned on imaging assessment of potential regional nodal and distant metastatic sites. According to the American Joint Committee of Cancer eighth edition of the TNM classification (Table 1), CS1 GCTTs have no evidence of metastases, with stage IA primary tumors confined to the testis without lymphovascular invasion and stage IB tumors demonstrating lymphovascular invasion or disease extending outside of the testis. Stage II GCTTs have RLN involvement only and stage III GCTTs have distant metastasis (Table 1).

The International Germ Cell Cancer Collaborative Group (IGCCCG) in 1997 developed a prognostic system for advanced GCTT¹⁶ based on histology, primary site, metastatic disease, and STMs. Patients are categorized into

Table 1. (a) TNM classification for testicular cancer (AJCC, 2018, eighth edition.), (b) Tumor stage grouping of TNM subsets for germ cell testicular tumors, (c) IGCCCG Staging system for metastatic germ cell testicular tumors

<i>(a)</i>				
Primary Tumor (T)				
TX	The primary tumor cannot be assessed.			
T0	There is no evidence of primary tumor.			
Tis	Carcinoma in situ (noninvasive cancer cells).			
T1	Tumor limited to the testis (including rete testis) without lymphovascular invasion			
	T1a—Tumor smaller than 3 cm (applies only to pure seminoma)			
	T1b—Tumor larger than 3 cm (applies only to pure seminoma).			
T2	Tumor limited to the testis (including rete testis) with lymphovascular invasion			
	OR			
	Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without vascular invasion.			
T3	Tumor invades the spermatic cord with or without lymphovascular invasion.			
T4	Tumor invades scrotum with or without lymphovascular invasion.			
Lymph Node (N)				
NX	Regional lymph nodes cannot be assessed.			
N0	No regional lymph node metastasis.			
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to 5 nodes positive, none more than 2 cm in greatest dimension.			
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or more than 5 nodes positive, none more than 5 cm; or evidence of extra-nodal extension of tumor.			
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension.			
Metastasis (M)				
M0	No distant metastasis.			
M1	Distant metastasis			
	M1a—Nonretroperitoneal nodal or pulmonary metastasis			
	M1b—Nonpulmonary visceral metastasis			
Serum Tumor Markers (S)				
	LDH (U/L)	HCG (mIU/mL)	AFP (ng/mL)	
SX	Not available	Not available	Not available	
S0	Normal	Normal	Normal	
S1*	<1.5 × Normal	<5000 (mIU/mL)	<1000 (ng/mL)	
S2*	1.5-10 × Normal	5000-50,000 (mIU/mL)	1000-10,000 (ng/mL)	
S3*	>10 × Normal	>50,000 (mIU/mL)	>10,000 (ng/mL)	
<i>(b)</i>				
Stage	T	N	M	S
Stage 0	Tis (in situ)	N0	M0	S0
Stage I	T1-T4	N0	M0	SX
Stage IA	T1	N0	M0	S0
Stage IB	T2-T4	N0	M0	S0
Stage IS	Any T	N0	M0	S1-S3
Stage II	Any T	N1-N3	M0	SX
Stage IIA	Any T	N1	M0	S0-S1

Continued

Table 1. Continued

(a)				
Primary Tumor (T)				
Stage IIB	Any T	N2	M0	S0-S1
Stage IIC	Any T	N3	M0	S0-S1
Stage III	Any T	Any N	M1	SX
Stage IIIA	Any T	Any N	M1a	S0-S1
Stage IIIB	Any T	N1-N3	M0	S2
Stage IIIC	Any T	Any N	M1a	S2
	Any T	N1-N3	M0	S3
	Any T	Any N	M1a	S3
	Any T	Any N	M1b	Any S
(c)				
Prognosis group Seminoma			Nonseminoma	
Good	There are no distant metastases other than to the lungs. AFP is normal and other serum tumor markers can be any level.		The primary tumor is in the testicle, or a primary extragonadal tumor is in the retroperitoneum. There are no distant metastases other than to the lungs. All serum tumor markers are normal (S0) or slightly above normal levels (S1).	
Intermediate	There are distant metastases to organs other than the lungs. AFP is normal and other serum tumor markers can be any level.		The primary tumor is in the testicle, or a primary extragonadal tumor is in the retroperitoneum. There are no distant metastases other than to the lungs. At least 1 serum tumor marker level is high (S2).	
Poor	This group isn't used for seminomas.		One of the following applies: <ul style="list-style-type: none"> • There is a primary extragonadal tumor in the mediastinum (the area between the lungs). • There are distant metastases in organs other than the lungs. • At least 1 serum tumor marker level is very high (S3). 	

AFP, alpha-fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.

* All the markers must be in the stated range to be considered S1.

+ Only 1 marker needs to be in the stated range to be considered S2 or S3.

either good, intermediate, or poor prognostic groups¹⁶ with >90%, 75%, and 50% cure rates, respectively (Table 1c).

INITIAL MANAGEMENT OF THE PRIMARY TUMOR

Radical Orchiectomy

RO includes an inguinal orchidectomy with the removal of the spermatic cord to the internal inguinal ring; being both a therapeutic and diagnostic procedure. It cures >80% of men with CS1 seminoma and 70% CS1 nonseminoma. Scrotal violation by trans-scrotal orchiectomy or biopsy may risk local tumor seeding with recurrence, and pelvic or inguinal lymph node metastasis.

Contralateral Testicular Biopsy During Orchiectomy

GCNIS is considered to be the premalignant lesion for most GCTTs (except YST, mature teratoma, or spermatocytic seminoma)¹⁷ with 40% developing GCTT within 3 years and 50% within 5.¹⁸ Loss of PTEN, p18 expression, and gain of chromosome 12p have all been associated with progression of GCNIS to GCTT.¹⁹ GCNIS occurs in $\leq 1\%$ of normal males. Risk-factors include history of contralateral GCTT, an atrophic contralateral testis (highest if age <31), male-factor infertility, cryptorchidism, disorders of sexual differentiation, and testicular microlithiasis.²⁰ The European Association of Urology (EAU) guidelines recommend contralateral testicular biopsy in patients with GCTT and, (i) contralateral testicular volume <12 mL, (ii) history of cryptorchidism or poor spermatogenesis, and, (iii) age <40 years.²¹ Some European centers perform routine contralateral testicular biopsies during RO with the philosophy that early detection and radiation treatment (RT) of GCNIS will better preserve hormonal function than future RO.²² However, in North-America, testicular biopsy is recommended only in patients with unilateral GCTT and concomitant risk-factors for contralateral disease.²² Routine contralateral biopsy is not supported in this region, as recurrence can occur following radiotherapy, with hypogonadism reaching up to 40%.²³

Partial Orchiectomy

Partial orchiectomy (PO) should be considered for patients with bilateral masses, solitary testis tumors, or suspected benign mass. Typically, PO is indicated for small organ confined tumors, <2 cm, preferably in a polar location, and away from the mediastinum testis. PO should be applicable for tumors that can be removed with sufficient remaining testicular tissue for endocrine function.²⁴ Favorable outcomes (survival with preserved endocrine function and fertility) have been reported in experienced centers, although local recurrence rates may reach 27% without adjuvant RT.²⁴ The overall survival (OS) rates for bilateral disease are comparable with those with unilateral disease, and long-term testosterone production was preserved in 90% of patients at 7-year follow-up.²⁵

Semen Cryopreservation

GCTT can result in infertility, by the malignancy itself or the associated treatments.²⁶ Pre-existing subfertility in patients with GCTT further lowers their success in future reproduction. Sperm cryopreservation is a widely available reproduction option for cancer patients.²⁷ The American Society of Clinical Oncology guidelines recommend that patients of reproductive age are referred for semen cryopreservation before treatment,²⁸ ideally before undergoing RO, but definitely before chemotherapy and radiotherapy.²⁹ However, sperm preservation rates in cancer patients are low with an even lower usage of preserved sperm (<10%),³⁰ caused by sociologic and psychological factors.³¹

MANAGEMENT BY STAGE

Clinical Stage I Seminoma

Accounts for 80% of new seminomas with cancer specific survival (CSS) approaching 100% regardless of initial therapy.³² Treatment options include active surveillance (AS) or adjuvant therapy with chemotherapy or radiation. The use of AS has increased to minimize the potential late effects of adjuvant treatment while maintaining high cure-rates.

Approximately 15% of CS1 patients have subclinical metastatic disease and will progress on AS, usually in the RLN, making adjuvant treatment unnecessary in approximately 85% of patients.²¹ Large primary tumor size (>4 cm) and rete testis invasion have been controversially identified as risk-factors for relapse.³³

AS now represents the preferred management approach in most guidelines.^{21,34,35} Several trials have shown an almost 100% CSS rate³⁶ with relapse risk (RRs) between 13%-19%. Approximately 99% of the relapses are cured with radiation and/or chemotherapy.

Typical surveillance protocols include periodic physical examination, STMs, chest radiographs, and abdominal CT imaging. Over 90% of relapses occur in the RLN during the first 3 years of AS and are detected by abdominal CT (87%).³⁶ Suboptimal compliance with follow-up has not been demonstrated to reduce OS.¹⁰

Adjuvant chemotherapy with single-dose carboplatin reduces RRs to 1.8%-8.6%,³⁷ and is an accepted alternative to AS. The MRC TE19 trial demonstrated noninferiority for adjuvant carboplatin compared to radiation with a 5-year RR of 5.3% vs 4%.³⁸ Recurrence usually occurs in the RLN, making abdominal surveillance imaging mandatory. Relapse after adjuvant carboplatin may be treated with salvage radiotherapy, cisplatin-based chemotherapy,¹⁰ or retroperitoneal lymph-node dissection (RPLND) if the recurrence manifests as a small retroperitoneal mass.³⁹

Adjuvant RT to the RLN has been the mainstay treatment historically. The traditional approach was a total dose of 25 Gy in 20 fractions to the paraaortic and ipsilateral pelvic nodes (with a dog-leg field) which achieved a CSS rate of nearly 100%. When relapse

occurs, treatment includes bleomycin+etoposide +cisplatin (BEP)*3 or etoposide+cisplatin (EP)*4, with excellent cure rates.¹⁰ However, adjuvant radiotherapy is not recommended due to its higher risk of induced second nongerm cell malignancies.^{21,40,41} Following a median follow-up of almost 22 years, radiotherapy for early-stage seminoma was found to increase secondary neoplasms in the organs within the radiation field by 53%, resulting in CSS decrease of 46%.⁴⁰

Clinical Stage 1 Nonseminoma

Accounts for 20% of new nonseminomatous GCTT and the majority are cured by RO alone. However, 20%-30% have occult retroperitoneal or distant metastases and will relapse if managed by AS.⁴² Most occur within 2 years but late relapses (LR) beyond 5 years have been documented in 1%-5% of cases.³ Relapse occurs in approximately 15% of low-risk patients and up to 50% of high-risk patients.⁴³ Adjuvant treatments will be unnecessary in approximately 70% of patients.⁴² Long-term data supports nonrisk-adapted surveillance which achieves long-term survival outcomes comparable with adjuvant chemotherapy and RPLND.

Two independent histologic features in primary CS1 nonseminoma tumor have been demonstrated to be risk-factors for occult metastatic disease:

- LVI in the primary tumor carries a 48% 5-year RR vs 14%-22% in patients without LVI⁴⁴
- Pure EC⁴⁵—45%-90% RR

The RR in patients on AS decreases over time after RO. This has been termed conditional risk of relapse.⁴⁶ However, universal AS (without risk-stratification) with delayed therapy for relapse is commonly considered the standard of care.⁴² Most follow-up protocols involve frequent monitoring in years 1 and 2 with clinical assessment, STMs, chest imaging, and abdominal-pelvic imaging.⁴⁷ The standard approach for AS patients relapsing is chemotherapy, according to IGCCCG risk group. Select patients with normal STMs and nonbulky RLN disease (<3 cm) may be considered for RPLND. This should be offered only to patients who refuse surveillance and have a contraindication to adjuvant chemotherapy. Patients should be treated with chemotherapy if they have persistent elevated STMs, bulky retroperitoneal disease with rapid progression, symptomatic tumor-related back pain, or adenopathy in the supra-hilar or pelvic regions, or tumor association with the renal hilum. These should all exclude patients from undergoing RPLND.⁴⁸ Due to the high CSS rates in AS with salvage treatment, and low relapse rates if adjuvant chemotherapy is given, the role of RPLND has diminished significantly. RPLND has a 7% higher risk of recurrence when compared to adjuvant chemotherapy,⁴⁹ with no differences in quality of life.⁵⁰

Adjuvant chemotherapy as an alternative to AS with BEP*2 was introduced in the prospective MRC trial⁵¹ with excellent results and reduction of short- and long-term

morbidity. BEP*1 also significantly increases the 2-year recurrence-free survival to 99.4% compared to primary RPLND.⁴⁹ Despite the excellent results achieved with primary chemotherapy, it has several important drawbacks:

- 70%-80% of patients are unnecessarily treated.
- Early and late toxicities.
- Chemotherapy is ineffective against teratoma.
- Follow-up abdominopelvic CT imaging is required.
- Relapse after chemotherapy poses a challenge, because it may be resistant to conventional chemotherapy.

An alternative to chemotherapy is primary RPLND, with the following supporting its justification:

- Systemic disease (outside of the retroperitoneum) is rare in CS1.
- RPLND provides pathologic staging of the retroperitoneum and the risk of subsequent abdominopelvic relapse is reduced to $\leq 2\%$, eliminating the need for routine surveillance imaging.
- With pN1 disease, cure rates after RPLND monotherapy exceed 75%.⁵²
- Metastatic teratoma is chemoresistant and curable with surgery alone.
- RPLND with nerve-sparing no longer results in loss of antegrade ejaculation.
- Patients who relapse after RPLND can be effectively salvaged with chemotherapy.
- Unlike systemic chemotherapy, RPLND has minimal short- and long-term morbidity, when performed by experienced surgeons at high-volume centers.

The anatomic limits of a full bilateral template RPLND include the skeletonized renal vessels and crus of the diaphragm. The lower limits include the external iliac vessels on the ipsilateral side and the bifurcation of the great vessels on the contralateral side. Prospective identification and preservation of the postganglionic fibers exiting the sympathetic chain is the objective of the nerve-sparing RPLND resulting in ejaculation preservation $\geq 95\%$ of cases. "In field" recurrence after RPLND is rare (1%-2%) beyond 2 years.⁴² The risk of recurrence with a modified smaller template is considered by some to be sufficiently high to require follow-up CT imaging, thus negating 1 of the principle benefits of RPLND over surveillance. While some experts agree (including our own group) that a full bilateral template is preferred,⁵³ others support the merit of either a full bilateral or modified template in low-stage disease.⁴²

RPLND has a very low mortality rate (<1%), but the overall complication rate has been reported as 10.6%-24%.⁵⁴ Complications include a 1% risk of bowel obstruction, 18% risk of ileus, a 0%-1.7% risk of lymphocele and a 0.2%-2.1% risk of chylous ascites. Pulmonary embolism and deep vein thrombosis occur in $\leq 1\%$ of cases. [Figure 1](#) summarizes CS1 GCTT therapy according to the EAU guidelines.

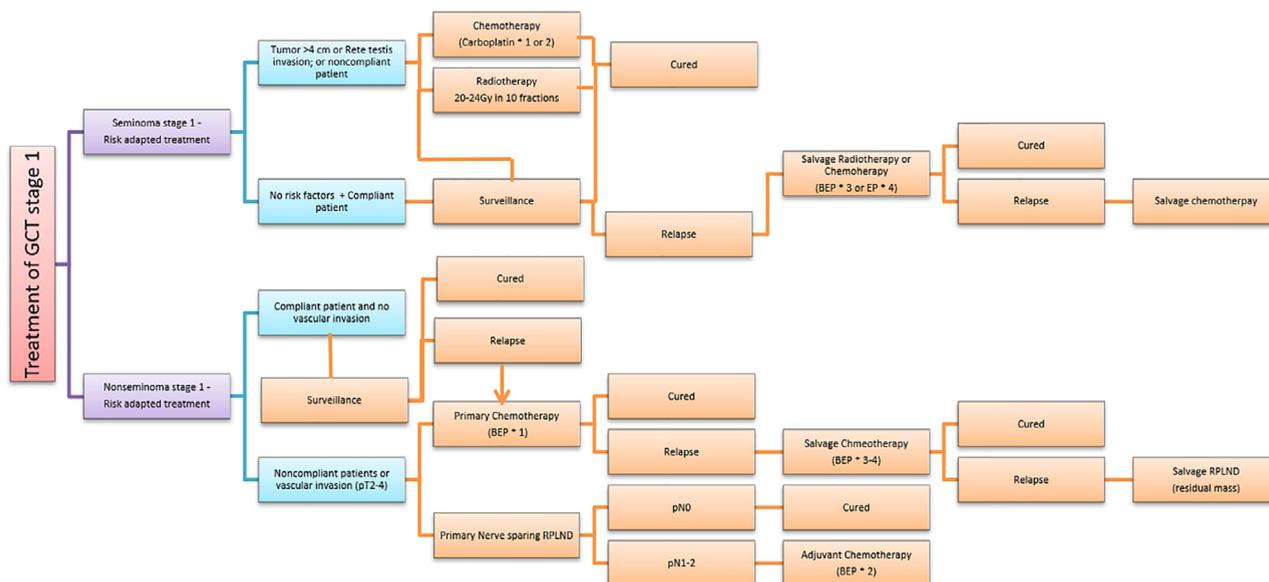


Figure 1. Stage 1 GCTT treatment adapted from the EAU guidelines 2018. (Color version available online.)

Clinical Stage 2A/B Seminoma

The preferred treatment option for low-volume disease (confined to the retroperitoneum with RLN <3 cm) is radiation, with a dose of 30-36 Gy, including a concurrent boost to the gross nodal volume of 10 Gy in 20 fractions. This yields relapse-free survival of 92% for stage IIA and 90% for stage IIB, with OS approaching 100%.⁵⁵

Chemotherapy with BEP*3 or EP*4 is the alternative to radiotherapy. Chemotherapy is preferred for patients with bulkier disease since the RR in these cases is higher than with radiotherapy alone. Although more toxic than radiotherapy, BEP*3 or EP*4 achieves a similar level of disease control.

Clinical Stage 2A/B Nonseminoma

Patients with high-volume stage II disease or increasing STMs should receive BEP*3 or EP*4⁵⁶ according to the IGCCCG criteria, followed by residual-tumor resection if indicated. For patients with a low-volume stage II and normal or low-level stable STMs, primary RPLND can be considered. The cure rate for chemotherapy or primary RPLND is approximately 98%.⁵⁶

Clinical Stage 2C/3 Seminoma and Nonseminoma According to IGCCCG Risk Classification

Good Prognosis Seminoma. Figure 2 summarizes EAU guidelines treatment of metastatic GCTT. BEP*3, or EP*4 are preferable to carboplatin chemotherapy.⁵⁷

Intermediate Prognosis Seminoma. While no randomized trial is available, BEP*4 or Etoposide+Cisplatin+Ifosfamide (VIP) are recommended.

Good Prognosis Nonseminoma. BEP*3 or EP*4 is recommended without dose reductions at 21-day intervals. Only

fever with granulocytopenia <1000/mm³ or thrombocytopenia <100,000/IU should delay subsequent cycles.

Intermediate Prognosis Nonseminoma. BEP*4 is the standard of care. A randomized trial comparing BEP*4 +/- Paclitaxel (T-BEP) found no significant improvement in OS.⁵⁸

Poor Prognosis Nonseminoma. BEP*4 is the standard of care. Three randomized trials have shown no OS advantage for high-dose chemotherapy in this group.⁵⁹⁻⁶¹ Intensifying treatment with dose-dense chemotherapy improves progression free survival but not OS in patients with a slow decline in STMs.⁶² The EAU guidelines demonstrate strong evidence that patients with an unfavorable decline in STMs after BEP*1 should be switched to a more intensive regimen.²¹

THERAPY FOR RESIDUAL DISEASE AFTER INITIAL TREATMENT

Seminoma Residual Mass

The Seminoma PET (SEMPET) study⁶³ demonstrated a high negative predictive value of Fluorodeoxyglucose (FDG) PET/CT >2 months after chemotherapy in patients with residual retroperitoneal masses.²¹ If positive on PET with no volume increase, a second scan should be performed 6-8 weeks later, or a biopsy performed. Evidence of progressive disease should prompt either salvage chemotherapy or radiotherapy. Patients with persistent elevated STMs should be treated with salvage chemotherapy. In progressing patients without elevated STMs, RPLND is recommended, despite the difficult resection that is expected, caused by the extensive desmoplastic reaction surrounding the masses.

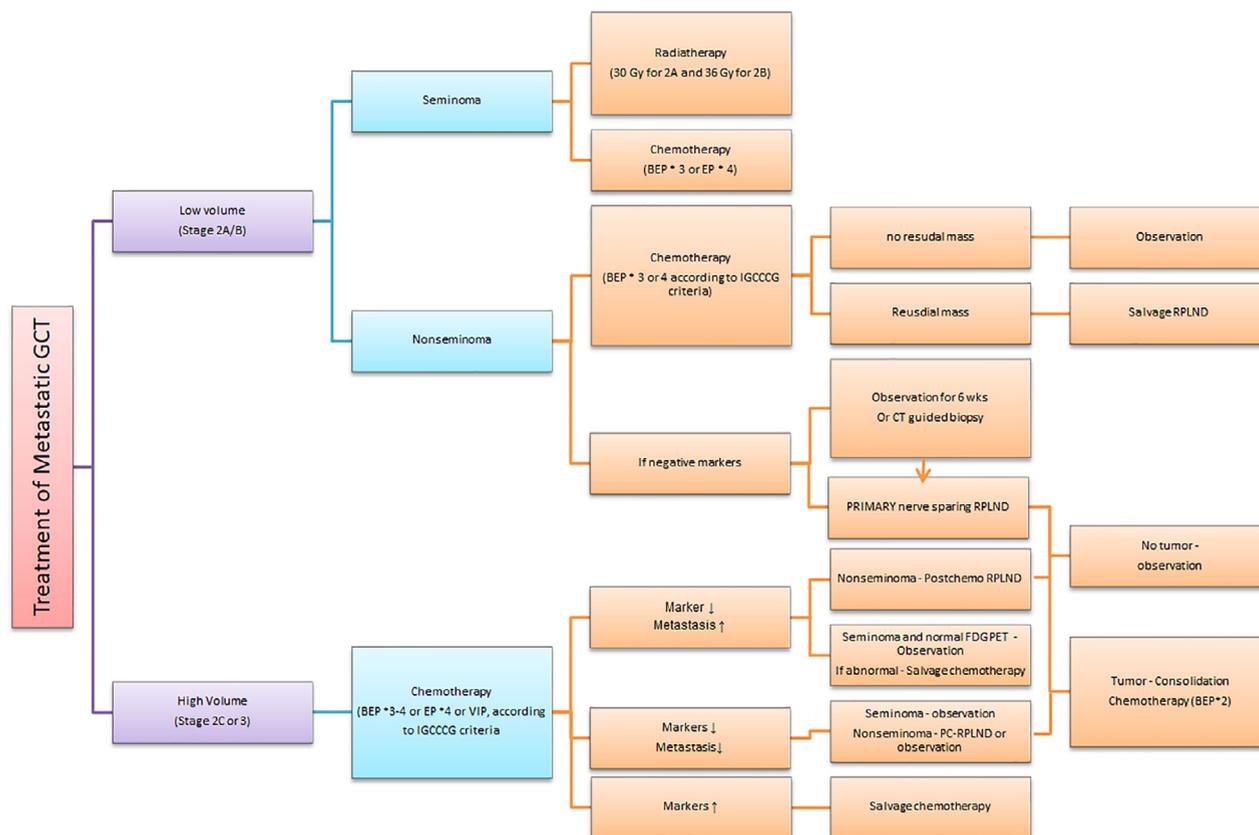


Figure 2. Treatment of metastatic GCTT adapted from the EAU guidelines 2018. (Color version available online.)

Nonseminoma Residual Mass

Following first-line BEP chemotherapy, most masses have a complete response (CR) (normal markers with no residual disease controversially defined as ≤ 1 cm with few completely resolving on CT) and only 6%-10% of those that do not achieve CR contain viable cancer (50% mature teratoma, 40% necrosis-fibrosis).⁶⁴ Currently, there are no clinical tools that can reliably predict the histology of a postchemotherapy mass. However, after reimaging following chemotherapy, patients may be stratified into 3 distinct response groups based on the residual retroperitoneal mass size and posttreatment STM levels:

- CR with a low RR of <10%, surveillance is recommended.²¹
- Partial response of the mass and/or persistently elevated STMs after chemotherapy, representing 5%-15% of the patients, accounting for most of the disease specific mortality.
- An intermediate group of patients with normalized or low stable STM and radiologically detectable residual masses >10 mm. In this setting, postchemo-RPLND will provide histological verification which leads to accurate prognosis by removal of residual teratoma and chemoresistant viable cancer.

In patients with residual mass, postchemo-RPLND is the standard treatment. A full bilateral template nerve-

sparing procedure is recommended. Overall morbidity for open postchemo-RPLND ranges from 12%-32%.⁶⁵

THERAPY FOR RELAPSING DISEASE

Reoperative RPLND

Some patients will relapse in the retroperitoneum or have residual disease after incomplete RPLND. Salvage chemotherapy will rarely compensate for an inadequate initial RPLND. RPLND with complete resection of all metastatic retroperitoneal disease is critical for long-term relapse-free survival. In appropriately selected patients, effective management can be performed with reoperative RPLND with survival between 63%-91.3%.⁶⁶

Salvage Therapy for Relapsing or Refractory Disease

Patients relapsing after first line chemotherapy will usually receive cisplatin-based combination salvage chemotherapy with long-term remissions in approximately 50% of patients. The regimen of choice is 4 cycles of cisplatin+Ifosfamide plus either etoposide, paclitaxel, or gemcitabine.⁶⁷ OS improvement of 10%-15% for high-dose salvage therapy compared to standard-dose therapy has been shown.⁶⁸

Desperation RPLND

A subset of patients will continue to have persistently elevated STMs with a residual mass. They should

proceed directly to surgery, known as desperation RPLND. The incidence of viable GCTT at desperation RPLND is high, approximately 80%, with 20% harboring teratoma or fibrosis.⁶⁹ However, the lack of viable disease in the retroperitoneum, suggest that it may either reside in extraretroperitoneal sites, or that systemic disease is present. The 5-year survival rates for patients undergoing desperation RPLND after second line chemotherapy is 30%.⁶⁹ Risk-factors associated with poor survival include increasing STMs, reoperative surgery, and viable GCTT.⁶⁹

Late Relapse Therapy

LR is defined as recurrence >2 years after apparent cure following chemotherapy for metastatic disease, with/without surgery for residual disease. LR occurs in 1.4% of seminoma and 3.2% of nonseminoma cases.⁷⁰ LR is a distinct clinical entity based on clinical presentation, pattern of histology, and poor OS. Forty to fifty percent occur within 2-5 years of initial therapy.⁷¹ Over 30% can present >10 years after CR, with the longest reported time to relapse of 37.7 years.⁷¹ The retroperitoneum is the most common site, accounting to 45%-70% of the LRs, regardless of initial histology, primary treatment, or clinical presentation. Teratoma is found in up to 60% of patients with LR, and viable GCTTs are found in 60%-70%.⁷¹ Because of the high-rate of teratoma, LR is most likely to respond to surgery. The overall prognosis for LR is poor with survival-rates of approximately 30%-60%.⁷² LR in patients who had received previous chemotherapy has significantly worse 5-year CSS.⁷¹ The presence of teratoma or necrosis is associated with favorable outcomes.⁷¹

FUTURE DIRECTIONS

Although most GCCTT patients will be cured, a constant rate of mortality continues to ensue, and considerable morbidity still exists resulting from therapy. Several important ongoing clinical trials worth mentioning include The WATCHman (NCT03360994) trial, where a secure, online interface will be provided to all virtual follow-up visits as an alternative to costly and time-consuming travel for in-person visits, for AS patients. Trials assessing imaging modalities include the TENY trial (NCT03436901) which aims to reduce the risk of radiation-induced secondary cancers by replacing CT scans with nonionizing whole body-MRI. Furthermore, the TRISST MRC TE24 trial (NCT00589537) is a randomized phase III trial comparing 4 different MRI and CT scan schedules in patients with CS1 seminoma. Several trials are attempting to find improved treatments for refractory GCTT, including Gemcitabine, Carboplatin and VELIPARIB (ABT-888) (NCT02860819), Cabazitaxel (NCT02478502), Everolimus (NCT01466231), Avelumab (NCT03403777), Brentuximab Vedotin (NCT02689219), and Durvalumab and Tremelimumab (APACHE trial, NCT03081923). Lastly, the ability of testosterone replacement in reducing the risk of cardiovascular disease is evaluated in GCTT survivors,

in the EINSTEIN study (NCT02991209). Outlined below are some challenges and future research being developed.

Imaging-radiomics

Imaging continues to improve, and progression can be detected earlier with smaller tumor volume. Following chemotherapy, imaging cannot reliably differentiate between residual cancer or necrosis/fibrosis. Radiomics is an emerging form of automated image analysis acquiring large amounts of data from images and producing quantitative decisions about defined tumor regions.

Biomarkers and Genetics

The introduction of more sensitive and specific biomarkers for diagnosis, staging, and recurrence, would allow clinicians to better select patients for additional treatment. To date, several studies have examined the clinical applicability of molecular biomarkers (micro-RNA [miRNA], circulating mitochondrial DNA, and circulating tumor-cells) for early detection, staging, and surveillance of GCTTs. miRNAs are small regulatory noncoding RNA (about 18-25 nucleotides) that bind to complementary sequences in mRNA and can regulate gene expression. Serum miRNAs can be used to detect patients with locally-advanced disease,⁷³ and predict viable disease postchemotherapy in nonseminoma.⁷⁴ Notably, miR-371a-3p was demonstrated to be more sensitive (84.7%) and specific (99%) for identification of GCTT than standard STMs.⁷³ Furthermore, in contrast to STMs, miR-371a-3p predicted viable disease in residual masses following chemotherapy, with an area under the curve of 0.874, 95% CI 0.774-0.974, $p < 0.0001$.⁷⁴

Inherited variations in certain genes, such as KITLG, SPRY4, DMRT1, TERT, and ATF7IP, appear to increase the risk of GCTT.^{75,76} GCTT was increased threefold per copy of the major allele of KITLG (OR = 3.08, 95% CI = 2.29-4.13), and increased nearly 40% per copy of the major allele of SPRY4 (OR = 1.39, 95% CI = 1.16-1.66).⁷⁵ Additionally, TERT-CLPTM1L locus on chromosome 5, ATF7IP, a regulator of TERT on chromosome 12, and DMRT1 on chromosome 9 have been shown to increase GCTT disease by 33%-54%, 27%, and 37%, respectively.⁷⁶ Lastly, epigenetic aberrations, especially DNA hypermethylation, have been linked to resistance to platinum-based chemotherapy with poor outcomes.⁷⁷

Centralization of Care

A growing body of evidence indicates that increased hospital and surgeon volume predict improved outcomes.⁷⁸ Movement in favor of centralization of care is expanding worldwide.⁷⁰

Late Relapse

The biologic and molecular differences between early and LR needs to be further studied, to identify potential therapeutic targets.

Malignant Transformation of Teratoma

The biologic and molecular basis for malignant transformation of teratoma needs to be further explored to make systemic therapy more effective.

CONCLUSIONS

GCTTs are the most commonly diagnosed cancer in young men with cure rates >95%. GCTTs most commonly manifest as CS1, generally curable by RO alone. As part of the risk-adapted treatment strategy, AS is the preferred management approach for CS1. Chemotherapy remains the mainstay of therapy for advanced disease, although surgical management is integral to the multimodality treatment. Treatment should be centralized in high-volume experienced centers with multidisciplinary teams including dedicated medical, radiation, and uro-oncologists.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.urology.2018.12.025>.

References

1. SEER Cancer Statistics Factsheets: Testis Cancer. National Cancer Institute. Bethesda, MD, <http://seer.cancer.gov/statfacts/html/testis.html>. Accessed September 5, 2016.
2. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin*. 2014;64:252–271.
3. Kollmannsberger C, Moore C, Chi KN, et al. Non-risk-adapted surveillance for patients with stage I nonseminomatous testicular germ-cell tumors: diminishing treatment-related morbidity while maintaining efficacy. *Ann Oncol*. 2010;21:1296–1301.
4. Fossa SD, Chen J, Schonfeld SJ, et al. Risk of contralateral testicular cancer: a population-based study of 29,515 U.S. men. *J Natl Cancer Inst*. 2005;97:1056–1066.
5. Oldenburg J, Fossa SD, Nuver J, et al. Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(suppl 6):vi125–vi132.
6. Stevenson SM, Lowrance WT. Epidemiology and diagnosis of testis cancer. *Urol Clin North Am*. 2015;42:269–275.
7. Moul JW. Timely diagnosis of testicular cancer. *Urol Clin North Am*. 2007;34:109–117. abstract vii.
8. Sagalowsky AI. Treatment options for patients with stage I nonseminomatous testis cancer: it's all good. *Eur Urol*. 2011;59:563–565.
9. Bernard B, Sweeney CJ. Diagnosis and treatment of testicular cancer: a clinician's perspective. *Surg Pathol Clin*. 2015;8:717–723.
10. Pearce SM, Liauw SL, Eggener SE. Management of low-stage testicular seminoma. *Urol Clin North Am*. 2015;42:287–298.
11. Eble JN. Spermatocytic seminoma. *Hum Pathol*. 1994;25:1035–1042.
12. Gholam D, Fizazi K, Terrier-Lacombe MJ, Jan P, Culine S, Theodore C. Advanced seminoma—treatment results and prognostic factors for survival after first-line, cisplatin-based chemotherapy and for patients with recurrent disease: a single-institution experience in 145 patients. *Cancer*. 2003;98:745–752.
13. Cao D, Humphrey PA. Yolk sac tumor of the testis. *J Urol*. 2011;186:1475–1476.
14. Leibovitch I, Foster RS, Ulbright TM, Donohue JP. Adult primary pure teratoma of the testis. The Indiana experience. *Cancer*. 1995;75:2244–2250.
15. Logothetis CJ, Samuels ML, Trindade A, Johnson DE. The growing teratoma syndrome. *Cancer*. 1982;50:1629–1635.

16. International Germ Cell Cancer Collaborative Group. International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol*. 1997;15:594–603.
17. Klein FA, Melamed MR, Whitmore Jr WF. Intratubular malignant germ cells (carcinoma in situ) accompanying invasive testicular germ cell tumors. *J Urol*. 1985;133:413–415.
18. von der Maase H, Rorth M, Walbom-Jorgensen S, et al. Carcinoma in situ of contralateral testis in patients with testicular germ cell cancer: study of 27 cases in 500 patients. *Br Med J (Clin Res ed)*. 1986;293:1398–1401.
19. Di Vizio D, Cito L, Boccia A, et al. Loss of the tumor suppressor gene PTEN marks the transition from intratubular germ cell neoplasias (ITGCN) to invasive germ cell tumors. *Oncogene*. 2005;24:1882–1894.
20. Harland SJ, Cook PA, Fossa SD, et al. Intratubular germ cell neoplasia of the contralateral testis in testicular cancer: defining a high risk group. *J Urol*. 1998;160:1353–1357.
21. Albers P, Albrecht W, Algaba F, et al. Guidelines on testicular cancer: 2015 Update. *Eur Urol*. 2015;68:1054–1068.
22. Sharma P, Dhillon J, Sexton WJ. Intratubular germ cell neoplasia of the testis, bilateral testicular cancer, and aberrant histologies. *Urol Clin North Am*. 2015;42:277–285.
23. Dieckmann KP, Lauke H, Michl U, Winter E, Loy V. Testicular germ cell cancer despite previous local radiotherapy to the testis. *Eur Urol*. 2002;41:643–649. discussion 9–50.
24. Lawrentschuk N, Zuniga A, Grabowski AC, Rendon RA, Jewett MA. Partial orchiectomy for presumed malignancy in patients with a solitary testis due to a prior germ cell tumor: a large North American experience. *J Urol*. 2011;185:508–513.
25. Heidenreich A, Weissbach L, Holtl W, et al. Organ sparing surgery for malignant germ cell tumor of the testis. *J Urol*. 2001;166:2161–2165.
26. Magelssen H, Haugen TB, von Doring V, Melve KK, Sandstad B, Fossa SD. Twenty years experience with semen cryopreservation in testicular cancer patients: who needs it. *Eur Urol*. 2005;48:779–785.
27. Schmidt KL, Carlsen E, Andersen AN. Fertility treatment in male cancer survivors. *Int J Androl*. 2007;30:413–418. discussion 8–9.
28. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol*. 2006;24:2917–2931.
29. Hamano I, Hatakeyama S, Ohyama C. Fertility preservation of patients with testicular cancer. 2017;16: 240–251.
30. Neal MS, Nagel K, Duckworth J, et al. Effectiveness of sperm banking in adolescents and young adults with cancer: a regional experience. *Cancer*. 2007;110:1125–1129.
31. Pacey AA, Merrick H, Arden-Close E, et al. Monitoring fertility (semen analysis) by cancer survivors who banked sperm prior to cancer treatment. *Hum Reprod*. 2012;27:3132–3139.
32. Jones G, Arthurs B, Kaya H, et al. Overall survival analysis of adjuvant radiation versus observation in stage I testicular seminoma: a surveillance, epidemiology, and end results (SEER) analysis. *Am J Clin Oncol*. 2013;36:500–504.
33. Aparicio J, Germa JR, Garcia del Muro X, et al. Risk-adapted management for patients with clinical stage I seminoma: the Second Spanish Germ Cell Cancer Cooperative Group study. *J Clin Oncol*. 2005;23:8717–8723.
34. Wood L, Kollmannsberger C, Jewett M, et al. Canadian consensus guidelines for the management of testicular germ cell cancer. *Can Urol Assoc J*. 2010;4:e19–e38.
35. Motzer RJ, Jonasch E, Agarwal N, et al. Testicular Cancer, Version 2.2015. *J Natl Compr Cancer Netw*. 2015;13:772–799.
36. Kollmannsberger C, Tandstad T, Bedard PL, et al. Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. *J Clin Oncol*. 2015;33:51–57.
37. Chung P, Mayhew LA, Warde P, Winquist E, Lukka H. Management of stage I seminomatous testicular cancer: a systematic review. *Clin Oncol (R Coll Radiol)*. 2010;22:6–16.
38. Oliver RT, Mead GM, Rustin GJ, et al. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on

- relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). *J Clin Oncol*. 2011;29:957–962.
39. Fischer S, Tandstad T, Wheatler M, et al. Outcome of men with relapse after adjuvant carboplatin for clinical stage I seminoma. *J Clin Oncol*. 2017;35:194–200.
 40. Horwich A, Fossa SD, Huddart R, et al. Second cancer risk and mortality in men treated with radiotherapy for stage I seminoma. *Br J Cancer*. 2014;110:256–263.
 41. van den Belt-Dusebout AW, de Wit R, Gietema JA, et al. Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. *J Clin Oncol*. 2007;25:4370–4378.
 42. Kovac E, Stephenson AJ. Management of stage I nonseminomatous germ cell tumors. *Urol Clin North Am*. 2015;42:299–310.
 43. Zuniga A, Kakiashvili D, Jewett MA. Surveillance in stage I nonseminomatous germ cell tumours of the testis. *BJU Int*. 2009;104:1351–1356.
 44. Albers P, Siener R, Kliesch S, et al. Risk factors for relapse in clinical stage I nonseminomatous testicular germ cell tumors: results of the German Testicular Cancer Study Group Trial. *J Clin Oncol*. 2003;21:1505–1512.
 45. Heidenreich A, Sesterhenn IA, Mostofi FK, Moul JW. Prognostic risk factors that identify patients with clinical stage I nonseminomatous germ cell tumors at low risk and high risk for metastasis. *Cancer*. 1998;83:1002–1011.
 46. Nayan M, Jewett MA, Hosni A, et al. Conditional risk of relapse in surveillance for clinical stage I testicular cancer. *Eur Urol*. 2017;71(1):120–127.
 47. Daugaard G, Gundgaard MG, Mortensen MS, et al. Surveillance for stage I nonseminoma testicular cancer: outcomes and long-term follow-up in a population-based cohort. *J Clin Oncol*. 2014;32:3817–3823.
 48. Stephenson AJ, Bosl GJ, Motzer RJ, et al. Retroperitoneal lymph node dissection for nonseminomatous germ cell testicular cancer: impact of patient selection factors on outcome. *J Clin Oncol*. 2005;23:2781–2788.
 49. Albers P, Siener R, Krega S, et al. Randomized phase III trial comparing retroperitoneal lymph node dissection with one course of bleomycin and etoposide plus cisplatin chemotherapy in the adjuvant treatment of clinical stage I Nonseminomatous testicular germ cell tumors: AUO trial AH 01/94 by the German Testicular Cancer Study Group. *J Clin Oncol*. 2008;26:2966–2972.
 50. Flechtner HH, Fischer F, Albers P, Hartmann M, Siener R. Quality-of-life analysis of the german prospective multicentre trial of single-cycle adjuvant bep versus retroperitoneal lymph node dissection in clinical stage I nonseminomatous germ cell tumours. *Eur Urol*. 2016;69:518–525.
 51. Cullen MH, Stenning SP, Parkinson MC, et al. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. *J Clin Oncol*. 1996;14:1106–1113.
 52. Foster RS, Donohue JP. Retroperitoneal lymph node dissection for the management of clinical stage I nonseminoma. *J Urol*. 2000;163:1788–1792.
 53. Large MC, Sheinfeld J, Eggener SE. Retroperitoneal lymph node dissection: reassessment of modified templates. *BJU Int*. 2009;104:1369–1375.
 54. Heidenreich A, Albers P, Hartmann M, et al. Complications of primary nerve sparing retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell tumors of the testis: experience of the German Testicular Cancer Study Group. *J Urol*. 2003;169:1710–1714.
 55. Chung PW, Gospodarowicz MK, Panzarella T, et al. Stage II testicular seminoma: patterns of recurrence and outcome of treatment. *Eur Urol*. 2004;45:754–759. discussion 9–60.
 56. Donohue JP, Thornhill JA, Foster RS, Bihrl R, Rowland RG, Einhorn LH. The role of retroperitoneal lymphadenectomy in clinical stage B testis cancer: the Indiana University experience (1965 to 1989). *J Urol*. 1995;153:85–89.
 57. Bokemeyer C, Kollmannsberger C, Stenning S, et al. Metastatic seminoma treated with either single agent carboplatin or cisplatin-based combination chemotherapy: a pooled analysis of two randomized trials. *Br J Cancer*. 2004;91:683–687.
 58. de Wit R, Skoneczna I, Daugaard G, et al. Randomized phase III study comparing paclitaxel-bleomycin, etoposide, and cisplatin (BEP) to standard BEP in intermediate-prognosis germ-cell cancer: intergroup study EORTC 30983. *J Clin Oncol*. 2012;30:792–799.
 59. Daugaard G, Skoneczna I, Aass N, et al. A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). *Ann Oncol*. 2011;22:1054–1061.
 60. Motzer RJ, Nichols CJ, Margolin KA, et al. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. *J Clin Oncol*. 2007;25:247–256.
 61. Droz JP, Kramar A, Biron P, et al. Failure of high-dose cyclophosphamide and etoposide combined with double-dose cisplatin and bone marrow support in patients with high-volume metastatic nonseminomatous germ-cell tumours: mature results of a randomised trial. *Eur Urol*. 2007;51:739–746. discussion 47–8.
 62. Olofsson SE, Tandstad T, Jerkeman M, et al. Population-based study of treatment guided by tumor marker decline in patients with metastatic nonseminomatous germ cell tumor: a report from the Swedish-Norwegian Testicular Cancer Group. *J Clin Oncol*. 2011;29:2032–2039.
 63. De Santis M, Becherer A, Bokemeyer C, et al. 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. *J Clin Oncol*. 2004;22:1034–1039.
 64. Carver BS, Serio AM, Bajorin D, et al. Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. *J Clin Oncol*. 2007;25:5603–5608.
 65. Mosharafa AA, Foster RS, Koch MO, Bihrl R, Donohue JP. Complications of post-chemotherapy retroperitoneal lymph node dissection for testis cancer. *J Urol*. 2004;171:1839–1841.
 66. Pedrosa JA, Masterson TA, Rice KR, Bihrl R, Beck SD, Foster RS. Reoperative retroperitoneal lymph node dissection for metastatic germ cell tumors: analysis of local recurrence and predictors of survival. *J Urol*. 2014;191:1777–1782.
 67. Fizazi K, Delva R, Caty A, et al. A risk-adapted study of cisplatin and etoposide, with or without ifosfamide, in patients with metastatic seminoma: results of the GETUG S99 multicenter prospective study. *Eur Urol*. 2014;65:381–386.
 68. Lorch A, Beyer J, Bascoul-Mollevi C, et al. Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. *J Clin Oncol*. 2010;28:4906–4911.
 69. Beck SD, Foster RS, Bihrl R, Einhorn LH, Donohue JP. Pathologic findings and therapeutic outcome of desperation post-chemotherapy retroperitoneal lymph node dissection in advanced germ cell cancer. *Urol Oncol*. 2005;23:423–430.
 70. Beyer J, Albers P, Altena R, et al. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. *Ann Oncol*. 2013;24:878–888.
 71. Sharp DS, Carver BS, Eggener SE, et al. Clinical outcome and predictors of survival in late relapse of germ cell tumor. *J Clin Oncol*. 2008;26:5524–5529.
 72. Dieckmann KP, Albers P, Classen J, et al. Late relapse of testicular germ cell neoplasms: a descriptive analysis of 122 cases. *J Urol*. 2005;173:824–829.
 73. Syring I, Bartels J, Holdenrieder S, Kristiansen G, Muller SC, Ellinger J. Circulating serum miRNA (miR-367-3p, miR-371a-3p, miR-372-3p and miR-373-3p) as biomarkers in patients with testicular germ cell cancer. *J Urol*. 2015;193:331–337.

74. Leao R, van Agthoven T, Figueiredo A, et al. Serum miRNA predicts viable disease post-chemotherapy in testicular non-seminoma germ cell tumor patients. *J Urol*. 2018;200(1):126–135.
75. Kanetsky PA, Mitra N, Vardhanabhuti S, et al. Common variation in KITLG and at 5q31.3 predisposes to testicular germ cell cancer. *Nat Genet*. 2009;41:811–815.
76. Turnbull C, Rapley EA, Seal S, et al. Variants near DMRT1, TERT and ATF7IP are associated with testicular germ cell cancer. *Nat Genet*. 2010;42:604–607.
77. Sonnenburg D, Spinella MJ, Albany C. Epigenetic targeting of platinum resistant testicular cancer. *Curr Cancer Drug Targets*. 2016;16:789–795.
78. Williams SB, Ray-Zack MD, Hudgins HK, et al. Impact of centralizing care for genitourinary malignancies to high-volume providers: a systematic review. *Eur Urol Oncol* 2018; in press.