Management of Testicular Germ Cell Tumors

Christopher E. Wee, MD, and Timothy D. Gilligan, MD, MS

Department of Hematology and Medical Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio

Corresponding author:
Timothy D. Gilligan, MD, MS
Department of Hematology and Medical Oncology
Cleveland Clinic Taussig Cancer Institute
9500 Euclid Ave, CA-60
Cleveland, OH 44195
Tel (216) 444-0391
Fax (216) 636-9286
Email: gilligt@ccf.org

Abstract: Over the past half century, advancements in treatment have led to cures in an overwhelming majority of patients with testicular germ cell tumors. Astute clinical decision-making, informed by the abundant data from published clinical trials, is essential for achieving a cure whenever possible and minimizing the toxicity of treatment. Important remaining challenges include reducing the risk of secondary malignancies and other late effects of chemotherapy and radiation therapy, and developing curative treatments for patients with cancer that is refractory to current therapies. This article reviews the current treatment landscape and highlights recent discoveries in diagnosis and staging, emerging biomarkers for disease, and treatment for relapsed/refractory disease. Treatment algorithms for testis cancer are complex and clinicians should apply them carefully, not only to optimize short-term, disease-related outcomes, but also to maximize long-term survival and quality of life.

Keywords
Testicular germ cell tumors, testis cancer

Introduction

Although testis cancer represents less than 1% of all new cancer cases and 0.1% of all cancer deaths, it remains the most common cancer among young men in developed nations.[1,2] Germ cell tumors (GCTs) are the predominant histology; less-common pathologies include lymphomas and sex cord–stromal tumors. Prognoses for patients with testicular cancer are generally favorable, and most patients with metastatic disease can be cured.[3,4] Undertreatment can result in avoidable treatment failures, whereas overtreatment can result in unnecessary toxicity. We provide a clinically pragmatic review of GCTs in postpubertal males, including current management paradigms, recent advancements, and opportunities for future investigation.

Epidemiology and Biology

The vast majority of testicular GCTs in adolescent and adult males are type II testicular GCTs, which arise from germ cell neoplasia in situ and are associated with extra copies of the short arm of chromosome 12, often manifesting as isochromosome 12p.[5] Type II testicular GCTs

are thought to arise from primordial germ cells and can develop into multiple different histologies, including seminoma, embryonal carcinoma, yolk sac tumor, teratoma, and choriocarcinoma. When a tumor is 100% seminoma, it is referred to as a seminoma. If any other elements are present, even if the tumor is 99% seminoma, the tumor is referred to as a nonseminoma or nonseminomatous germ cell tumor (NSGCT). Seminomas represent 50% to 60% of testicular GCTs.[6] Most NSGCTs represent a mix of different histologies and are sometimes referred to as mixed GCTs. GCTs are associated with the serum tumor markers alpha fetoprotein (AFP), beta human chorionic gonadotropin (β-HCG), and lactate dehydrogenase (LDH), but none of these are pathognomonic for testis cancer or GCTs. Seminomas do not produce AFP, and an elevated AFP thus indicates the presence of nonseminomatous elements. Type III testicular GCTs are referred to as spermatocytic tumors.[7] They were previously labeled as *spermatocytic seminomas*, but they are biologically distinct from seminomas and have a much more benign natural history.[8]

Testis cancer is the most common cancer among adolescent and young adult males (typically between the ages of 15 and 40 years) in many Western nations. There is a significant incidence of testis cancer until age 60 years, after which it is rare. Great variation in incidence exists among different regions, with higher rates in Europe, North America, and Oceania than in Africa or Asia.[9] Similarly, it is more common in more-developed than less-developed regions. Clearly identified risk factors include cryptorchidism, a personal or family history of testis cancer, and HIV/AIDS. Having a first-degree relative with testis cancer is associated with a substantially elevated risk, especially if the relative is a brother.[10] Male infertility is also associated with an increased risk of developing testis cancer.[5]

Over the last century, the incidence of testis cancer has been rising substantially, albeit with great regional variation.[9,11,12] The rate of increase is slowing significantly in developed nations but not in low- and middle-income countries.[13] Testis cancer mortality has declined dramatically in developed countries owing to improvements in treatment, but remains high in the developing world. The incidence to mortality ratio is 2:1 in parts of Asia and Africa vs 26:1 in Northern Europe.[13] Increases in incidence suggest an environmental cause, but specific environmental factors have not been definitively identified. The rise in testis cancer incidence has been accompanied by a rise in congenital genitourinary anomalies in baby boys as well as declining sperm counts. Common pathways have been hypothesized that focus on endocrine disrupters in the environment, such as phthalates and certain pesticides.[14] However, no chemicals have been definitively linked to the risk of developing testis cancer.[5] Because the suspected cell of origin for malignant GCTs is a primordial germ cell that is only present prior to birth, an association with prenatal environmental exposures has been suspected. The strong association between birth cohort and testis cancer incidence also supports the hypothesis that prenatal or early childhood exposures may be key.[15]

Diagnosis, Staging, and Prognostic Groups

Postpubertal males with testis cancer typically present with a testicular mass, but they may also present with testicular pain, testicular atrophy, or gynecomastia. They may also present with the signs, symptoms, or complications of metastatic disease, such as back pain (from retroperitoneal [RP] adenopathy) or thromboembolic disease. A male suspected of having testis cancer should undergo a transscrotal ultrasound. If a tumor is detected, an inguinal orchiectomy should be performed promptly to remove the involved testis and establish a histologic diagnosis. The serum tumor markers AFP, β-HCG, and LDH should ideally be measured before and after orchiectomy. Imaging studies should include a computed tomography (CT) or magnetic resonance imaging (MRI) scan, both with intravenous contrast of the abdomen and pelvis, and a chest CT scan. For seminomas, a chest x-ray is adequate for thoracic imaging if abdominal and pelvic imaging does not reveal metastatic disease. Sperm banking should be offered to patients prior to orchiectomy if the procedure will leave them with no functioning testicle as well as to all patients prior to undergoing chemotherapy, radiation therapy, or RP lymph node dissection.

There are 3 stages of testis cancer. Stage I GCTs are confined to the testis and epididymis (invasion of the spermatic cord or scrotum may be present), stage II GCTs include metastatic disease to the RP lymph nodes, and stage III GCTs are characterized by metastatic disease beyond the RP lymph nodes. However, NSGCTs with RP lymph node metastases are considered stage III rather than stage II if there are highly elevated postorchiectomy serum tumor markers (AFP >1000 ng/mL, β-HCG >5000 mU/mL, or LDH >1.5 times the upper limit of normal). In testis cancer, pelvic lymph node metastases are considered distant metastases because the testes' lymphatic drainage is to the retroperitoneum.

It is essential to note that for staging purposes, it is the postorchiectomy values of serum tumor markers that matter. If the markers are elevated prior to orchiectomy and return to normal afterward, then they are considered normal for staging purposes. The biological half-life of AFP is less than 7 days, although that of β-HCG is less than 3 days. For patients undergoing treatment with chemotherapy, the serum tumor marker levels on day 1 of the first cycle of chemotherapy should be used for staging

Table 1. Common Chemotherapy Regimens for Germ Cell Tumors

Disease Stage	Regimen	Number of Cycles
Stage I seminoma	Single-agent carboplatin[35]	2[a]
Stage I NSGCT	BEP[93,94]	1
Pathologic stage II GCTs (pN1-3)[b]	EP[58]	2
Good-risk disseminated GCTs (stage II-IIIA)	BEP[61,c]	3
	EP[95]	4
Intermediate-risk and poor-risk GCTs (stage IIIB-C)	BEP[66,67,d]	4
	VIP[66,67]	4
Relapsed GCT previously treated with BEP × 3 or EP × 4	TIP[80]	4
	VeIP[81]	4
	High-dose carboplatin and etoposide[82,e]	2[e]
Adjuvant therapy for patients with residual viable malignant GCT in completely resected residual masses following first-line chemotherapy	VIP, TIP, or EP[78,96]	2

BEP, bleomycin, etoposide, and cisplatin; GCT, germ cell tumor; EP, etoposide and cisplatin; NSGCT, nonseminomatous germ cell tumor; TIP, paclitaxel, ifosfamide, and cisplatin; VeIP, vinblastine, ifosfamide, and cisplatin; VIP, etoposide, ifosfamide, and cisplatin.

[a]Some experts recommend a single cycle of carboplatin (area under the curve, 7 mg/mL per minute) for stage I seminoma, but lower relapse rates have been reported with 2 cycles.

[b]Some experts recommend a full course of 3 cycles of BEP or 4 cycles of EP for patients with pathologic stage IIC (pN3) disease.

[c]Based on evidence of greater efficacy, 3 cycles of BEP is generally preferred over 4 cycles of EP for patients with good-risk disease who do not have a contraindication to bleomycin.

[d]Based on evidence of reduced toxicity, 4 cycles of BEP is preferred over 4 cycles of VIP for patients with intermediate- or poor-risk disease who do not have a contraindication to bleomycin.

[e]The standard high-dose chemotherapy regimen may change in the future depending on the results of the TIGER trial.

and risk stratification.[16]

The eighth edition of the American Joint Committee on Cancer staging manual included minor changes to pathologic staging. These changes included subdividing pure seminomas based on the size of the primary tumor (using a 3-cm cutoff), categorizing epididymal and hilar soft tissue invasion as pT2 disease, and considering discontinuous spermatic cord involvement as M1 disease.[17] Although these changes may result in upstaging of disease, whether or not this upstaging should lead to changes in clinical practice remains unclear.[18] Upstaging localized disease could result in more frequent administration of adjuvant therapy or treating localized disease as systemic disease. Most metastatic GCTs can be cured, so more aggressive treatment based on upstaging may expose more patients to treatment-related toxicity without improving overall prognosis.

The tumor markers AFP, β-HCG, and LDH are important in staging, risk stratification, diagnosis, and surveillance of GCTs. However, these tumor markers are not 100% sensitive nor 100% specific, as evidenced by the fact that roughly 25% of stage I NSGCTs and 18% of stage I seminomas relapse despite having had normal tumor markers prior to relapse, and a substantial proportion of patients have normal markers when metastatic disease is detected. Given these limitations, researchers are searching for improved biomarkers, with microRNAs as a leading candidate. MicroRNAs are noncoding RNAs involved in gene expression regulation and can become dysregulated in patients with cancer, contributing to carcinogenesis.[19] For patients with GCTs, miR-371a-3p in particular has demonstrated promise, predicting active germ cell malignancy with high specificity and positive predictive value.[20] In the largest prospective study to date involving 616 patients with testicular GCTs and 258 controls, Dieckmann and colleagues noted that serum levels of miRNA-371a-3p by polymerase chain reaction testing had a sensitivity of 90.1% and a specificity of 94% when used for the primary diagnosis of GCT, significantly outperforming conventional tumor markers. Notably, miR-371a-3p correlated with tumor size and stage, changed with treatment effects, and was elevated in recurrences.[21] Several

prospective clinical trials are underway that are examining this technology in a multitude of clinical scenarios.

Imaging

Ultrasound is the preferred imaging modality for detecting testicular masses. Staging of patients diagnosed with testis cancer should include CT scans of the abdomen and pelvis, and either a chest x-ray or CT scan of the chest. MRI scans can be used as an alternative for abdominopelvic imaging, but consistency of modalities should be maintained during surveillance.[22-24] Outside of assessing postchemotherapy residual masses for patients with pure seminoma, positron emission tomography (PET) scans have limited value and should not be routinely performed. PET scans should not be used to assess treatment response for residual masses in patients with NSGCTs.

Stage I

Seminoma

The prognosis for stage I seminoma is excellent, and most patients are cured by the orchiectomy alone. Postoperatively, patients can be managed with surveillance, adjuvant radiation therapy, or adjuvant chemotherapy. Most major guidelines recommend surveillance as the preferred management for stage I seminoma.[25-27] Multiple studies have reported 99% or higher disease-specific survival with surveillance. Surveillance offers the benefit of reducing the risk of exposure to radiation therapy or chemotherapy, both of which are associated with acute and late toxicities.[28-30]

For patients in whom surveillance is not preferable (eg, patient preference or concerns regarding adherence to surveillance schedule), we recommend single-agent carboplatin over radiation owing to studies reporting an increased mortality from secondary malignancies following radiation therapy.[31-33] A randomized controlled trial comparing a single dose of carboplatin (area under the curve, 7 mg/mL per minute) to radiation therapy demonstrated similar relapse-free rates at 5 years (94.7% vs 96.0%) and a clear reduction in contralateral GCT (hazard ratio, 0.22; 95% CI, 0.05-0.95; *P*=.03) for patients treated with carboplatin.[34] Several phase 2 studies reported consistently lower relapse rates with 2 doses of carboplatin, and we prefer 2 doses over a single dose.[35] For example, the Spanish Germ Cell Cancer Group reported that 10-year disease-free survival was 97% and 10-year overall survival (OS) was 100% among 412 patients with clinical stage I seminoma who were at higher-than-average risk of relapse; these patients were treated with 2 doses of carboplatin (area under the curve, 7 mg/mL per minute) 21 days apart.[36] (Carboplatin and other common chemotherapy regimens used to treat GCTs are listed in Table 1.) However, surveillance is the preferred approach for patients who are willing and able to undergo surveillance owing to the concern about the potential risk of secondary malignancies and other late toxicities from carboplatin.

Nonseminoma

For patients with clinical stage I nonseminoma and normal serum tumor markers, reasonable postoperative management options include surveillance, adjuvant chemotherapy, and nerve-sparing RP lymph node dissection (RPLND). The presence of lymphovascular invasion (LVI) or a predominance of embryonal carcinoma histology are risk factors for relapse, although LVI appears to be the strongest risk factor.[37] One retrospective study of patients managed with active surveillance noted relapsed disease in 44% in patients with LVI vs 14% of those without LVI.[38] Prospective trials using either 1 or 2 cycles of adjuvant bleomycin, etoposide, and cisplatin (BEP) have reduced recurrence rates to less than 5%.[39,40] Although a German randomized trial demonstrated improved 2-year recurrence-free survival with adjuvant BEP over RPLND (99% vs 92%, respectively), the authors noted a relatively high rate of RP relapses in this community-based study, in contrast to only 1.2% of patients in a tertiary care–based single-arm study.[40,41] Thus, although RPLND can be an appropriate treatment to reduce recurrence risk while avoiding toxicity from chemotherapy, consideration of a surgical team's expertise is recommended. Although there can be toxicity and complications from adjuvant chemotherapy or RPLND, patients managed with surveillance who experience disease relapse will often require higher-intensity and longer-duration treatment. All options are appropriate, as disease-specific survival approaches 99% regardless of initial postoperative management. Most guidelines favor surveillance for low-risk disease but differ on the preferred option for high-risk disease.[25-27] Shared decision-making is important, particularly for high-risk disease.[42] If tumor markers are persistently elevated after orchiectomy and imaging studies show no metastatic disease, the disease is classified as stage IS and should be treated similar to metastatic NSGCTs based on risk stratification.

Stage II

Seminoma

Stage II seminoma is generally treated with either radiation therapy or chemotherapy (BEP × 3 or EP × 4). Historically, radiation therapy has been favored for less bulky disease (IIA and early stage IIB), although chemotherapy has been favored for bulkier disease.[43] Cutoffs of 3 cm and 5 cm have been used to recommend chemotherapy

over radiation therapy. The preference of chemotherapy for men with bulkier disease is based on studies showing high relapse rates after radiation in such patients.[44,45] For patients with less bulky disease, chemotherapy and radiation therapy appear to have similar efficacy. However, in the absence of randomized controlled trials, it is impossible to definitively recommend one modality over the other. Numerous case series have reported the outcomes of chemotherapy and radiation therapy for stage II seminoma with varying results.[44-49] A systematic review of studies published from 2010 to 2021 reported that relapse-free survival relapse rates were similar with radiation therapy (0%-4%) and chemotherapy (0%) in stage IIA disease, whereas the relapse rate was higher with radiation (9.5%-21.1%) than chemotherapy (0%-14.2%) in stage IIB disease.[50] Five-year OS ranged from 90% to 100%. Although some studies have investigated combining carboplatin with involved-field radiation therapy, this approach remains investigational.[51]

Given the concerns for secondary malignancies and other significant treatment-related toxicity associated with both radiation and chemotherapy, RPLND continues to be explored in this population.[52-54] Recent studies of RPLND have reported relapse rates as high as 30%, which is substantially higher than those for radiation therapy or chemotherapy. However, the benefit of reducing the risk of secondary malignancies and other late effects from those modalities may be greater than the benefit of a lower relapse rate.[55-57] Depending on the results of ongoing studies of RPLND for stage II seminoma, it may become another standard treatment option in the future, but cannot be recommended outside of a clinical trial at this time. Stage IIC disease (any lymph node >5 cm) should be treated with primary chemotherapy only.

Nonseminoma

Stage IIA. Treatment options for stage II NSGCT include RPLND and chemotherapy (BEP × 3 or EP × 4). Treatment recommendations for stage II NSGCT are largely influenced by lymph node size. If RP lymph nodes are no larger than 2 cm across at their greatest diameter, primary RPLND can cure the majority of patients (80%-90%) and pathologically downstage some patients to stage I if tissue shows no active GCT in the RP nodes. This gives the patient a greater likelihood of avoiding the acute and late toxicity of chemotherapy. If RPLND reveals either pathologic stage I or IIA disease, then the standard practice is surveillance, though adjuvant chemotherapy can be considered for stage IIA disease. The risk of relapse for stage IIA disease is only approximately 10%, and a trial comparing adjuvant chemotherapy to surveillance for pathologic stage II disease reported no difference in OS. Adjuvant chemotherapy with 2 cycles of EP is recommended for patients with pathologic stage IIB or IIC disease because they are at much higher risk of relapse (approximately 50%), and adjuvant chemotherapy reduces that risk to approximately 1%.[58,59]

Stage IIB/C. If nodes are more than 2 cm across at their greatest diameter, primary chemotherapy (BEP × 3 or EP × 4) is generally preferred over RPLND because the relapse rates for bulky disease are higher. Nonrandomized data suggest improved outcomes when selecting primary treatment modality (chemotherapy vs RPLND) based on risk factors, such as lymph node size.[60]

Stage III

Unlike other solid tumor malignancies, GCTs tend to be very sensitive to platinum-based chemotherapy, and most patients with metastatic disease can be cured. Risk stratification using the International Germ Cell Consensus Classification staging system should guide treatment decisions.[61] Stratification criteria appear in Table 2.

Good Risk

Good-risk disease should preferably be treated with 3 cycles of BEP. For patients at increased risk of bleomycin pulmonary toxicity (eg, >50 years of age, chronic kidney disease, or chronic obstructive pulmonary disease or other serious lung disease) or wanting to avoid exposure to bleomycin, an alternative is 4 cycles of EP. A randomized trial of 257 patients with good-risk metastatic NSGCTs reported more deaths in the EP arm (12 vs 5) and a slightly inferior event-free survival rate (86% vs 91%), but these differences were not statistically significant.[62] Dose reductions should be avoided, given that a randomized trial of a deintensified BEP regimen resulted in inferior survival compared with standard BEP for good-risk nonseminomas.[63] Similarly, carboplatin should not be substituted for cisplatin, given that carboplatin-based regimens have consistently been found to be inferior to cisplatin-based regimens.[64-66] The prognosis for good-risk disease is favorable, with a 5-year OS of approximately 90%.[61]

Patients with good-risk disease includes those with seminoma whose metastases are limited to lymph nodes and lungs, regardless of serum tumor marker levels. However, many experts consider a very high β-HCG (eg, >1000 mU/mL) to be incompatible with pure seminoma, regardless of histopathologic findings, and an elevated AFP indicates that the tumor is not a pure seminoma. The question of whether to take LDH levels into account is harder to resolve because a recent international study reported that an LDH level greater than 2.5 times the upper limit of normal was associated with a worse prognosis among otherwise good-risk seminoma patients (3-year progression-free survival [PFS] and OS

Table 2. Risk Stratification Based on the International Germ Cell Consensus Classification

Good-Risk	**Seminoma** Metastases are limited to lungs and/or lymph nodes	**Treatment:** BEP × 3 or EP × 4
	Nonseminoma (if *all* items present) Testicular or retroperitoneal primary tumor Metastases are limited to lungs and/or lymph nodes Tumor markers: • AFP <1000 ng/mL • β-HCG <1000 mU/mL • LDH <3× ULN	
Intermediate-Risk	**Seminoma** Presence of metastases in sites other than lungs or lymph nodes	**Treatment:** BEP × 4 or VIP × 4
	Nonseminoma (if *all* items present) Testicular or retroperitoneal primary tumor Metastases are limited to lungs and/or lymph nodes At least 1 serum tumor marker in the intermediate range and none higher than intermediate-risk range: • AFP 1000-10,000 ng/mL • β-HCG 5000-50,000 mU/mL • LDH 3-10× ULN	
Poor-Risk	**Nonseminoma (if *any* items present):** Mediastinal primary tumor Presence of metastases in sites other than lungs or lymph nodes (eg, liver, brain, bones) Tumor markers: • AFP >10,000 ng/mL • β-HCG >50,000 mU/mL • LDH >10× ULN	

AFP, alpha fetoprotein; BEP, bleomycin, etoposide, cisplatin; β-HCG, beta human chorionic gonadotropin; EP, etoposide, cisplatin; LDH, lactate dehydrogenase; ULN, upper limit of normal; VIP, etoposide, ifosfamide, cisplatin.

International Germ Cell Cancer Collaborative Group. *J Clin Oncol.* 1997;15(2):594-603.[61]

of 80% and 92%, respectively, vs 92% and 97% for other good-risk patients).[67] Whether such patients should be treated as having intermediate-risk disease or with 3 cycles of BEP plus a fourth cycle with EP is an unresolved question.[68]

Intermediate and Poor Risk

Treatment paradigms for intermediate- and poor-risk disease are similar, with risk stratification affecting prognosis rather than clinical decision-making. The standard treatment is 4 cycles of BEP. For patients in whom bleomycin is contraindicated, etoposide, ifosfamide, and cisplatin (VIP) is an alternative regimen resulting in similar OS and PFS in both intermediate- and poor-risk disease.[69,70] Although using VIP avoids bleomycin-induced pulmonary toxicity, VIP does result in increased hematologic toxicity. Based on historical data, the 5-year OS for intermediate- and poor-risk disease was 79% and 48%, respectively.[61] However, these data are based on patients treated between 1975 and 1990. More recently, data from 1990 to 2013 found that patients with intermediate-risk seminomas had a 5-year OS of 88%, and a meta-analysis of patients with NSGCTs treated after 1989 reported pooled 5-year survival estimates of 83% (intermediate risk) and 71% (poor risk).[67,71]

Residual Masses After Chemotherapy

Seminoma

Residual masses in patients with seminoma are usually benign, and surveillance is a safe option.[72,73] Based

on data showing that the likelihood of viable residual seminoma increases with larger residual mass size,[74] some advocate for surveillance of masses less than 3 cm and the use of a fluorodeoxyglucose (FDG) PET scan for masses 3 cm or larger.[75] This is based on data from the SEMPET trial, which reported 100% accuracy for masses larger than 3 cm.[76] However, subsequent studies have reported false-positive rates of approximately 75%, and enthusiasm for PET scans in this setting has greatly declined.[77,78] For patients who have a positive PET scan, we recommend either repeating the PET scan at least 6 weeks later or performing resection or biopsy (biopsy should be extensive to mitigate sampling error) to confirm whether viable seminoma is present. Enlarging residual masses on surveillance should be treated as relapsed disease and managed with chemotherapy or, less frequently, resection, depending on the clinical circumstances. It is important to note that treated seminomas are often characterized by a dense scirrhous reaction that can make resection technically difficult and increase the rate of surgical complications.[73,78,79]

Nonseminoma

If tumor markers are normal, resection of all masses larger than 1 cm is the standard of care whenever feasible.[80] There is no role for FDG-PET in the evaluation of residual masses in nonseminomas. For masses in the retroperitoneum, an RPLND is performed, and masses elsewhere (eg, lungs, liver, brain) should also be resected when feasible. Masses less than 1 cm should be observed closely. The histopathology of residual masses may show fibrosis and necrosis, teratoma, or residual GCT. If there is residual GCT, 2 cycles of adjuvant chemotherapy are recommended for patients who have previously received first-line but not second- or third-line chemotherapy.[81]

Relapsed Disease

Despite the significant advancements that have resulted in a cure for many patients with GCTs, a minority of patients will experience disease relapse. For patients with stage I disease who experience relapse in the retroperitoneum, RPLND can be considered for nonbulky disease (lymph nodes <2 cm) if tumor markers are normal. In one report of 45 patients undergoing surveillance for stage I NSGCT who experienced disease relapse in the retroperitoneum, RPLND alone (without further therapy) was curative in 82%.[82]

For most patients with relapsed disease, however, cytotoxic chemotherapy is the standard. The choice of regimen depends on prior exposure to chemotherapy, medical comorbidities, and contraindications to specific agents. For patients who are chemotherapy-naive or whose only prior chemotherapy was carboplatin (for stage I seminoma), chemotherapy selection should be determined by risk stratification criteria for de novo stage III disease (eg, good-risk: BEP × 3 or EP × 4, intermediate- or poor-risk: BEP × 4 or VIP × 4). For patients who received 1 or 2 cycles of BEP for stage I or pathologic stage II NSGCT, the chemotherapy regimen used for patients at standard risk should also be given, although we avoid exposing patients to more than 4 cycles of bleomycin-containing chemotherapy owing to the risk of pulmonary complications.

For patients who experience disease relapse after first-line chemotherapy for advanced-stage disease (eg, BEP × 3, EP × 4, BEP × 4, VIP × 4), treatment with either standard-dose or high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) are options. Paclitaxel, ifosfamide, and cisplatin (TIP)[83] and vinblastine, ifosfamide, and cisplatin (VeIP)[84] are both acceptable options for standard-dose chemotherapy, whereas carboplatin plus etoposide is the most commonly used high-dose chemotherapy regimen.[85]

HDCT with ASCT has demonstrated efficacy in heavily pretreated patients with relapsed GCTs. However, it is unclear whether or not to use HDCT with ASCT instead of standard-dose chemotherapy in the second line. Retrospective analyses have supported the use of HDCT with ASCT as the first salvage treatment for relapsed GCT. Based on a database of 1984 patients with relapsed GCT, one analysis found that HDCT was superior to standard-dose chemotherapy in both 2-year PFS (49.6% vs 27.8%) and 5-year OS (53.2% vs 40.8%).[86] The international phase 3 TIGER trial is comparing salvage conventional-dose chemotherapy with HDCT with ASCT in the second line, with a primary endpoint of OS.[87] As of December 2022, this trial has completed accrual and we await the results with anticipation.[88]

Prognosis is poor for patients with multiple disease relapses or platinum-refractory disease, although treatment with chemotherapy can still be beneficial. The combination of gemcitabine, oxaliplatin, and paclitaxel was shown to have efficacy in cisplatin-refractory disease or relapse after HDCT with ASCT. The overall response was 51%, with 5% achieving a complete response. Fifteen percent remained in remission after chemotherapy with or without residual tumor resection at a median follow-up of 5 months.[89]

The efficacy of checkpoint inhibitors for relapsed/refractory GCTs is disappointing. A single-arm phase 2 trial of pembrolizumab (Keytruda, Merck) demonstrated no responses in 12 patients who had received at least 2 prior lines of therapies.[90] Thus, outside of a clinical trial or a biomarker-selected cohort (such as mismatch repair deficiency, microsatellite instability, or tumor mutation

burden–high cancers), checkpoint inhibitors have no role at this time. Personalized treatment of refractory GCTs based on molecular or genomic profiling has thus far been disappointing because targetable mutations are rarely identified; further studies in this area are needed to develop effective targeted therapies for patients with testis cancer.[91]

Survivorship

Although cisplatin-based chemotherapy has dramatically increased the cure rate for testicular GCTs, it has also resulted in toxicity that can compromise both quality and length of life.[31,92-95] Radiation therapy for testis cancer has also been associated with decreased life expectancy.[31,33] These findings have led to increased interest in expanding the role of surgery to reduce exposure to chemotherapy and radiation therapy. Chemotherapy side effects and late toxicities include peripheral neuropathy, high-pitch hearing loss, tinnitus, cardiovascular disease, reduced pulmonary and renal function, Raynaud phenomenon, hypogonadism, and infertility.[94,96] Both radiation therapy and chemotherapy are associated with an increased risk of developing secondary malignancies, which have been associated with reduced life expectancy.[31,32] Radiation therapy and chemotherapy have also both been associated with an increased incidence of erectile dysfunction.

Disclosures

Dr Wee is an advisory board consultant for Bayer and Janssen. Dr Gilligan has no disclosures.

References

1. SEER cancer stat facts: testicular cancer. National Cancer Institute Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/testis.html. Accessed December 6, 2022.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55(2):74-108.
3. Ko JJ, Bernard B, Tran B, et al. Conditional survival of patients with metastatic testicular germ cell tumors treated with first-line curative therapy. *J Clin Oncol*. 2016;34(7):714-720.
4. Lauritsen J, Kier MG, Mortensen MS, et al. Germ cell cancer and multiple relapses: toxicity and survival. *J Clin Oncol*. 2015;33(28):3116-3123.
5. Cheng L, Albers P, Berney DM, et al. Testicular cancer. *Nat Rev Dis Primers*. 2018;4(1):29.
6. Chia VM, Quraishi SM, Devesa SS, Purdue MP, Cook MB, McGlynn KA. International trends in the incidence of testicular cancer, 1973-2002. *Cancer Epidemiol Biomarkers Prev*. 2010;19(5):1151-1159.
7. Williamson SR, Delahunt B, Magi-Galluzzi C, et al; Members of the ISUP Testicular Tumour panel. The World Health Organization 2016 classification of testicular germ cell tumours: a review and update from the International Society of Urological Pathology testis consultation panel. *Histopathology*. 2017;70(3):335-346.
8. Rabade K, Panjwani PK, Menon S, et al. Spermatocytic tumor of testis: a case series of 26 cases elucidating unusual patterns with diagnostic and treatment dilemmas. *J Cancer Res Ther*. 2022;18(suppl):S449-S454.
9. Park JS, Kim J, Elghiaty A, Ham WS. Recent global trends in testicular cancer incidence and mortality. *Medicine (Baltimore)*. 2018;97(37):e12390.
10. Kharazmi E, Hemminki K, Pukkala E, et al. Cancer risk in relatives of testicular cancer patients by histology type and age at diagnosis: a joint study from five Nordic countries. *Eur Urol*. 2015;68(2):283-289.
11. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International testicular cancer incidence trends: generational transitions in 38 countries 1900-1990. *Cancer Causes Control*. 2015;26(1):151-158.
12. Trabert B, Chen J, Devesa SS, Bray F, McGlynn KA. International patterns and trends in testicular cancer incidence, overall and by histologic subtype, 1973-2007. *Andrology*. 2015;3(1):4-12.
13. Znaor A, Lortet-Tieulent J, Jemal A, Bray F. International variations and trends in testicular cancer incidence and mortality. *Eur Urol*. 2014;65(6):1095-1106.
14. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod*. 2001;16(5):972-978.
15. Brenner DR, Heer E, Ruan Y, Peters CE. The rising incidence of testicular cancer among young men in Canada, data from 1971-2015. *Cancer Epidemiol*. 2019;58:175-177.
16. Gilligan TD, Seidenfeld J, Basch EM, et al; American Society of Clinical Oncology. American Society of Clinical Oncology clinical practice guideline on uses of serum tumor markers in adult males with germ cell tumors. *J Clin Oncol*. 2010;28(20):3388-3404.
17. Al-Obaidy KI, Magers MJ, Idrees MT. Testicular cancer: contemporary updates in staging. *Surg Pathol Clin*. 2022;15(4):745-757.
18. Sahin AA, Gilligan TD, Caudell JJ. Challenges with the 8th edition of the AJCC Cancer Staging Manual for breast, testicular, and head and neck cancers. *J Natl Compr Canc Netw*. 2019;17(5.5):560-564.
19. Peng Y, Croce CM. The role of microRNAs in human cancer. *Signal Transduct Target Ther*. 2016;1:15004.
20. Nappi L, Thi M, Lum A, et al. Developing a highly specific biomarker for germ cell malignancies: plasma miR371 expression across the germ cell malignancy spectrum. *J Clin Oncol*. 2019;37(33):3090-3098.
21. Dieckmann KP, Radtke A, Geczi L, et al. Serum levels of microRNA-371a-3p (M371 test) as a new biomarker of testicular germ cell tumors: results of a prospective multicentric study. *J Clin Oncol*. 2019;37(16):1412-1423.
22. Pasoglou V, Van Nieuwenhove S, Van Damme J, et al. Whole body MRI in the detection of lymph node metastases in patients with testicular germ cell cancer. *Life (Basel)*. 2022;12(2):212.
23. Joffe JK, Cafferty FH, Murphy L, et al; TRISST trial management group and investigators. imaging modality and frequency in surveillance of stage I seminoma testicular cancer: results from a randomized, phase III, noninferiority trial (TRISST). *J Clin Oncol*. 2022;40(22):2468-2478.
24. Pierorazio PM, Cheaib JG, Tema G, et al. Performance characteristics of clinical staging modalities for early stage testicular germ cell tumors: a systematic review. *J Urol*. 2020;203(5):894-901.
25. Gilligan T, Lin DW, Aggarwal R, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Testicular cancer. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf. Updated January 26, 2023. Accessed March 1, 2023.
26. Stephenson A, Eggener SE, Bass EB, et al. Diagnosis and treatment of early stage testicular cancer: AUA guideline. *J Urol*. 2019;202(2):272-281.
27. Oldenburg J, Berney DM, Bokemeyer C, et al; ESMO Guidelines Committee and EURACAN. Testicular seminoma and non-seminoma: ESMO-EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022;33(4):362-375.
28. Groll RJ, Warde P, Jewett MA. A comprehensive systematic review of testicular germ cell tumor surveillance. *Crit Rev Oncol Hematol*. 2007;64(3):182-197.
29. Petrelli F, Coinu A, Cabiddu M, et al. Surveillance or adjuvant treatment with chemotherapy or radiotherapy in stage I seminoma: a systematic review and meta-analysis of 13 studies. *Clin Genitourin Cancer*. 2015;13(5):428-434.
30. Pierorazio PM, Albers P, Black PC, et al. Non-risk-adapted surveillance for stage I testicular cancer: critical review and summary. *Eur Urol*. 2018;73(6):899-907.
31. Hellesnes R, Myklebust TA, Fosså SD, et al. Testicular cancer in the cisplatin era: causes of death and mortality rates in a population-based cohort. *J Clin Oncol*. 2021;39(32):3561-3573.
32. Groot HJ, Lubberts S, de Wit R, et al. Risk of solid cancer after treatment of testicular germ cell cancer in the platinum era. *J Clin Oncol*. 2018;36(24):2504-2513.
33. Kier MG, Hansen MK, Lauritsen J, et al. Second malignant neoplasms and cause of death in patients with germ cell cancer: a Danish nationwide cohort study. *JAMA Oncol*. 2016;2(12):1624-1627.

34. 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(8):957-962.
35. Steiner H, Scheiber K, Berger AP, et al. Retrospective multicentre study of carboplatin monotherapy for clinical stage I seminoma. *BJU Int*. 2011;107(7):1074-1079.
36. Aparicio J, García Del Muro X, Maroto P, et al. Patterns of relapse and treatment outcome after active surveillance or adjuvant carboplatin for stage I seminoma: a retrospective study of the Spanish Germ Cell Cancer Group. *Clin Transl Oncol*. 2021;23(1):58-64.
37. Blok JM, Pluim I, Daugaard G, et al. Lymphovascular invasion and presence of embryonal carcinoma as risk factors for occult metastatic disease in clinical stage I nonseminomatous germ cell tumour: a systematic review and meta-analysis. *BJU Int*. 2020;125(3):355-368.
38. 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(1):51-57.
39. Tandstad T, Ståhl O, Håkansson U, et al; SWENOTECA. One course of adjuvant BEP in clinical stage I nonseminoma mature and expanded results from the SWENOTECA group. *Ann Oncol*. 2014;25(11):2167-2172.
40. Albers P, Siener R, Krege S, et al; German Testicular Cancer Study Group. 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(18):2966-2972.
41. Heidenreich A, Albers P, Hartmann M, et al; German Testicular Cancer Study Group. 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(5):1710-1714.
42. Oldenburg J, Aparicio J, Beyer J, et al. Personalizing, not patronizing: the case for patient autonomy by unbiased presentation of management options in stage I testicular cancer. *Ann Oncol*. 2015;26(5):833-838.
43. Warde P, Huddart R, Bolton D, Heidenreich A, Gilligan T, Fossa S. Management of localized seminoma, stage I-II: SIU/ICUD Consensus Meeting on Germ Cell Tumors (GCT), Shanghai 2009. *Urology*. 2011;78(4)(suppl):S435-S443.
44. Chung PW, Gospodarowicz MK, Panzarella T, et al. Stage II testicular seminoma: patterns of recurrence and outcome of treatment. *Eur Urol*. 2004;45(6):754-759.
45. Detti B, Livi L, Scoccianti S, et al. Management of stage II testicular seminoma over a period of 40 years. *Urol Oncol*. 2009;27(5):534-538.
46. Domont J, Massard C, Patrikidou A, et al. A risk-adapted strategy of radiotherapy or cisplatin-based chemotherapy in stage II seminoma. *Urol Oncol*. 2013;31(5):697-705.
47. Hallemeier CL, Pisansky TM, Davis BJ, Choo R. Long-term outcomes of radiotherapy for stage II testicular seminoma—the Mayo Clinic experience. *Urol Oncol*. 2013;31(8):1832-1838.
48. Glaser SM, Vargo JA, Balasubramani GK, Beriwal S. Stage II testicular seminoma: patterns of care and survival by treatment strategy. *Clin Oncol (R Coll Radiol)*. 2016;28(8):513-521.
49. Garcia-del-Muro X, Maroto P, Gumà J, et al. Chemotherapy as an alternative to radiotherapy in the treatment of stage IIA and IIB testicular seminoma: a Spanish Germ Cell Cancer Group Study. *J Clin Oncol*. 2008;26(33):5416-5421.
50. Heinzelbecker J, Schmidt S, Lackner J, et al. Therapy of clinical stage IIA and IIB seminoma: a systematic review. *World J Urol*. 2022;40(12):2829-2841.
51. Papachristofilou A, Bedke J, Hayoz S, et al. Single-dose carboplatin followed by involved-node radiotherapy for stage IIA and stage IIB seminoma (SAKK 01/10): a single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2022;23(11):1441-1450.
52. Alsyouf M, Daneshmand S. Clinical stage II seminoma: management options. *World J Urol*. 2022;40(2):343-348.
53. Hu B, Daneshmand S. Retroperitoneal lymph node dissection as primary treatment for metastatic seminoma. *Adv Urol*. 2018;2018:7978958.
54. Tabakin AL, Shinder BM, Kim S, et al. Retroperitoneal lymph node dissection as primary treatment for men with testicular seminoma: utilization and survival analysis using the national cancer data base, 2004-2014. *Clin Genitourin Cancer*. 2020;18(2):e194-e201.
55. Daneshmand S, Cary C, Masterson TA, et al. SEMS trial: result of a prospective, multi-institutional phase II clinical trial of surgery in early metastatic seminoma [ASCO GU abstract 375]. *J Clin Oncol*. 2021;39(6)(suppl).
56. Albers P, Hiester A, Grosse Siemer R, Lusch A. The PRIMETEST trial: interim analysis of a phase II trial for primary retroperitoneal lymph node dissection (RPLND) in stage II A/B seminoma patients without adjuvant treatment [ASCO GU abstract 507]. *J Clin Oncol*. 2019;37(7)(suppl).
57. Hiester A, Che Y, Lusch A, et al. Phase 2 single-arm trial of primary retroperitoneal lymph node dissection in patients with seminomatous testicular germ cell tumors with clinical stage IIA/B (PRIMETEST) [published online November 10, 2022]. *Eur Urol*. doi:10.1016/j.eururo.2022.10.021.
58. Williams SD, Stablein DM, Einhorn LH, et al. Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. *N Engl J Med*. 1987;317(23):1433-1438.
59. McHugh DJ, Funt SA, Silber D, et al. Adjuvant chemotherapy with etoposide plus cisplatin for patients with pathologic stage II nonseminomatous germ cell tumors. *J Clin Oncol*. 2020;38(12):1332-1337.
60. Stephenson AJ, Bosl GJ, Motzer RJ, Bajorin DF, Stasi JP, Sheinfeld J. Nonrandomized comparison of primary chemotherapy and retroperitoneal lymph node dissection for clinical stage IIA and IIB nonseminomatous germ cell testicular cancer. *J Clin Oncol*. 2007;25(35):5597-5602.
61. International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol*. 1997;15(2):594-603.
62. Culine S, Kerbrat P, Kramar A, et al; Genito-Urinary Group of the French Federation of Cancer Center (GETUG T93BP). Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). *Ann Oncol*. 2007;18(5):917-924.
63. Toner GC, Stockler MR, Boyer MJ, et al; Australian and New Zealand Germ Cell Trial Group. Comparison of two standard chemotherapy regimens for good-prognosis germ-cell tumours: a randomised trial. *Lancet*. 2001;357(9258):739-745.
64. Horwich A, Sleijfer DT, Fosså SD, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *J Clin Oncol*. 1997;15(5):1844-1852.
65. Bokemeyer C, Köhrmann O, Tischler J, et al. A randomized trial of cisplatin, etoposide and bleomycin (PEB) versus carboplatin, etoposide and bleomycin (CEB) for patients with 'good-risk' metastatic non-seminomatous germ cell tumors. *Ann Oncol*. 1996;7(10):1015-1021.
66. Bajorin DF, Sarosdy MF, Pfister DG, et al. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. *J Clin Oncol*. 1993;11(4):598-606.
67. Beyer J, Collette L, Sauvé N, et al; International Germ Cell Cancer Classification Update Consortium. Survival and new prognosticators in metastatic seminoma: results from the IGCCCG-Update Consortium. *J Clin Oncol*. 2021;39(14):1553-1562.
68. Fedyanin M, Tryakin A, Bulanov A, et al. Chemotherapy intensification in patients with advanced seminoma and adverse prognostic factors. *J Cancer Res Clin Oncol*. 2015;141(7):1259-1264.
69. de Wit R, Stoter G, Sleijfer DT, et al; European Organization for Research and Treatment of Cancer. Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. *Br J Cancer*. 1998;78(6):828-832.
70. Hinton S, Catalano PJ, Einhorn LH, et al. Cisplatin, etoposide and either bleomycin or ifosfamide in the treatment of disseminated germ cell tumors: final analysis of an intergroup trial. *Cancer*. 2003;97(8):1869-1875.
71. van Dijk MR, Steyerberg EW, Habbema JD. Survival of non-seminomatous germ cell cancer patients according to the IGCC classification: an update based on meta-analysis. *Eur J Cancer*. 2006;42(7):820-826.
72. Ravi R, Ong J, Oliver RT, Badenoch DF, Fowler CG, Hendry WF. The management of residual masses after chemotherapy in metastatic seminoma. *BJU Int*. 1999;83(6):649-653.
73. Quek ML, Simma-Chiang V, Stein JP, Pinski J, Quinn DI, Skinner DG. Post-chemotherapy residual masses in advanced seminoma: current management and outcomes. *Expert Rev Anticancer Ther*. 2005;5(5):869-874.
74. Flechon A, Bompas E, Biron P, Droz JP. Management of post-chemotherapy residual masses in advanced seminoma. *J Urol*. 2002;168(5):1975-1979.
75. Albany C, Kesler K, Cary C. Management of residual mass in germ cell tumors after chemotherapy. *Curr Oncol Rep*. 2019;21(1):5.
76. 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 postche-

motherapy seminoma: an update of the prospective multicentric SEMPET trial. *J Clin Oncol*. 2004;22(6):1034-1039.
77. Cathomas R, Klingbiel D, Bernard B, et al. Questioning the value of fluorodeoxyglucose positron emission tomography for residual lesions after chemotherapy for metastatic seminoma: results of an international global germ cell cancer group registry [published online October 4, 2018]. *J Clin Oncol*. doi:10.1200/JCO.18.00210.
78. Decoene J, Winter C, Albers P. False-positive fluorodeoxyglucose positron emission tomography results after chemotherapy in patients with metastatic seminoma. *Urol Oncol*. 2015;33(1):23.e15-23.e21.
79. Mosharafa AA, Foster RS, Leibovich BC, Bihrle R, Johnson C, Donohue JP. Is post-chemotherapy resection of seminomatous elements associated with higher acute morbidity? *J Urol*. 2003;169(6):2126-2128.
80. Heidenreich A, Paffenholz P, Nestler T, Pfister D. Management of residual masses in testicular germ cell tumors. *Expert Rev Anticancer Ther*. 2019;19(4):291-300.
81. Fizazi K, Oldenburg J, Dunant A, et al. Assessing prognosis and optimizing treatment in patients with postchemotherapy viable nonseminomatous germ-cell tumors (NSGCT): results of the sCR2 international study. *Ann Oncol*. 2008;19(2):259-264.
82. Hamilton RJ, Nayan M, Anson-Cartwright L, et al. Treatment of relapse of clinical stage I nonseminomatous germ cell tumors on surveillance. *J Clin Oncol*. 2019;37(22):1919-1926.
83. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *J Clin Oncol*. 2005;23(27):6549-6555.
84. Loehrer PJ Sr, Gonin R, Nichols CR, Weathers T, Einhorn LH. Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. *J Clin Oncol*. 1998;16(7):2500-2504.
85. Adra N, Abonour R, Althouse SK, Albany C, Hanna NH, Einhorn LH. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumors: the Indiana University experience. *J Clin Oncol*. 2017;35(10):1096-1102.
86. Lorch A, Bascoul-Mollevi C, Kramar A, et al. Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database. *J Clin Oncol*. 2011;29(16):2178-2184.
87. Feldman DR, Huddart R, Hall E, Beyer J, Powles T. Is high dose therapy superior to conventional dose therapy as initial treatment for relapsed germ cell tumors? The TIGER Trial. *J Cancer*. 2011;2:374-377.
88. Completion of patient recruitment for international TIGER study [press release]. EORTC and Alliance for Clinical Trials in Oncology. https://www.eortc.org/blog/2022/12/19/completion-of-patient-recruitment-tiger-study. Updated December 19, 2022. Accessed March 6, 2023.
89. Bokemeyer C, Oechsle K, Honecker F, et al; German Testicular Cancer Study Group. Combination chemotherapy with gemcitabine, oxaliplatin, and paclitaxel in patients with cisplatin-refractory or multiply relapsed germ-cell tumors: a study of the German Testicular Cancer Study Group. *Ann Oncol*. 2008;19(3):448-453.
90. Adra N, Einhorn LH, Althouse SK, et al. Phase II trial of pembrolizumab in patients with platinum refractory germ-cell tumors: a Hoosier Cancer Research Network Study GU14-206. *Ann Oncol*. 2018;29(1):209-214.
91. Bokemeyer C, Oing C, Russell K, et al. Molecular profiling of testicular cancer [ASCO abstract 4515]. *J Clin Oncol*. 2014;32(15)(suppl).
92. Lauritsen J, Hansen MK, Bandak M, et al. Cardiovascular risk factors and disease after male germ cell cancer. *J Clin Oncol*. 2020;38(6):584-592.
93. Kerns SL, Fung C, Monahan PO, et al; Platinum Study Group. Cumulative burden of morbidity among testicular cancer survivors after standard cisplatin-based chemotherapy: a multi-institutional study. *J Clin Oncol*. 2018;36(15):1505-1512.
94. Chovanec M, Abu Zaid M, Hanna N, El-Kouri N, Einhorn LH, Albany C. Long-term toxicity of cisplatin in germ-cell tumor survivors. *Ann Oncol*. 2017;28(11):2670-2679.
95. Fung C, Fossa SD, Williams A, Travis LB. Long-term morbidity of testicular cancer treatment. *Urol Clin North Am*. 2015;42(3):393-408.
96. Fung C, Sesso HD, Williams AM, et al; Platinum Study Group. Multi-institutional assessment of adverse health outcomes among north american testicular cancer survivors after modern cisplatin-based chemotherapy. *J Clin Oncol*. 2017;35(11):1211-1222.