Review Article

Systemic therapy for primary and extragonadal germ cell tumors: prognosis and nuances of treatment

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Abstract: Testicular germ cell tumors are the most common solid tumors in young men. These cancers represent a success story of modern medicine in our ability to cure young patients and offer decades of life, with a 5-year survival rate of approximately 95%. This review outlines the staging and risk classification of testicular cancers, and reviews the current state of knowledge and standard of care for the systemic treatment of testicular germ cell tumors with chemotherapy, focusing on the relevant clinical data supporting each treatment regimen. This review also briefly highlights current areas of active investigation, notably in the relapsed and refractory setting, including ongoing clinical trials.

Keywords: Neoplasms; germ cell and embryonal; non-seminomatous germ cell tumor; testicular germ cell tumor; seminoma

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Introduction

Although uncommon in the overall population, testicular germ cell tumors are the most common solid tumors in young men between the ages of 20 and 34, with an estimated 9,310 cases diagnosed in the United States in 2018, with approximately 400 deaths (1). In general, testicular germ cell tumors carry an excellent prognosis, with a 5-year survival rate of approximately 95% (1). An increasing incidence of testicular cancers has been observed, for uncertain reasons (2-5). Testicular germ cell tumors account for the vast majority of malignant tumors arising in the testes; these tumors also occasionally arise in extragonadal sites, such as the retroperitoneum and anterior mediastinum (6,7). Risk factors for testicular cancer include cryptorchidism, family history, and prior history of testicular cancer (8,9).

Testicular germ cell tumor is classically divided into two major subtypes: pure seminoma and non-seminoma (10). Non-seminomas are comprised of four major tumor types: embryonal carcinoma, choriocarcinoma, yolk sac tumor, and teratoma (10). Non-seminomas are typically more clinically aggressive, and the presence of any of the four histologic subtypes will define a tumor as a non-seminoma. A well-established standard of care exists for the majority of testicular germ cell tumors, leading to a high overall survival rate. This review seeks to provide an overview of the current standard of care for systemic therapy of testicular germ cell tumors, including nuances of treatment and briefly explores current areas of active research and future directions for therapy.

Staging and risk classification

The American Joint Committee on Cancer (AJCC) staging system for testicular germ cell tumors, most recently

Table 1 AJCC prognostic staging system

Stage	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage IA	pT1	N0	M0	S0
Stage IB	pT2-pT4	N0	M0	S0
Stage IS	Any T	N0	M0	S1–3
Stage IIA	Any T	N1	M0	S0–1
Stage IIB	Any T	N2	M0	S0–1
Stage IIC	Any T	N3	M0	S0–1
Stage IIIA	Any T	Any N	M1a	S0–1
Stage IIIB	Any T	N1–3	M0	S2
	Any T	Any N	M1a	S2
Stage IIIC	Any T	N1–3	M0	S3
	Any T	Any N	M1a	S3
	AnyT	Any N	M1b	Any S

Adapted from the AJCC Cancer Staging Manual, 8th ed [2017] (11).

in its eighth edition, incorporates tumor (T), node (N), and metastatic (M) status of the tumor as well as post-orchiectomy serum tumor markers (S), which are unique to this tumor type (11). In addition to incorporating tumor markers into staging, testicular germ cell tumor staging is unique insofar as it lacks a "stage IV" designation—tumors are staged from stage 0 to stage III (11) (*Table 1*, AJCC Staging System). The serum tumor markers of interest in this disease include alpha fetoprotein (AFP), beta-human chorionic gonadotropin (beta-hCG), and lactate dehydrogenase (LDH) (12). These tumor markers are obtained post-orchiectomy, on the first day of the first cycle of chemotherapy, and during therapy for assessment of response.

Risk classification criteria were standardized by the International Germ Cell Cancer Consensus Group (IGCCCG) in 1997 on the basis of post-orchiectomy tumor markers and extent of measurable disease (13). Non-seminomas are stratified into good-, intermediate-, and poor-risk status on the basis of location of the primary tumor, presence of non-pulmonary visceral metastases, and levels of post-orchiectomy markers (13) (*Figure 1*, IGCCCG Risk Stratification for Non-seminoma) (13). Seminomas are stratified solely into good- or intermediate-risk on the basis of non-pulmonary visceral metastases, reflecting the overall favorable prognosis of this disease entity. Tumor markers are not used to assign prognosis in pure seminoma (*Figure 2*, IGCCCG Risk Stratification for Seminoma) (13).

Risk status	
Good risk	Testicular or retroperitoneal primary tumor and No non-pulmonary visceral metastases and all post-orchiectomy markers: • AFP <1,000 ng/mL • hCG <5,000 IU/L • LDH <1.5× ULN
Intermediate risk	Testicular or retroperitoneal primary tumor and No non-pulmonary visceral metastases and any post-orchiectomy markers: • AFP 1,000–10,000 ng/mL • hCG 5,000–50,000 IU/L • LDH 1.5–10× ULN
Poor risk	Mediastinal primary tumor or Non-pulmonary visceral metastases or any post-orchiectomy markers: • AFP >10,000 ng/mL • hCG >50,000 IU/L • LDH >10× ULN

Figure 1 IGCCCG risk stratification of nonseminoma (13).

Risk status	
Good risk	No non-pulmonary visceral metastases and • Normal AFP • Any hCG • Any LDH
Intermediate risk	Presence of non-pulmonary visceral metastases and • Normal AFP • Any hCG • Any LDH

Figure 2 IGCCCG risk stratification of seminoma (13).

Pure seminoma

Pure seminoma is staged and risk stratified according to the criteria outlined above. Notably, AFP is not associated with pure seminoma—elevated AFP signifies non-seminoma unless an alternative explanation is present, e.g., liver

disease. Tumor marker staging for pure seminoma is on the basis of beta-hCG and LDH. Treatment decisions are typically not made on the basis of an isolated LDH level alone. Stage I seminoma carries an excellent prognosis, with a disease-free survival of 99% with treatment (14). Management options for stage I pure seminoma include active surveillance, chemotherapy with single agent carboplatin, and radiation therapy.

While most patients with stage I pure seminoma are cured with orchiectomy alone, it is estimated that 15% to 20% of patients relapse after initial orchiectomy, which has been demonstrated in prospective trials of surveillance (15-18). In a retrospective analysis of 2,483 patients with stage I germ cell tumors undergoing active surveillance, a relapse rate of 13% was identified among patients with stage I pure seminoma, with a median time to relapse of 14 months, and, as noted above, a 5-year disease-free survival of 99% (19,20). For patients who are unable to or prefer not to pursue a schedule of active surveillance, options include adjuvant carboplatin or radiation therapy.

The initial results of a randomized trial comparing adjuvant carboplatin to radiation therapy for stage I pure seminoma were reported by Oliver *et al.* in 2005, in which 1,477 patients were randomized to receive either a single cycle of carboplatin (n=560) or radiation therapy (n=885) (21). At a follow-up time point of three years, similar relapse-free survival rates were observed (94.8% in the carboplatin arm versus 95.9% in the radiation therapy arm) (21). The final results of this trial were reported in 2011, and demonstrated a similar 5-year relapse-free survival rate of 96% in the radiation therapy arm and 94.7% in the carboplatin arm (hazard ratio =1.25, P=0.37) (22).

Trials have also explored the use of two cycles of adjuvant chemotherapy. In the 2nd and 3rd Spanish Germ Cell Cancer Cooperative Group Studies, two cycles of adjuvant carboplatin were shown to reduce the rate of relapse for high risk (defined as tumors >4 cm and invasion of the rete testis) stage I seminoma, yielding a 5-year relapse-free survival rate of 96.2% (16,23). The overall survival at five years in these trials was 100% (16,23). Similarly, in the Hellenic Cooperative Oncology Group trial of 138 stage I seminoma patients, two cycles of adjuvant carboplatin demonstrated a 5-year relapse-free survival rate of 96.8% (24). In a head-to-head comparison of surveillance, one cycle of carboplatin, and two cycles of carboplatin in 725 stage I seminoma patients, the relapse rate with one cycle of carboplatin was observed to be 5% versus 1.5% with two cycles of carboplatin at a median follow-up of thirty months (25). The relapse rate was 8.2% with surveillance. Adjuvant radiation therapy is also an acceptable approach for stage I seminoma, albeit with an associated increase risk in secondary malignancies (26,27). A detailed discussion of radiation therapy is beyond the scope of this review. Stage Is is an uncommon form of pure seminoma, in which persistent elevation of tumor markers is observed following orchiectomy. Systemic treatment is not indicated for elevated markers alone, until there is clinical evidence of metastatic disease.

Stage II disease is defined by the presence of lymph node involvement. Clinical N1 (cN1) disease is defined as metastasis with a lymph node mass 2 cm or smaller in the greatest dimension or multiple lymph nodes, with none larger than 2 cm in the greatest dimension. Clinical N2 (cN2) disease includes metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in the greatest dimension or multiple lymph nodes, with any one mass larger than 2 cm but not larger than 5 cm. Clinical N3 (cN3) disease is defined as metastasis with lymph node mass greater than 5 cm in the largest dimension. On this basis, stage IIA encompasses cN1 disease, while cN2 defines stage IIB and cN3 defines stage IIC. Treatment options for stage IIA and IIB seminoma includes adjuvant radiation therapy or chemotherapy. Standard chemotherapy regimens include bleomycin, etoposide, and cisplatin (BEP) for three cycles or etoposide and cisplatin (EP) for four cycles. Mixed evidence has been observed in comparison with radiation therapy (28-30). In one retrospective study of 1,772 stage II seminoma patients following orchiectomy, 5-year overall survival was higher with radiation therapy compared to chemotherapy for stage IIA patients, however no difference was observed in stage IIB patients (31). Similarly, in a retrospective study of 1,885 stage II seminoma patients receiving either adjuvant chemotherapy or radiation therapy, overall survival was improved with radiation therapy in stage IIA, but not in stage IIB patients (32). These studies are limited by their retrospective and non-randomized nature, however in general practice either chemotherapy or radiation therapy are acceptable for stage II seminoma, with chemotherapy preferred for stage IIB disease.

For stage IIC or stage III seminoma, disease is stratified into good or intermediate risk on the basis of non-pulmonary visceral metastasis. For good risk disease, standard chemotherapy options, as above, include three cycles of BEP or four cycles of EP. Primary mediastinal seminoma is treated by risk status used for gonadal seminoma with three cycles of BEP or four cycles of EP. Equivalency of

three cycles versus four cycles of BEP was established by de Wit *et al.* in a 2001 randomized 2×2 factorial clinical trial, in which patients were randomized to three versus four cycles of BEP in a 5-day or 3-day cycle (33). The trial demonstrated a difference in progression free survival of –1.0%, which met the pre-specified limit for equivalence of 5% (33). Four cycles of EP were established as an acceptable treatment regimen in a 2005, single arm clinical trial of 289 patients with good risk metastatic germ cell tumor, in which a relapse rate of 6% was observed, and 3% death at a median follow-up of 7.7 years (34). Of note, this trial included both pure seminoma and non-seminomatous germ cell tumors. In a retrospective analysis of 223 patients with good risk disease treated between 1985 and 2011 with four cycles of EP versus three cycles of BEP, the 10-year overall survival rate was 91% *vs.* 98% respectively (P<0.01) (35). The adjusted risk of death, however, did not reach statistical significance (35). Although these two regimens (four cycles of EP versus three cycles of BEP) are commonly held to be equivalent, there is active debate regarding the exclusion of bleomycin, which is explored below.

For intermediate risk disease, treatment options include four cycles of BEP or four cycles of etoposide, ifosfamide (with mesna), and cisplatin (VIP) (36-38). The VIP regimen was studied in the GETUG S99 study, in which 132 patients were included; good risk patients received EP for four cycles, which intermediate risk patients were treated with four cycles of VIP (39). For the 24 patients with intermediate risk disease, a 3-year progression free survival rate of 83% was observed, with a 3-year overall survival rate of 87% (39). As noted above, seminoma does not include a poor risk category.

Non-seminoma

As described above, the category of non-seminoma tumors includes all non-seminomatous tumors, mixed seminoma and non-seminoma tumors, and histologic seminoma tumors with elevated AFP. For stage I non-seminoma, treatment options following orchiectomy include surveillance, surgery with nerve-sparing retroperitoneal lymph node dissection (RPLND), or chemotherapy with one cycle of BEP. With regard to surveillance, an estimated 70–75% of patients with stage I non-seminomatous germ cell tumor is cured by orchiectomy alone, with an estimated death rate of less than three percent with appropriate surveillance (40,41). The comparison of one cycle of BEP to unilateral RPLND for stage I non-seminoma was studied in a randomized trial of 382 patients, which, after a median follow-up of 4.7 years, identified two relapses in the BEP arm, compared to 13 in the surgery arm (P=0.0011) (42). Notably, the choice of unilateral RPLND rather than bilateral nerve sparing RPLND has led to criticism of this study. In the SWENOTECA trial, 745 patients with stage I non-seminoma were stratified to adjuvant BEP versus surveillance based on the presence of lymphovascular tumor invasion (43). A relapse rate of 3.2% was observed in the presence of lymphovascular invasion, versus 1.6% without, at 5 years (43). In the final analysis of the SWENOTECA trial, the 5-year overall survival rate was 100% (44). Other studies have examined the use of two cycles of BEP, with high rates of relapse-free survival exceeding 95%, at the risk of higher rates of toxicity (45-49).

Following RPLND, management options are driven by nodal status. Patient with pN0 disease are managed by surveillance. For pN1 disease, while surveillance is the preferred option, chemotherapy with two cycles of BEP or EP is an acceptable option. For pN2 disease, chemotherapy with two cycles of BEP or EP is preferred, however, surveillance may be considered. For pN3 disease, chemotherapy with three cycles of BEP or four cycles of EP represents the favored treatment approach. In a case series of 40 stage I non-seminoma patients treated with two cycles of BEP all patients were alive at a median follow-up of 113.2 months with the exception of one incidental death, and no relapses were observed, except for one patient with a tumor in the contralateral testicle (49,50). For stage IS patients, the tumors are treated as good risk tumors, with three cycles of BEP or four cycles of EP, as above (51,52). For stage II non-seminoma, management strategies are similar to above, including RPLND, or chemotherapy with three cycles of BEP or four cycles of EP (53-57). In the case of RPLND, for patients with pN2 or pN3 disease, a relapse rate >50% after RPLND has been observed (56,57). The risk of relapse may be reduced to <1% with the addition of adjuvant chemotherapy with EP or BEP (58,59).

In metastatic non-seminoma, treatment is driven by risk stratification as outlined above in *Figure 1*. Non-seminomas is divided into good-, intermediate-, and poor-risk on the basis of post-orchiectomy tumor markers and sites of disease. Good risk disease is typically treated with three cycles of BEP or four cycles of EP, on the basis of the de Wit trial described above (33,35). For both regimens, a cure rate of approximately 90% has been observed (60,61). As noted above, the therapeutic equivalency of four cycles of

Table 2 Overall survival of non-seminomatous germ cell tumors stratified by stage and histologic subtype

Stage	Histologic subtype					
	Yolk sac seminoma	Mixed yolk sac	Mixed chorio.	Mixed seminoma	Embryonal	All subtypes
Stage IIIC	44% (4/9)	65% (17/26)	71% (15/21)	75% (6/8)	83% (5/6)	67% (47/70)
Stage IIIB	67% (4/6)	90% (19/21)	92% (11/12)	92% (12/13)	100% (10/10)	90% (56/62)
Stages I, II, IIIA	90% (73/81)	96% (189/196)	100% (32/32)	99% (79/80)	100% (96/96)	97% (465/485)
All stages	84% (81/96)	93% (225/243)	89% (58/65)	96% (97/101)	99% (111/112)	93% (568/617)

Chorio, choriocarcinoma. Data derived from Tu *et al*., *Cancer* 2016. (80).

EP versus three cycles of BEP has been actively debated and is described in further detail below.

For intermediate-risk non-seminoma, in one head-to-head comparison of four cycles of BEP and four cycles of VIP was studied in a randomized clinical trial of 84 patients (62). No difference was observed in relapse rate or overall survival at a median follow-up of 7.7 years, with a 5-year progression free survival of 85% in the VIP arm and 83% in the BEP arm (HR=0.83) (62). This trial was stopped early. In a randomized trial of 304 patients with advanced germ cell tumors, a similar 2-year overall survival was observed for both the VIP and the BEP arms (63). In both trials, significantly greater hematologic toxicity was observed in the VIP arm. Given the toxicity and efficacy profile of these two regimens, a BEP regimen is typically preferred. Similarly, four cycles of BEP or VIP are acceptable for poor-risk non-seminoma, with a preference for BEP. For these patients, fewer than 50% will achieve long-lasting complete response (61).

In the setting of relapsed disease or incomplete response to initial therapy, options include conventional chemotherapy or high dose chemotherapy with autologous stem cell rescue. Surgical resection of residual masses is recommended. The VeIP regimen (vinblastine, ifosfamide, cisplatin) was studied in a single arm clinical trial of 135 patients with progressive, disseminated germ cell tumors following treatment with etoposide and platinum-based chemotherapy (64). Among these patients, 49.6% achieved complete remission (64). The TIP regimen (paclitaxel, ifosfamide, cisplatin) has also been studied as a salvage regimen. In a series of 14 patients treated with TIP salvage therapy, five showed a complete or partial response, and with a median follow-up of 41.0 months, the median overall survival was 21.1 months (65). In a study of forty-three patients including both favorable risk and platinum-refractory germ cell tumor patients, one of six patients with cisplatin-refractory disease and five of ten patients with relapsed disease achieved durable complete response (66).

The data in support of high dose chemotherapy and autologous stem cell rescue derive from a retrospective review of 173 patients with metastatic testicular cancer that had progressed after cisplatin-containing chemotherapy, who were given two consecutive courses of high dose carboplatin and etoposide and 11 patients who received one course (67). Among the total 184 patients, 116 experienced complete remission without relapse at a median follow-up of 48 months (67). Of the 135 patients who received this treatment in the second line setting, 94 patients were disease free; in the third line setting, 22 of 49 patients were disease free at the time of follow-up (67).

For patients with relapsed disease after second-line therapy, treatment options include surgical salvage if feasible, and treatment with either conventional or high dose chemotherapy as above, if either regimen has not yet been administered. Pembrolizumab immunotherapy may also be considered in the setting of microsatellite instability or deficient mismatch repair (MSI-H/dMMR) tumors. For patients with platinum-refractory tumors, palliative regimens that have been studied include combinations of gemcitabine with paclitaxel or oxaliplatin, or oral etoposide. In a phase II study of salvage gemcitabine/oxaliplatin in 18 patients with cisplatin-refractory non-seminoma, one patient achieved complete remission, and two patients achieved partial remission, with all three cases characterized by testicular primary embryonal carcinoma (68). In a study of 35 patients who had been pretreated with platinum, an overall response rate of 46% was observed (69). the GEMOX (gemcitabine/oxaliplatin) regimen was also studied in a trial of 29 patients with cisplatin non-seminoma, with 9 patients (32%) achieving complete or partial response (70). For the gemcitabine/paclitaxel combination, in a retrospective review of 31 patients, ten achieved objective

response, with six complete remissions (71,72). The combination of gemcitabine, oxaliplatin, and paclitaxel has also been studied, in a trial of 63 patients with refractory germ cell tumor (73). In this trial, an overall response rate of 44% was observed, with complete remissions seen in eight patients, and a median overall survival of 13.3 months (73). Finally, in a phase II study of oral etoposide in 21 evaluable patients, response was observed in 11 patients (74). For all patients with relapsed or refractory disease, referral to a high-volume center with experience treating these tumors as well as enrollment in clinical trial is advisable.

Areas of active investigation

The exclusion of bleomycin is an area of much debate. In the GETUG T93BP trial of 257 patients with good-risk metastatic germ cell tumors, patients were randomized to four cycles of EP versus three cycles of BEP, with equivalency defined as a maximum 10% absolute difference in favorable response (60). A similar favorable response was observed in both groups (95% for three cycles of BEP versus 97% for four cycles of EP), with a non-statistically significant difference in event-free survival (93% for BEP versus 86% for EP, P=0.052), as well as for overall survival (97% for BEP versus 93% for EP) (60). At 4 years, in the intent-to-treat analysis, overall survival was 92% in the EP arm versus 96% in the BEP arm, with no significant differences in pulmonary toxicity observed (60). In light of these differences, the choice of a 10% margin of equivalence is open to debate, and has led some groups to argue in favor of the superiority of the BEP regimen (75). In other clinical trials, a trend towards superiority with the inclusion of BEP has been observed. In a trial of 419 patients with good-risk metastatic non-seminoma, a complete response rate of 95% was observed with four cycles of BEP, compared with 87% with four cycles of EP, with four cancer-related deaths in the BEP arm compared with eight in the EP arm (76). In one study of three cycles of BEP versus three cycles of EP in 171 patients with good risk disease, an overall survival of 95% was observed in the BEP arm versus 86% in the EP arm, without significant difference in toxicity, although it must be noted that only three cycles of EP is not a recommended treatment regimen (77). By contrast, a single-center retrospective study of 944 patients treated with four cycles of EP demonstrated an overall survival outcome of 97.9% (78). Further study on the exclusion of bleomycin for good risk disease is therefore warranted.

In addition to chemotherapy selection, another key area of active investigation focuses on mechanisms of chemoresistance. Although a large majority of patients with testicular germ cell tumors are cured, a small group, as described above, develops refractory disease. Intratumoral heterogeneity has been hypothesized to contribute to the emergence of chemoresistance, and was studied in a retrospective study of 275 patients (79). In this study, cases were divided into pure embryonal carcinoma (pure E); mixed embryonal carcinoma, yolk sac tumor, and teratoma (EYT); and mixed embryonal carcinoma, yolk sac tumor, seminoma, and teratoma (EYST) (79). Patients with the EYST phenotype had the highest cancer-specific mortality rate and tended to undergo somatic transformation (79). In a similar retrospective study of 615 patients, stratification of patients into histologic subtype demonstrated that patients with a mixed yolk sac-seminoma phenotype had the poorest clinical outcome (80) (*Table 2*, Overall survival of non-seminomatous germ cell tumor by stage and histologic subtype). These histologic subtypes therefore have prognostic implications with regards to somatic transformation and drug resistance and may offer an avenue for patient selection and optimization of treatment choice. Novel biomarkers are also under intensive investigation, such as glypican-3 (GPC3), which has been identified in lethal, cisplatin-resistant tumors and represents potential therapeutic target (81).

Finally, in terms of active clinical studies, the ongoing TIGER trial (NCT02375204) is a randomized, phase III trial comparing conventional-dose chemotherapy using the TIP regimen with high dose chemotherapy plus autologous stem cell transplant in the relapsed, refractory setting (82). A number of novel therapeutic strategies are being investigated in germ cell tumors, including an accelerated scheduled of BEP (NCT02582697), immune checkpoint blockade with durvalumab and tremelimumab (NCT03158064), avelumab (NCT03403777), cabazitaxel (NCT02115165), and the tyrosine kinase inhibitor sorafenib (NCT00772694).

In summary, while testicular germ cell tumors represent a success story of modern medicine in our ability to cure young patients and offer decades of life, many areas of active investigation remain, particularly in the relapsed and refractory setting.

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Footnote

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