Surgical Management of Patients with Advanced Germ Cell Tumors Following Salvage Chemotherapy: Memorial Sloan Kettering Cancer Center (MSKCC) Experience.

Mariam Imnadze Miller[1], Andrew Feifer[2], Darren R. Feldman, Brett S. Carver, George J. Bosl, Robert J. Motzer, Dean F. Bajorin, and Joel Sheinfeld

OBJECTIVE To characterize clinical and pathologic outcomes of cisplatin-refractory or relapsed germ cell tumor (GCT) patients who underwent retroperitoneal lymph node dissection (RPLND) following salvage chemotherapy with either conventional or high dose regimens.

METHODS Data were reviewed to identify all patients treated with TIP or TICE salvage chemotherapy between 1994 and 2011(n = 184) at our institution. We report clinicopathologic and outcomes data on 131 patients who were further managed with surgical resection. Using Cox-proportional hazards models, predictors of disease-specific survival (DSS) were analyzed.

RESULTS Median follow-up was 7.3 years. Of the 112 patients who underwent postsalvage chemotherapy RPLND, histology was reported as viable GCT in 30 (27%), teratoma only in 26 (23%) and fibrosis in 56 (50%). 5-year DSS for the entire cohort was 74% (95% confidence interval 63%-80%). On multivariable analysis, viable GCT histology at RPLND or extra-RPLND resection predicted for worse DSS (hazard ratio 7.37, $P = .003$).

CONCLUSIONS Our data suggest that approximately half of the patient with cisplatin-refractory or relapsed GCT salvaged with TIP or TICE chemotherapy and evidence of residual disease are at risk of harboring either viable GCT or teratoma. This finding underlines the critical role of surgery in the multimodality approach to the management of this advanced disease entity. If retroperitoneal disease exists prior to salvage chemotherapy, we recommend postchemotherapy resection in all eligible patients. UROLOGY 124: 174–178, 2019. © 2018 Elsevier Inc.

Patients with advanced germ cell tumors (GCT) of the testis are managed with well-established treatment paradigms including cisplatin-based induction chemotherapy.[1] However, up to a third of patients experience disease relapse or progression following initial treatment, requiring salvage chemotherapy.[2] Recent studies have highlighted the role of taxane-based regimens in this setting and although no widely accepted standard has yet been recognized, several prognostic factors have been identified to guide the selection of initial salvage regimens between conventional dose chemotherapy and high dose chemotherapy.[3]

Our institutional experience has shown that careful selection of appropriate candidates for treatment with conventional dose chemotherapy (CDCT) with paclitaxel, ifosfamide and cisplatin (TIP) yields an approximately 70% complete response with chemotherapy alone or in combination with surgery, including 63% durable complete response. Prognostic factors for achieving a favorable outcome with CDCT have previously been reported. These include patients with (1) gonadal primary tumors who had a partial, marker negative, or complete response to induction chemotherapy, and (2) that lasted more than 6 months. Patients with late relapse of disease (defined as disease-free interval greater than 2 years duration) were included.[4]

[1] *Since completion of this work, Dr. Miller's affiliation has changed to Alaska Native Medical Center.*

[2] *Since completion of this work, Dr. Feifer's affiliation has changed to University of Toronto.*

Financial Disclosure: *The Sidney Kimmel Center for Prostate and Urologic Cancers, by funds provided by the Capri Foundation and T32 CA082088 from the National Cancer Institute (MIM).*

From the Urology Service, Department of Surgery, Sidney Kimmel Center for Prostate and Urological Cancers, Memorial Sloan Kettering Cancer Center, New York, NY; and the Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Address correspondence to: Mariam Imnadze Miller, M.D., Alaska Native Medical Center, 4315 Diplomacy Drive, Anchorage, AK 99508. E-mails: mimiller@anthc.org; mari.sasha311@gmail.com

https://doi.org/10.1016/j.urology.2018.09.024
0090-4295

Patients with unfavorable clinicopathologic features were treated with high dose chemotherapy (HDCT) with paclitaxel plus ifosfamide followed by high−dose carboplatin and etoposide with stem cell support (TICE). Unfavorable features included (1) extra-gonadal primary tumor, (2) progression of disease following an incomplete response to first line chemotherapy, or (3) progression of disease following ifosfamide and cisplatin-based CDCT. As we have previously reported, approximately 50% of patients achieve a complete response with HDCT alone or in combination with surgery.[5]

There is paucity of published data on clinical and pathologic outcomes for patients who undergo retroperitoneal lymph node dissection (RPLND) following salvage chemotherapy with either conventional or high dose regimens, and the role of surgery in this setting continues to evolve. Our approach has been to recommend resection of all residual disease following either CDCT or HDCT whenever surgically feasible. We report our institutional experience with cisplatin-refractory or relapsed patients who underwent surgical management following TIP or TICE salvage chemotherapy.

MATERIALS AND METHODS

Following institutional review board approval, we performed a retrospective review of our prospectively collected testicular cancer database to identify all patients who were treated with either salvage CDCT (TIP) or with HDCT (TICE) between 1994 and 2011 at our institution (n = 181). Following salvage chemotherapy, surgical resection was offered to all eligible patients, with evidence of retroperitoneal disease prior to salvage chemotherapy. Fifty patients did not undergo postsalvage chemotherapy surgical resection: 30 patients declined any further intervention following complete biochemical and radiographic response and 20 patients experienced disease progression. These patients were excluded from further analysis.

A total of 131 patients were further managed with surgical resection. A total of 112 patients underwent postsalvage chemotherapy RPLND and 24 patients had additional, concurrent or staged resections of extra-retroperitoneal sites. A total of 19 underwent resection of extra-retroperitoneal sites only. Templates for RPLND varied slightly by surgeon and the year of the operation. However, for the second half of the study period, these operations were performed mainly by a single surgeon and full, bilateral infrahilar template was most commonly used. For patients with evidence of extra-retroperitoneal disease, the goal of the operation was resection of all visible disease either concurrently with RPLND or as a staged procedure. Patients with findings of viable nonteratomatous GCT on postsalvage chemotherapy surgical histology received no further treatment and were placed on routine postoperative surveillance. Patients who were found to have teratoma with somatic type malignancy received adjuvant histology-directly chemotherapy.

We report clinicopathologic and outcomes data on this heterogeneous group of patients, the majority of whom were initially diagnosed and treated at outside institutions and referred to us with relapsed or cisplatin-refractory disease. Univariable and multivariable Cox-proportional hazards models were constructed to predict disease-specific mortality. Multivariable models included factors found to be clinically significant ($P < .05$) on univariate analysis. Survival curves were estimated from the time of postsalvage chemotherapy surgery using the Kaplan-Meier method. The log-rank test was used to test differences between groups. All statistical analysis was conducted using STATA 12.0 (Stata Corp., College Station, TX).

Table 1. Clinicopathologic characteristics of patients at initial diagnosis (n = 131)

Characteristic	No. Patients (%)
Age, median (IQR)	30 (24, 38)
Diagnosis site	
Testis	100 (76)
Retroperitoneum	15 (11)
Mediastinum	3 (2)
Unknown	13 (10)
Histology	
Mixed NSGCT	78 (60)
Pure seminoma	15 (11)
Pure embryonal	17 (13)
Pure yolk sac	8 (6)
Choriocarcinoma	7 (5)
Teratoma	2 (2)
Unknown	4 (3)
Any teratoma	46 (35)
Initial clinical stage (N = 123)	
I	10 (8)
II	43 (35)
III	70 (57)
IGCCCG risk before induction chemotherapy (n = 127)	
Good	58 (45)
Intermediate	25 (20)
Poor	44 (35)
First chemotherapy regimen	
BEP × 3 or 4	79 (60)
EP × 4	41 (31)
VIP	2 (2)
Other (POMB, PVB,VAB-6)	9 (7)
PC-RPLND after induction chemotherapy	40 (31)
Histology at initial PC-RPLND (n = 33)	
Fibrosis/Necrosis	12 (36)
Teratoma	13 (39)
Viable nonteratomatous GCT	8 (25)

BEP, bleomycin, etoposide and cisplatin; EP, etoposide and cisplatin; GCT, germ cell tumor; IGCCCG, international germ cell consensus classification group; IQR, interquartile range; NSGCT, nonseminomatous germ cell tumor; PC-RPLND, postchemotherapy retroperitoneal lymph node dissection; POMB, cisplatin, vincristine, methotrexate and bleomycin; PVB, cisplatin, vinblastine and bleomycin; VAB-6, vincristine, bleomycin, cisplatin, cyclophosphamide, and dactinomycin; VIP, vincristine, ifosfamide and cisplatin.

RESULTS

Table 1 summarizes the clinicopathologic characteristics of the study cohort at initial diagnosis. Median age of our cohort was 30 (IQR 24, 38). The majority of the patients (76%) presented with a testicular primary tumor and found to have mixed nonseminomatous germ cell tumor (60%). Fifteen patients (11%) had pure seminoma. Less than 10% of patients were classified as stage I on initial presentation and about half were international germ cell consensus classification group (IGCCCG) good risk at

Table 2. Clinicopathologic characteristic at disease progression or relapse

Characteristic	No. Patients (%)
Indication for second-line chemotherapy	
Disease progression	27 (21)
Disease relapse	104 (79)
No. patient with late relapse of disease	30 (23)
Second chemotherapy regimen	
TIP	76 (58)
TICE	40 (30)
VeIP/VIP	9 (7)
BEP/EP	5 (4)
VAB-6	1 (1)
Third chemotherapy regimen (n = 25)	
TIP	7 (28)
TICE	16 (64)
Other	2 (8)
RP mass size postsalvage chemotherapy, median (range), cm	3.1 (0.5-27)
Postsalvage chemotherapy RP histology (n = 112)	
Fibrosis/Necrosis	56 (50)
Teratoma	26 (23)
Viable non-teratomatous GCT	30 (27)
Postsalvage chemotherapy extra-RP histology (n = 43)	
Fibrosis/Necrosis	26 (60)
Teratoma	4 (10)
Viable nonteratomatous GCT	13 (30)

BEP, bleomycin, etoposide and cisplatin; EP, etoposide and cisplatin; extra-RP, extra-retroperitoneal; GCT, germ cell tumor; RP, retroperitoneal; TICE, paclitaxel, ifosfamide, carboplatin and etoposide; TIP, paclitaxel, ifosfamide and cisplatin; VAB-6, vinblastine, bleomycin, cisplatin, cyclophosphamide, and dactinomycin; VeIP, vinblastine, ifosfamide and cisplatin; VIP, vincristine, ifosfamide and cisplatin.

induction chemotherapy. Etoposide and cisplatin, with or without bleomycin, were the most common regimens at induction (91%). Forty patients underwent RPLND following induction chemotherapy. Histology was available for 33 out of 40 and included 12 (36%) fibrosis/necrosis, 13 (39%) teratoma, and 8 (25%) viable GCT. These 40 patients relapsed with median time to relapse of 14.4 months (IQR 3.6-106 months).

Table 2 summarizes the clinicopathologic features of the study cohort at disease progression or relapse. Twenty seven (21%) patients were cisplatin-refractory—defined as biochemical or radiographic evidence of progressive disease within 4 weeks of last cisplatin-based therapy—and 104 patients (79%) relapsed following initial response to induction chemotherapy. Second line chemotherapy regimen was TIP in 58% and TICE in 30% of patients. Twenty five patients received 3 or more chemotherapy regimens. The retroperitoneum was the only site of residual disease in 88 (67%) patients. In addition to the retroperitoneum, 24 patients had disease outside the retroperitoneum. A total of 19 patients had extra-retroperitoneal disease only following salvage chemotherapy: in these patients, the site of extra-retroperitoneal disease was pulmonary in 11 patients, mediastinum in 4, brain in 2, and liver in 2.

The median size of residual retroperitoneal mass prior to postsalvage chemotherapy RPLND was 3.1 cm (range 0.5-27 cm). A total of 112 patients underwent postsalvage chemotherapy RPLND with the following histologic distribution: 56 (50%) fibrosis, 30 (27%) residual nonteratomatous viable GCT and 26 (23%) had teratoma only on final pathology. A total of 43 patients underwent resection of extra-retroperitoneal sites, including 19 patients whose postsalvage chemotherapy surgical management consisted solely of resection of extra-retroperitoneal sites. The extra-retroperitoneal histologic distribution was similar to that of retroperitoneal histology for viable disease (30%), including 2 patients with teratoma with somatic type malignancy (1 in the mediastinum and 1 in the lung), and a higher frequency of fibrosis (60%) and a lower frequency for teratoma (10%).

Concordance rates for retroperitoneal and extra-retroperitoneal histology for 24 patients who underwent either concurrent or staged procedures were analyzed (Supplementary Table 1). When necrosis/fibrosis was found in the retroperitoneum, similar histology was found in the other resected sites 80% of the time (P = .021). However, concordance rates were not as high for teratoma (50%) or viable GCT (60%).

There were 30 (22%) patients in this study cohort who met the criteria for late relapse (LR), defined as disease-free interval of greater than 2 years. Median time to relapse from induction chemotherapy was 8.7 years (range 2.1-23.1 years). At the time of presentation, none of these patients were candidates for surgery either due to multiple sites of metastasis or unresectable disease. The majority of patients with LR (24 out of 30, 80%) were treated with TIP. Patients with LR had worse histologic findings compared to those who did not meet criteria for late relapse: 20% vs 60 % with necrosis/fibrosis, 44 % vs 22 % with viable GCT, and 36% vs 20% with teratoma, respectively (P = .002). Eight of the 30 patients (27%) with LR eventually died of their disease, with the median time to death of 1.7 years (range 7 months-3 years).

Our cohort also included 15 (11%) patients who were initially diagnosed with pure seminoma—14 of whom underwent postsalvage chemotherapy RPLND and 1 underwent liver resection with negative histology. Of the 14 patients who underwent postsalvage chemotherapy RPLND, 13 had fibrosis/necrosis and 1 was found to have viable seminoma at resection.

A total of 19 of 131(15%) patients had elevated AFP levels prior to undergoing postsalvage chemotherapy RPLND, with a median level of 130 (IQR 24.8-390.7). Of these, 11 (58%) had viable nonteratomatous disease on resection and 6 (32%) had teratoma on retroperitoneal histology and 2 (11%) were found to have fibrosis/necrosis. Seventeen patients (13%) in this cohort had mildly elevated HCG levels prior to postsalvage chemotherapy surgery, with median HCG level of 3.4 (IQR 2.5-9.2). Of these, 7 (41%) had viable disease, 8 (47%) had necrosis/fibrosis, and 2 (12%) had teratoma on final pathology. One patient had both markers elevated prior to surgery (AFP at 19.4 and HCG 5.3) and he was found to have viable nonteratomatous GCT at surgery.

Table 3. Univariable and multivariable cox proportional hazards models for disease specific mortality

Variable	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinical stage (III vs ≤IIC)	2.08 (0.91-4.72)	.081	-	-
IGCCC risk (good vs intmd/poor)	2.80 (1.20-6.56)	.018	2.83 (1.20-6.68)	.017
Elevated STM at time of surgery				
AFP	0.69 (0.24-1.97)	.5	-	-
HCG	1.38 (0.53-3.60)	.5	-	-
Size of RP mass (≥5 cm vs <5 cm)	3.29 (1.19-9.05)	.021	2.41 (0.86-6.81)	.10
Resection of extra-RP sites	2.00 (0.98-4.05)	.056	-	-
Late relapse of disease	1.23 (0.57-2.68)	.6	-	-
Histology at RPLND (GCT vs teratoma/fibrosis)	5.07 (2.04, 12.6)	.0005	5.64 (1.70-18.70)	.005
Worst histology at RPLND or extra-RPLND resection (GCT vs teratoma/fibrosis)	8.37 (3.38, 20.73)	<.0001	7.37 (2.00-7.15)	.003

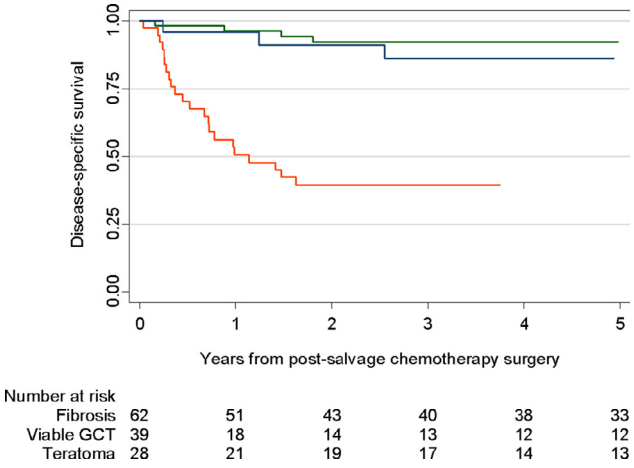

Figure 1. Disease-specific survival by worst histology on resection (retroperitoneal or extra-retroperitoneal): fibrosis (green line) vs teratoma (blue line) vs viable nonteratomatous disease (red line), ($P < .0001$ by log-rank test). (Color version available online.)

Table 3 summarizes the results of univariable and multivariable Cox proportional hazards models for disease-specific mortality. On univariate analysis significant predictive variables included clinical stage (III vs ≤IIC), IGCCCG risk, size or residual mass, and histology at resection. On multivariable analysis, IGCCCG risk and histology remained independently predictive of disease-specific outcomes. Presence of viable GCT on postsalvage chemotherapy resection was the most robust predictor of disease specific mortality with the hazard ratio of 7.37 (95% confidence interval [CI] 2.00-7.15, $P = .003$).

Median follow up time was 7.3 years. At last follow-up, 31 patients were dead of their disease. Five-year and 10-year disease specific survival (DSS) for the entire cohort was 74% (95% CI 65%-81%) and 73% (95% CI 63%-80%), respectively. Five-year-DSS by worst histology of any resected site was 92% (95% CI 80%-97%) for patients with fibrosis, 86% (95% CI 62%-95%) for teratoma and 39% (95% CI 24%-55%) for patients with viable GCT (Fig. 1). Five-year-DSS based on retroperitoneal histology were as follows: 89% (95% CI 76%-95%) for fibrosis/necrosis, 86% (95% CI 62%-95%) for teratoma and 47% (95% CI 27%-64%) for patients with viable GCT (Supplementary Figure 1).

DISCUSSION

Cisplatin-based induction chemotherapy remains mainstay of treatment for advanced GCT of the testis and cure is achieved in majority of patients. About a third of these patients experience disease progression or relapse following induction chemotherapy, requiring salvage treatment.[1-3] Historically, ifosfamide cisplatin and vinblastine has been used in salvage settings and approximately 50% achieve complete response, but only half of these are durable.[6] More recently, taxane-based regimens have emerged with promising results, although the choice between initial salvage treatment with either CDCT or HDCT continues to be explored.[7] At our institution, patients with features predictive of favorable response to CDCT were treated with TIP.[4] Those who did not meet criteria for TIP were treated with TICE.[5] Patients with residual disease underwent surgical resection whenever feasible.

There are several important findings of our study that merit attention. First, this was a study of a heterogeneous group of patients including those with poor prognostic features—including LR, mediastinal primaries, elevated tumor markers, and redo RPLND. Despite these facts, 10-year overall DSS for the entire cohort was 73%, indicating the remarkable ability to cure this disease even after 1 or more relapses. Histologic distribution at resection was noted to be 27% viable GCT, 50% fibrosis, and 23% teratoma. Not surprisingly, we found that IGCCCG risk at diagnosis and histology of resected specimens were factors predictive of disease-specific mortality. Histology (either retroperitoneal or extra-retroperitoneal) was the most robust predictor of disease specific mortality (hazard ratio 7.37; 95% CI 2.00-7.15, $P = .003$, viable cancer vs teratoma/fibrosis). Nonetheless, cure was possible in a significant proportion of patients with viable GCT at resection (39% 5-year DSS).

Historically, the rates of viable GCT following salvage chemotherapy have been reported to be much greater than those found in the current study. In a report by Fox et al, up to 55% of patients were found to have viable GCT in the retroperitoneum following salvage

chemotherapy with ifosfamide cisplatin and vinblastine.[8] In our study, the rate of viable nonteratomatous GCT was noted to be 27%. This observed difference may be due to the superiority of TIP/TICE salvage regimens compared to those used prior to the taxane era. We have previously reported on the outcome of patients undergoing RPLND after multiple lines of chemotherapy. Patients who had received taxol-based salvage chemotherapy (TIP or TICE) had a significantly lower incidence of viable GCT compared to those who were treated with other regimens (14% vs 42%).[9] Overall, histologic distribution in that study by Eggener et al was very similar to ours with 28% viable GCT, 21% teratoma, and 51% fibrosis.

In contrast to our findings, Rick et al[10] reported on 57 patients who underwent resection of residual disease following HDCT. The authors' reported histologic distribution of resected retroperitoneal sites differed from our study with a much higher rate of viable GCT (42% vs 27% in our cohort), lower rate of fibrosis (30% vs 50%), and similar rates of teratoma (28% vs 23%). With approximately 7-year follow-up time, similar to this report, 65% were alive compared to our finding of 76%. In concordance with our findings, patients with viable GCT had poorer outcomes. It is important to note that all patients in the study reported by Rick et al received a single dose of HDCT compared to our standard of 3 sequential cycles of HDCT, which could account for the difference in the rate of viable GCT detected. Additionally, unlike our study in which most patients with residual retroperitoneal disease underwent a full infrahilar bilateral template RPLND, the goal of surgery in the above mentioned study was to completely resect all visible disease, including majority of patients with "abdominal" lymph nodes. These factors combined could contribute to the differences in observed patient outcomes.

Several limitations of our study warrant discussion. Given the heterogeneity of our patient population it is difficult to draw concrete conclusions. All of our patients had favorable responses to salvage chemotherapy and were believed to be surgically resectable. This likely introduces a bias selecting the best patients with more favorable disease biology. Additionally, our cohort included 15 patients (11%) with pure seminoma, majority of whom had fibrosis on resection. This fact likely skewed our survival data toward more favorable outcome. On the other hand, our cohort also included a disproportionately large percentage of patients (23%) with LR and redo RPLNDs (40 patients), which likely skewed our survival data in the opposite direction, toward a worse outcome. Finally, we did not capture or report data on postsurgical complications, which admittedly would be an integral part of the decision making process in the management of this complex disease entity.

CONCLUSION

Our data suggests that patients with cisplatin-refractory or relapsed GCT treated with TIP or TICE salvage chemotherapy followed by resection of residual disease have a 10-year DSS of 73%. Approximately half of these patients will have findings of teratoma or viable nonteratomatous GCT at resection, underlying the critical role of postsalvage chemotherapy surgery in the management of this advanced disease entity. For these patients with otherwise ominous prognosis, resection of all residual disease, whenever technically feasible, may offer a reasonable, and perhaps the only chance for cure.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi:10.1016/j.urology.2018.09.024.

References

1. 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.
2. Bosl GJ, Motzer RJ. Testicular germ-cell cancer. *N Engl J Med.* 1997;337:242–253.
3. Beyer J, Stenning S, Gerl A, et al. High-dose versus conventional-dose chemotherapy as first-salvage treatment in patients with non-seminomatous germ-cell tumors. A matched-pair analysis. *Ann Oncol.* 2002;13:599–605.
4. 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;23:6549–6555.
5. Feldman DR, Sheinfeld J, Bajorin DF, et al. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis. *J Clin Oncol.* 2010;10:1706–1713.
6. Loehrer PJ, Gonin R, Nichols CR, et al. Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. *J Clin Oncol.* 1998;16:2500–2504.
7. Feldman DR, Huddart R, Hall E, et al. 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.
8. Fox EP, Weathers TD, Williams SD, et al. Outcome analysis for patients with persistent nonteratomatous germ cell tumor in post-chemot
herapy retroperitoneal lymph node dissections. *J Clin Oncol.* 1993;11:1294–1299.
9. Eggener SE, Carver BS, Loeb S, et al. Pathologic findings and clinical outcome of patients undergoing retroperitoneal lymph node dissection after multiple chemotherapy regimens for metastatic testicular germ cell tumors. *Cancer.* 2007;109:528–535.
10. Rick O, Bokemeye C, Weinknecht S, et al. Residual tumor resection after high-dose chemotherapy in patients with relapsed or refractory germ cell cancer. *J Clin Oncol.* 2004;22:3713–3719.