High-dose chemotherapy with autologous stem-cell transplantation for relapsed metastatic germ cell tumors: The Alberta experience

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ABSTRACT

Introduction: High-dose chemotherapy with autologous stem-cell transplantation (HDC-ASCT) is standard therapy for metastatic germ cell tumors (mGCTs) in patients whose disease progresses during or after conventional chemotherapy. We conducted a retrospective review of HDC-ASCT in relapsed mGCT patients in the province of Alberta, Canada over the past two decades.
Methods: Patients with mGCTs who received HDC-ASCT at two provincial

KEY MESSAGES

- Our retrospective quality assurance chart review confirmed that HDC-ASCT is an effective salvage therapy in the treatment of metastatic GCTs.
- Our findings indicate that patients with mGCTs can benefit from HDC-ASCT regardless of primary tumor site.
- Tandem HDC-ASCT treatments may result in higher OS and DFS rates compared to single HDC-ASCT, although larger patient sample sizes are required to reach firm conclusions.
- This study, along with upcoming ones, will help clinicians in making treatment decisions for patients with relapsed mGCTs.

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cancer referral centers from 2000–2018 were identified from institutional databases. Baseline clinical and treatment characteristics were collected, as well as overall survival (OS) and disease-free survival (DFS). Relevant prognostic variables were analyzed.
Results: Forty-three patients were identified. The median age was 28 years (range 19–56). A majority (95%) had non-seminoma histology and testis/retroperitoneal primary (84%). Twenty patients (47%) had poor-risk disease, as per The International Germ Cell Consensus Classification (IGCCC), at start of first-line chemotherapy. HDC-ASCT was used as second-line therapy in 65% of patients, and 58% of ASCT patients received tandem transplants. Median followup after ASCT was 22 months (range 2–181). At last followup, 42% of patients were alive without disease, including 3/7 (43%) of patients with primary mediastinal disease. Two-year and five-year DFS/OS ratios were 44%/65% and 38%/45%, respectively. Median OS and DFS for all patients were 30.0 months (13.3–46.6) and 8.0 months (0.9–15.1), respectively.
Conclusions: We found that HDC-ASCT is an effective salvage therapy in mGCT, consistent with existing literature. Patients appeared to benefit regardless of primary site. Though limited by small sample size, we found a numerical difference in DFS and OS between second- and third-line HDC-ASCT and single vs. tandem ASCT.

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INTRODUCTION

Germ cell tumours (GCTs) represent the most common malignancy affecting men aged under 40 years, and account for the greatest average number of years of life loss of any adolescent or adult malignancy.[1,2] The majority of patients with metastatic GCT (mGCTs) are cured with initial cisplatin-based chemotherapy with prognosis based on the International Germ Cell Consensus Classification (IGCCC).[3] However, patients with recurrent or progressive mGCTs after first-line chemotherapy have a poor prognosis despite further treatment, with 2-year DFS ranging from 6% to 75%, depending on clinical risk factors.[4]

Conventional dose chemotherapy (CDC) or high-dose chemotherapy with autologous stem-cell transplantation (HDC-ASCT) are both used as salvage treatment options for patients with relapsed mGCT after first-line treatment. CDC regimens such as ifosfamide, cisplatin and vinblastine (VeIP), etoposide (VIP) or paclitaxel (TIP), have been studied in single-arm trials, with long-term remission rates of 23 – 63% [5,6] Based on a single institution study from Indiana University, HDC-ASCT was studied in 184 patients with relapsed mGCT treated with 1 – 2 cycles of high-dose carboplatin and etoposide followed by ASCT. At a median follow-up of 48 months, 63% achieved a durable remission with 5-year OS of 65%.[7] A more recent retrospective analysis from the Indiana University reported 2-year progression-free survival (PFS) of 63% for 303 patients who received HDC-ASCT as second-line therapy and 2-year PFS of 49% for 61 patients who received HDC-ASCT as third-line or later therapy.[8] An international, multicenter

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series reported survival outcomes of 1594 patients with relapsed mGCT treated with either carboplatin-based HDC-ASCT or CDC, with 2-year PFS of 50% vs 28%, and 5-year OS of 53% vs 41%, favoring HDC-ASCT. The benefit was consistent across all prognostic groups, except low-risk patients. Adverse prognostic factors include extragonadal/mediastinal GCT, poor response to initial cisplatin-based chemotherapy, levels of alpha fetoprotein (AFP; µg/litre) and human chorionic gonadotropin (HCG; IU/litre) > 1000 at relapse, and presence liver/bone/brain metastases.[9]

To date, the only published randomized-control trial comparing CDC to HDC-ASCT failed to show superiority of HDC-ASCT, though this study was limited by its methodology with using outdated treatment protocols.[10] Moreover, although there was a sizeable patient population, a significant proportion of patients randomized to HDC-ASCT did not receive this treatment.[10] As such, the optimal salvage treatment strategy has not yet been well. Other unanswered questions related to HDC-ASCT include the optimal number of cycles required, predictive/prognostic factors for efficacy and timing of HDC-ASCT.

Alberta is a geographically diverse Canadian province with a population of approximately four million people. HDC-ASCT in Alberta is performed at two regional oncology referral centres: The Cross Cancer Institute (CCI) in Edmonton and the Tom Baker Cancer Center (TBCC) in Calgary. We sought to examine the outcomes of mGCT patients undergoing HDC-ASCT in Alberta as well as examine treatment patterns that may influence these outcomes.

METHODS

Male patients aged ≥18-year-old who received HDC-ASCT for mGCT of testicular, retroperitoneal, or mediastinal primary at CCI and TBCC from January 1st, 2000, to December 31st, 2018, were identified from prospective databases maintained at both centers. Both paper charts and electronic medical records were used to collect relevant patient data. DFS was defined as the first day of HDC to disease progression or death. OS was defined as the first day of HDC to death or censored at the time of last follow-up. Survival outcomes were analyzed using the Kaplan-Meier method and Cox's proportional hazard model. Prognostic variables were analyzed initially using univariate analysis and variables significant at $p < 0.10$ level were entered in the multivariable analysis. The final predictive model was chosen based on a p value < 0.05. Due to low patient numbers, i.e., patient sample sizes, multivariate analysis was not significantly powered and thus unstable. Hence, the final predicative model used to assess survival outcomes was univariant regression analysis. Data were processed in IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Adult patients who received HDC-ASCT for relapsed mGCT at Alberta cancer referral centres between 2000 and 2018 were identified. Seven patients did not meet eligibility criteria and were

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excluded from this study: one patient with a primary tumour of unknown origin; two patients with primary central nervous system GCTs; three female patients; and one patient who received HDC-ASCT as a first-line therapy. Figure 1 diagrams the selection criteria for the current study in CONSORT format.

Twenty-three patients (53.5%) were treated with HDC-ASCT at the CCI in Edmonton, while 20 patients (46.5%) were treated at the TBCC in Calgary. Median patient age was 28 years (range, 19 – 56 years). At start of HDC-ASCT, most patients had non-seminoma histology (95.3%, n=41), while six patients (4.6%) had seminoma. Likewise, most patients had either testicular or retroperitoneal primary tumours (83.7%, n=36), with seven patients (16.3%) having mediastinal primary tumours. Twenty patients had an IGCCC risk status of poor (46.5%) at HDC-ASCT initiation, while 16 patients had an IGCCC status of intermediate (37.2%), and 7 had a risk status of good (16.3%). Twenty-nine patients had platinum-sensitive disease and 14 had platinum-refractory disease, defined as progression within 4 weeks after the most recent cisplatin-based chemotherapy. Details of baseline patient demographics and clinical characteristics at HDC-ASCT introduction are listed in Table 1.

Most of the 43 patients either received, or were planned to receive, tandem HDC-ASCT treatment (table 2). Ultimately, 18 patients (41.8%) received single HDC-ASCT, while 25 patients (58.2%) received tandem HDC-ASCT. 10 patients (23.3% of total study patients) were originally intended to receive single HDC-ASCT, all occurring in 2007 and prior. An additional eight patients were originally planned to receive tandem therapy, but ultimately received single HDC-ASCT. These eight-patients did not receive a second cycle of HDC-ASCT due to two patients refusing, two toxicity events, two with insufficient stem cell collection, and two cases of progressive disease after the first HDC-ASCT treatment, each representing 5.6 % of the 43 total study patients. Of the 43 patients studied, 28 (65.1%) received HDC-ASCT as a second line treatment, while 15 patients (34.9%) received it as a third- or fourth-line treatment.

Median follow-up from HDC-ASCT initiation was 22 months (range, 3 – 181 months); the median follow-up for surviving patients was 60.5 months (range, 12 – 181 months) The Kaplan-Meier median DFS estimate for all patients was 8 months (Figure 2), with an observed DFS range of 0.9 – 15.1 months. 2-year and 5-year DFS rates were 44%, and 38%, respectively. When codified by treatment characteristics, 2-year DFS rates were 50% for second line HDC-ASCT, and 33% for third line or later therapy. Similarly, second line HDC-ASCT had a 5-year DFS of 45%, compared to a lower DFS of 25% when used as third line or later salvage therapy.

When categorized by primary tumour site, patients with mediastinal disease had a 2-year DFS of 57%, and a 5-year DFS of 43%, while patients with testicular or retroperitoneal primary tumours had 2-year and 5- year DFS rates of 41% and 38%, respectively. At last follow-up, forty-two percent of patients (18/43) were alive and disease-free, including the three patients who presented with poor prognosis primary mediastinal disease.

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The OS estimate for all patients was 30.0 months (Figure 3), with a range of 13.1 – 46.6 months. Patient 2-year and 5-year OS rates were 65% and 45%, respectively. Two-year OS was 71% in patients who received second line HDC-ASCT treatment, and 53% in those patients who received third or later line therapy. At 5-years, OS was 56% for patients receiving second line HDC-ASCT therapy, versus 23% for those receiving HDC-ASCT in the third- or fourth-line setting.

Patients with primary mediastinal disease showed OS of 71% at 2-years post-therapy initiation, and an OS rate of 54% at 5-years. Patients with primary testicular or retroperitoneal tumours had two year and 5-year OS rates of 64% and 43%, respectively. The 2-year DFS/OS ratio was 44%/65% for all patients, while at 5-years the DFS/OS decreased to 38%/45%, respectively.

Analysis of patient survival outcomes based on intention to treat (ITT) of single HDC-ASCT versus tandem therapy reveals these subsets to have IIT-comparative OS rates of 40% and 63% at 2-years post-therapy initiation, and OS rates of 40% and 48% at 5-years, respectively. Similarly, ITT DFS rates for tandem versus single therapy were 45% and 40% at 2-years, and 41% and 40% at 5-years post-therapy initiation, respectively. Statistical analysis by the Cox proportional-hazards model reveals a hazard rate ratio (HR) for OS between tandem versus single HDC-ASCT of 0.72 (95% CI: 0.28 – 1.84; p=0.493), and a tandem versus single HR for DFS of 0.70 (0.28 – 1.75; p=0.445). Two and 5-year patient survival outcomes relative to treatment and disease classifications are detailed in Table 3.

Univariate analyses were performed to assess the individual effects of disease or treatment variables on the predictive values of patient DFS and OS in the absence of all other covariates. Univariate Cox regression as the hazard model for of the effects of third line versus second line ASCT, site of primary tumour, or tandem versus single stem cell transplantation on patient 5-year DFS and OS are presented in Figures 4a and 4b. None of these variables presented significantly different hazard ratios for DFS or OS from analysis of our study cohort. However, second line ASCT showed a trend towards improved 5-year OS rates over third line ASCT with a hazard ratio of 2.1. Multivariate analysis was uninformative (data not shown) and so univariate regression analysis was the predicative model assessing survival outcomes.

DISCUSSION

The introduction of cisplatin-based chemotherapy regimens has revolutionized the management of metastatic germ cell tumors with more than 80% of patients expected to be cured after first line chemotherapy.[11] Despite this success, the management of patients with recurrent or progressive disease after first line therapy remains a challenge. The prognosis for these patients is poor, and no optimal treatment strategy has been identified. Options include CDC regimens including cisplatin, ifosfamide with either paclitaxel (TIP), etoposide (VIP), or vinblastine (VeIP), or HDC-ASCT.[6,7,12]

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Despite these treatment advances, prospective evidence supporting the superiority of one salvage strategy over another is lacking. The TIGER randomized study (ClinicalTrials.gov Identifier: NCT02375204), which compares CDT to HDC-ASCT using modern treatment regimens of 4 cycles of cisplatin, ifosfamide, paclitaxel (TIP) versus 1 – 2 cycles of ifosfamide and paclitaxel followed by 3 cycles of high-dose carboplatin and etoposide, is ongoing. The results of the TIGER study will provide needed clarity on optimal salvage strategies.

Regardless of a particular regimen, several retrospective and prospective studies have demonstrated that HDC-ASCT is an effective salvage therapy, with a significant proportion of patients achieving long-term disease-free survival.[7-10,13-15] Our study demonstrates the outcomes of HDC-ASCT performed at the two regional referral centres in Alberta over approximately the last two decades. Reassuringly, this study has demonstrated similar outcomes to those reported by other groups. Importantly, Alberta has a single-payer, publicly funded universal health care system that provides all oncology services, and thus these data are representative of the outcomes achieved in this population as a whole. Therefore, our data is qualitatively different from data reported by other centres, which can have bias based on geographic and socioeconomic referral patterns.

As such, this study adds to the literature demonstrating favorable survival outcomes in a contemporary patient population and treatment approach, adding evidence to the benefit of this treatment in a poor prognosis patient population. This study also confirms that outcomes achieved in the province of Alberta, Canada are similar to other centres, providing necessary quality assurance.

CONCLUSIONS

Our study has revealed several important observations. Notably, most patients were planned to receive tandem (58%), as opposed to single HDC-ASCT, and no single HDC-ASCT regimens were planned after 2007. In addition, tandem compared to single HDC-ASCT treatments demonstrated higher OS and DFS rates, although these outcome differences were not statistically significant. Larger patient numbers would have been required to reach firm conclusions on differential outcomes from these data. Nevertheless, a large, multicentre, retrospective study involving 2395 HDC-ASCT recipients found tandem resulted in superior PFS and OS compared to single.[13] The only study, to our knowledge, which compared single vs multiple HDC-ASCT cycles in a randomized, prospective fashion reported similar five-year PFS for both arms, but also fewer treatment related deaths in the tandem arm, resulting in higher OS.[14]

Our study has demonstrated that most patients (76%) who were planned to received tandem HDC-ASCT were able to receive it. Elsewhere, the disparity between planned and received tandem HDC-ASCT has been variably reported as low as 47% to as high as 94%.[8, 14-15] This variability is undoubtedly due to differences in time, patient populations, and treatment regimens used. Approximately two-thirds of the patients in our study received HDC-ASCT as their second line or first salvage therapy. While the choice of first salvage treatment is

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controversial and must take into consideration patient factors and preferences, the use of HDC-ASCT appears to achieve superior outcomes as first line salvage therapy when compared to second or later line of salvage.[8,13]

Finally, long-term survival can be achieved even in patients with a very poor prognosis, such as those with mediastinal primaries. In our series, 3 out of 7 patients achieved 5-year DFS after HDC-ASCT, similar to that of gonadal and retroperitoneal primaries. Other reported series have also demonstrated long term DFS in this and other high-risk populations, such as those with platinum refractory disease.[8] Consequently, the use of HDC-AST should be considered for the treatment of metastatic germ cell tumors even in those patients at highest risk.

This study is restricted in its small size and retrospective nature, limiting the conclusions that can be made when comparing differences in patient and treatment variables. In larger studies, the site of primary tumor, pre-treatment tumour markers, and platinum-sensitivity appear to be significant predictors of disease progression and survival. Future prospective studies are warranted to help identify patients who may be cured from CDC without the need for HDC-ASCT, given the potential toxicities. Our study did not specifically evaluate the short-term and long-term toxicities of HDC-ASCT. Nevertheless, this review provides important validation of the effectiveness of the use of HDC-ASCT as salvage therapy in male Alberta patients with relapsed/progressive advanced germ cell tumors.

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FIGURES AND TABLES

Figure 1. CONSORT diagram. Selection criteria from the current retrospective review. CNS: central nervous system; GCT: germ cell tumor; HDC-ASCT: high-dose chemotherapy with autologous stem-cell transplantation.

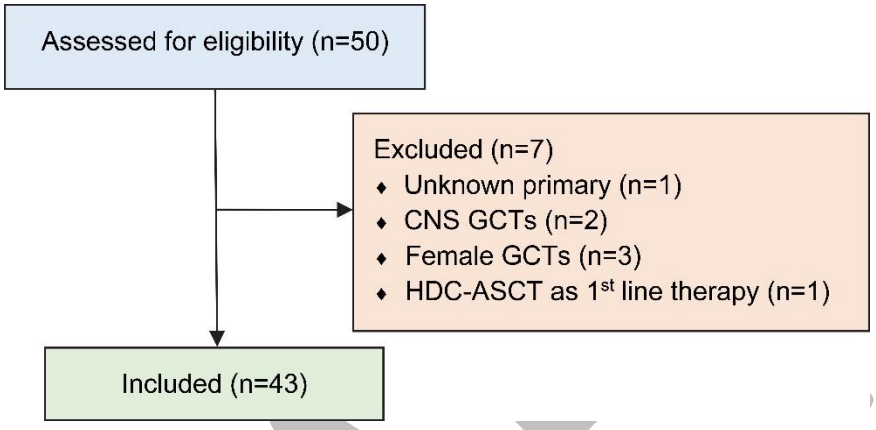

Figure 2. Kaplan-Meier estimates of disease-free survival (DFS). Hatched lines denote 95% confidence interval (95% CI).

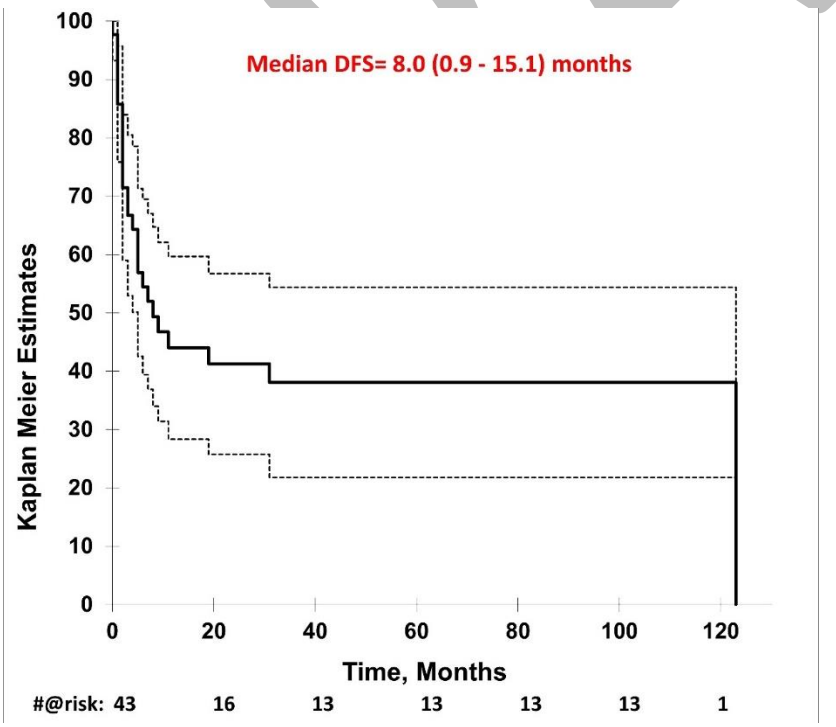

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Figure 3. Kaplan-Meier estimates of overall survival (OS). Hatched lines denote 95% confidence interval (95% CI).

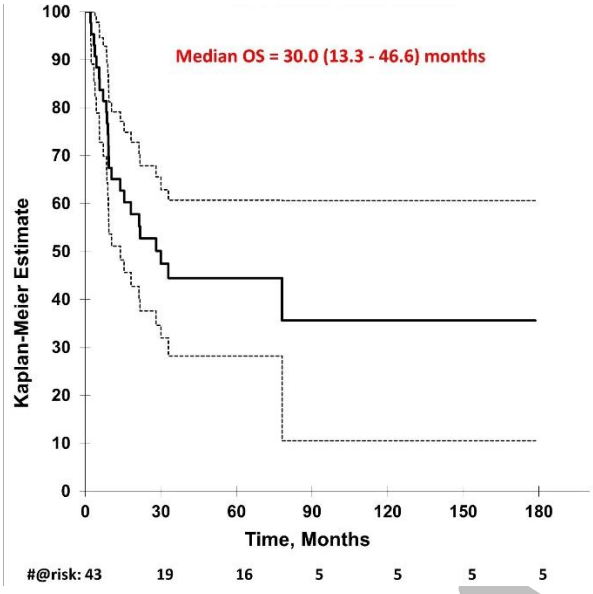
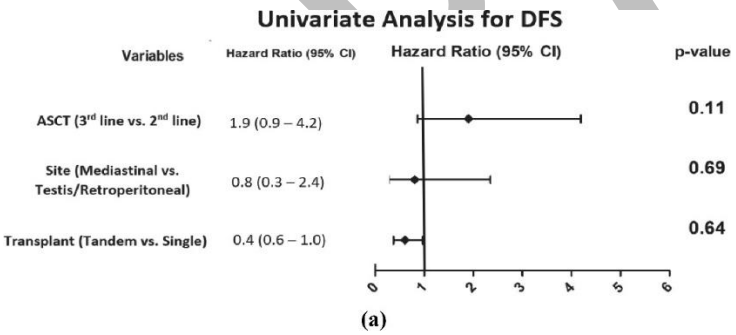


Figure 4. (a) Forest plot illustrating results of univariate analysis of prognostic variables on patient 5-year disease-free survival rates (DFS). (a) Forest plot illustrating results of univariate analysis of prognostic variables on patient 5-year overall survival (OS) rates. ASCT: autologous stem-cell transplantation; CI: confidence interval.



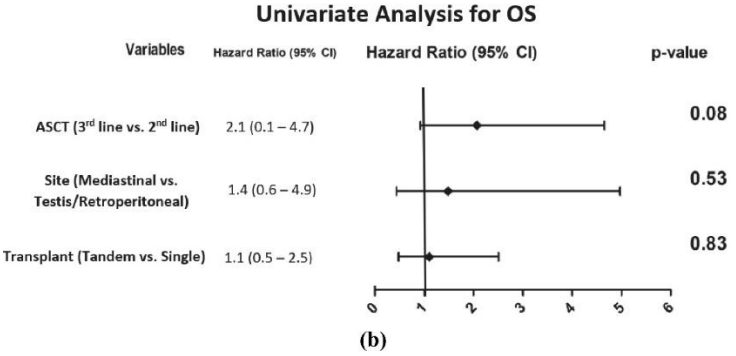


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Table 1. Baseline demographics at HDC-ASCT		
Demographic	**n**	**%**
Median age (range)	28	19 – 56 [1]
Site of HDC-ASCT		
Edmonton	23	53.5%
Calgary	20	46.5%
Histological type		
Seminoma	2	4.7%
Non-seminoma/mixed	41	95.3%
Site of primary		
Testis or retroperitoneal	36	83.7%
Mediastinal	7	16.3%
Risk status at first-line chemotherapy (IGCCC)		
Good	7	16.3%
Intermediate	16	37.2%
Poor	20	46.5%
Response to first-line chemotherapy		
Complete response	6	14.0%
Partial response	37	86.0%
Platinum sensitivity2		
Sensitive	29	67.4%
Refractory	14	32.6%
hCG level pre-ASCT		
≥1000 IU/litre	6	14.0%
≤1000 IU/litre	37	86.0%
αFP level pre-ASCT		
≥1000 μg/litre	2	4.7%
≤1000 μg/litre	41	95.3%
Beyer Lorch score[3]		
0–1	16	37.2%
2	7	16.3%
3	8	18.6%
4	7	16.3%
5–6	5	11.6%

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[1]Range. [2]Most recent cisplatin therapy. [3]IGCCG-2 prior to HDC-ASCT. αFP: alpha-fetoprotein; hCG: human chorionic gonadotropin; HDC-ASCT: high-dose chemotherapy with autologous stem-cell transplantation; IGCCC: The International Germ Cell Consensus Classification

Table 2. HDC-ASCT treatment characteristics		
Characteristic	**n**	**%**
Number of cycles of HDC-ASCT received		
Single	18	41.8%
Tandem	25	58.2%
Line of therapy when HDC-ASCT used		
2	28	65.1%
3	13	30.2%
4	2	4.7%
Reasons for not using tandem transplant		
Planned single	10	55.6%
Patient refusal	2	11.1.%
Toxicity	2	11.1.%
Insufficient collection	2	11.1.%
Progression after 1st transplant	2	11.1.%
HDC regiments		
Carboplatin + etoposide	16	37.2%
Carboplatin + etoposide + cyclophosphomide	21	48.8%
Carboplatin + etoposide + ifosfomide	4	9.3%
Carboplatin + thiotepa + cyclophosphamide	2	4.7%
Post-HDC-ASCT therapy		
None	19	44.2%
Salvage surgery	9	20.9%
Palliative chemotherapy	10	23.3%
Palliative radiotherapy	7	16.3%
Radical radiotherapy	2	4.7%
Pathology from salvage surgery		
Scar	3	7.0%
Teratoma	2	4.7%
Active germ cell	3	7.0%
Not available	1	2.3%

HDC-ASCT: high-dose chemotherapy with autologous stem-cell transplantation.

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Table 3. Survival outcomes				
Classification	**DFS (%)**		**OS (%)**	
	2-year	**5-year**	**2-year**	**5-year**
All patients	44	38	65	45
2nd-line HDC-ASCT	50	45	71	56
3rd-line or later HDC-ASCT	33	25	53	23
Single (n=10)	40	40	40	40
Tandem (n=33)	45	41	63	48
Mediastinal primary	57	43	71	54
Testis/retroperitoneal primary	41	38	64	43

DFS: disease-free survival; HDC-ASCT: high-dose chemotherapy with autologous stem-cell transplantation; OS: overall survival.

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