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ORIGINAL ARTICLE

Contemporary outcomes of salvage high-dose chemotherapy in advanced germ cell tumors: an analysis of the cellular therapy and immunobiology working party of the EBMT registry

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Background: The optimal salvage therapy for relapsed germ cell tumors (GCTs) remains undefined and the optimal timing for high-dose chemotherapy (HD-CT) is unclear. We analyzed data from the European Society for Blood and Marrow Transplantation registry to evaluate contemporary outcomes in patients treated with HD-CT across salvage lines.

Patients and methods: We extracted data of adult males with GCTs (excluding mediastinal primary) who received one or more courses of HD-CT with carboplatin and etoposide between 2000 and 2022. Patients treated within 3 months from diagnosis were excluded, as this was considered upfront therapy. Time from diagnosis to first HD-CT (TT) was categorized in 3-6, 6-12, and >12 months. A Cox model with restricted cubic splines was used to evaluate the nonlinear effect of TT on survival.

Results: Data from a total of 2204 patients were analyzed. Histology was available for 1074, of whom 69% had nonseminoma. Among 969 patients with primary site information, 69% had testicular GCT. International Prognostic Factors Study Group (IPFSG) categories were available for 500 patients: 17% very high, 38% high, 31% intermediate, 10% low, and 3.6% very low risk. TT was 3-6 months for 280 (13%), 6-12 months for 831 (38%), and >12 months for 1093 (50%). Of the patients, 1118 (51%) received three cycles of HD-CT. Median overall survival (OS) and progression-free survival (PFS) were 36.4 [95% confidence interval (CI) 30.3-58.7] and 9.9 months (95% CI 8.5-12.4), respectively. Spline analysis showed increasing hazard of progression and death with longer TT. No interaction was observed between TT and IPFSG risk for PFS ($P = 0.62$), whereas a significant interaction was found for OS ($P = 0.04$) in non—high-risk patients.

Conclusions: In the largest contemporary series of salvage HD-carboplatin—etoposide in GCTs, HD-CT was effective regardless of TT as a surrogate of salvage line, with a significant interaction in non—high-risk patients, suggesting a nonlinear association between HD-CT timing and OS.

Key words: high-dose chemotherapy, relapsed germ cell tumors, salvage therapy

INTRODUCTION

Germ cell tumors (GCTs) are among the most curable solid malignancies, even in the metastatic setting. Despite their aggressiveness, their marked sensitivity to cisplatin-based chemotherapy has dramatically improved patient outcomes over the past decades.[1,2] This therapeutic achievement, together with continuous advances in clinical management, has transformed GCTs from a once incurable

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condition into one of the most successful examples of curative systemic therapy among solid tumors.[3] However, ∼20%-30% of patients experience relapse after first-line chemotherapy, with individual relapse risk varying according to the International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic classification.[1,2,4,5] Unlike most other solid tumors, patients with relapsed GCTs after first-line chemotherapy may still achieve a cure with so-called salvage therapy. Nonetheless, the likelihood of cure at recurrence (or at progression, in cases of platinum-refractory disease) depends on prognostic factors defined by the International Prognostic Factor Study Group (IPFSG) classification.[6] In this setting, cure may still be achieved with either conventional-dose chemotherapy (CD-CT) or high-dose chemotherapy (HD-CT).[4,5,7] However, the optimal salvage strategy for relapsed GCTs remains uncertain.[8-11] Several single-arm studies or retrospective studies have investigated both strategies without providing a direct comparison.[4,5,7,12,13] The only randomized trial failed to demonstrate an improvement with HD-CT over CD-CT, but it was criticized for the regimen used, which was limited to just one cycle of HD-CT, as well as for methodological limitations.[14] Retrospective studies have attempted to address this open question, with the inherent limitations of such designs, and generally suggest the superiority of HD-CT as first salvage therapy, except for patients with very low and low risk according to the IPFSG classification.[8,9,11] In a recent retrospective analysis of 283 patients, improved response rates and survival outcomes were observed when HD-CT was administered as first-line salvage therapy rather than in later salvage settings.[15] This finding is consistent with the expectation that treatments are generally more effective in less heavily pretreated populations. However, the study did not allow a direct comparison between HD-CT and CD-CT as first salvage therapy, because patients who achieved a durable response to first-line CD-CT (and eventually did not need further salvage therapies with HD-CT) were not included in the analysis.[15] A definitive answer may come from the ongoing randomized TIGER trial (NCT02375204), which completed enrollment in October 2022, although results have not yet been published. At present, guidelines cannot unequivocally recommend a preferred salvage approach. Therefore, current recommendations emphasize management in high-volume referral centers with substantial expertise, where clinicians can assess and select, based on available evidence and personal experience, the most appropriate option between CD-CT and HD-CT for each patient.[16] Contemporary HD-CT regimens consist of high-dose carboplatin and etoposide (HD-carboplatin—etoposide [CE]), administered either as the CE regimen developed at Indiana University or as the TI-CE regimen from Memorial Sloan Kettering Cancer Center, in which HD-CT is preceded by two induction cycles of paclitaxel and ifosfamide.[5,7] A recent multicenter retrospective analysis comparing these two strategies showed no statistically significant differences in relapse-free survival or overall survival (OS). However, a significant improvement in OS was observed with TI-CE among patients with intermediate- and poor-risk disease according to the IGCCCG classification.[17] Given improvements in prognosis over recent years, driven by better patient management and the adoption of newer-generation treatment regimens, we aimed to capture contemporary survival outcomes for patients treated with HD-CT as salvage therapy and to assess the impact of HD-CT timing. To this end, we queried the European Society for Blood and Marrow Transplantation (EBMT) registry and extracted data on patients with GCTs treated with HD-carboplatin—etoposide between 2000 and 2022.

METHODS

Population

The EBMT registry is the largest European database of hematopoietic stem cell transplantation (HSCT). It also includes patients with solid tumors treated with HD-CT followed by HSCT. Informed consent for both HD-CT plus HSCT and data collection was obtained at each center in accordance with the regulations in force at the time of treatment. Since 1 January 2003, all transplant centers have been required to obtain written informed consent before registering patient data with the EBMT.

In this EBMT analysis, we identified adult males with extracranial GCTs who received at least one cycle of HD-carboplatin—etoposide between 2000 and 2022. Patients with primary mediastinal GCTs (PMGCTs) were excluded due to their distinct biology and prognosis. A recent analysis of PMGCTs treated with HD-CT and included in the EBMT registry has already been published, reporting data from 69 patients with mediastinal nonseminoma.[18] Since direct information on prior systemic therapy lines was unavailable, we used time to treatment from initial diagnosis to first HD-CT (TT) as a pragmatic, though imprecise, surrogate for treatment sequence. Shorter TT intervals likely correspond to earlier lines of therapy, whereas longer intervals suggest multiple prior treatments with CD-CT. To avoid including patients receiving upfront HD-CT, we excluded those treated within 3 months from diagnosis. TT of included patients was categorized as 3-6, 6-12, and >12 months. Additional variables extracted included age at first HD-CT, number of HD-CT cycles received, histology, primary tumor site (testis versus retroperitoneum), and IPFSG risk category. Despite the substantial sample size, the registry is limited by incomplete reporting of several key oncologic variables—in particular, histological subtype, primary site, and IPFSG risk categories—but also detailed prior treatment history, disease burden at relapse, and response to previous therapies. Because missingness was primarily related to nonsystematic reporting across participating centers rather than random variability, multiple imputation was not carried out and analyses were conducted using a complete-case approach for variables included in the statistical models.

Statistical analyses

Median follow-up was calculated according to the inverse Kaplan—Meier method. Progression-free survival (PFS) and

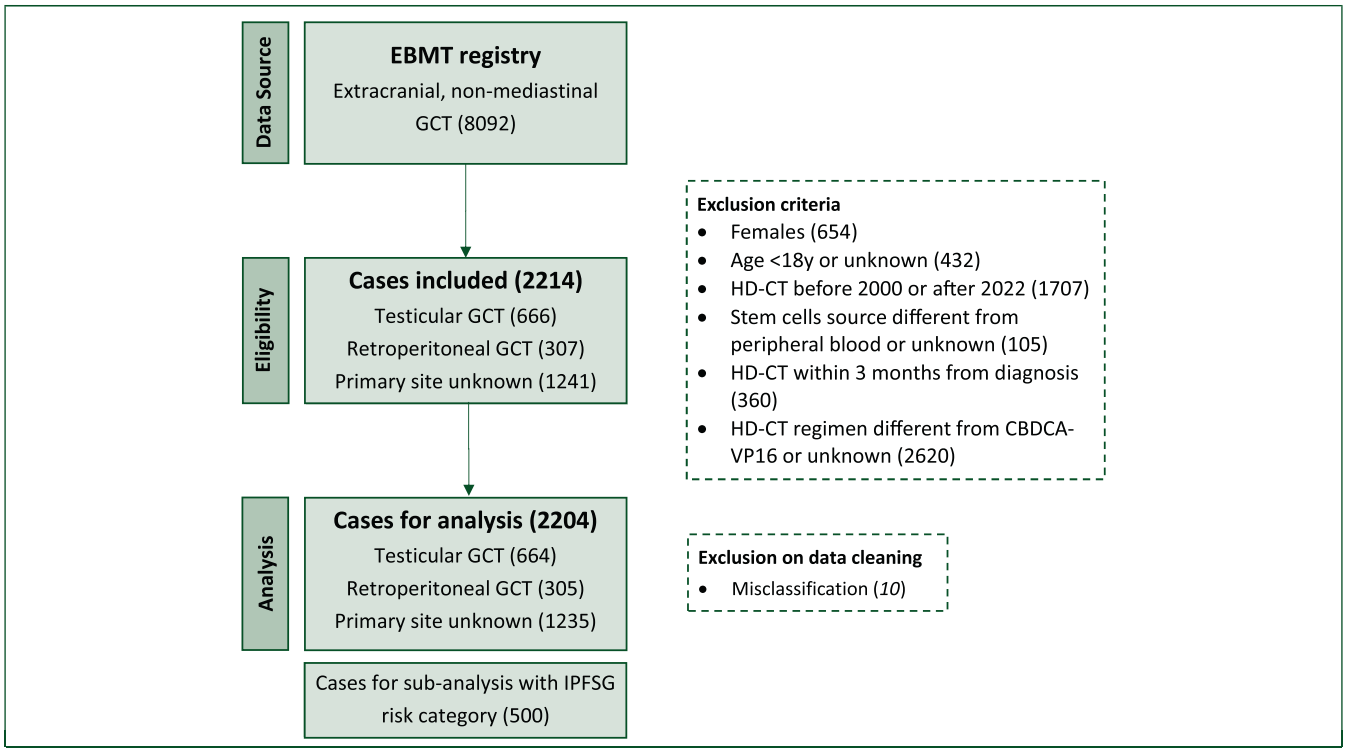


Figure 1. ESMO Guidance for Reporting Oncology real-World Evidence (GROW) flowchart illustrating the screening process of patients identified in the EBMT registry and included in the analyzed population.

CBDCA-VP16, carboplatin plus etoposide; EBMT, European Society for Blood and Marrow Transplantation; GCT, germ cell tumor; HD-CT, high-dose chemotherapy; IPFSG, International Prognostic Factor Study Group.

OS were estimated using the Kaplan—Meier method and differences between groups were assessed with the log-rank test. Univariable and multivariable Cox proportional hazards models were applied to evaluate the association between clinical variables and outcomes. To explore potential nonlinear effects of TT on survival, Cox proportional hazards models incorporating restricted cubic splines were fitted, with graphical visualization of the estimated hazard ratios (HRs) across the continuous range of TT. Effect modification by risk group was assessed by including an interaction term between TT and risk class. This approach allowed evaluation of whether progressively longer intervals between diagnosis and HD-CT, which plausibly reflect later lines of salvage therapy or delayed relapse, were associated with differential survival outcomes.

Due to incomplete IPFSG category data and the resulting small numbers of patients within each group, the very low, low, and intermediate risk categories were combined and compared against the high and very-high-risk groups. Analyses adjusted for IPFSG risk category were restricted to patients with available IPFSG data ($n = 500$). All tests were two-sided, with a significance level of $P < 0.05$. R software environment for statistical computing and graphics (R version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

RESULTS

Patient characteristics

Data from 2204 patients treated with HD-carboplatin—etoposide over the past two decades were extracted from the EBMT registry, representing the largest contemporary cohort of patients with GCTs receiving HD-CT (Figure 1). Median age at first HD-CT was 34 years (interquartile range 28-42). Histology was available for 1074 patients, of whom 746 (69%) had nonseminoma or mixed GCT and 328 (31%) had seminoma. The predominance of nonseminoma is expected, given its higher propensity for relapse compared with seminoma. Information on the primary tumor site was available for 969 patients: 305 (31%) had a retroperitoneal primary, whereas 664 (69%) had testicular GCTs (TGCTs). IPFSG prognostic categories, which estimate survival probability in patients requiring salvage therapy, were available for 500 patients. Among these, 83 (17%) were classified as very high risk, 191 (38%) as high risk, 156 (31%) as intermediate risk, 52 (10%) as low risk, and 18 (3.6%) as very low risk. The IGCCCG classification at the time of diagnosis of advanced disease was not available in the registry. TT was recorded for all patients: 3-6 months in 280 patients (13%), 6-12 months in 831 (38%), and >12 months in 1093 (50%). Among patients with a long TT, 529 had TT >24 months. Patients received one cycle of HD-CT in 469 cases (21%), two cycles in 617 (28%), and three cycles in 1118 (51%). Although the specific regimen was not reported, patients who received three cycles of HD-CT were likely treated with the TI-CE regimen. Baseline patient characteristics are summarized in Table 1.

Effects of clinical and therapeutic variables on survival

Median follow-up was 23.8 months [95% confidence interval (CI) 21.6-26.5]. Overall median OS and PFS were 36.4

Table 1. Patient characteristics

Characteristic	$N = 2204$
Age at first HD-CT, years (IQR)	34 (28, 42)
Cycles of HD-CT, *n* (%)	
1	469 (21%)
2	617 (28%)
3	1118 (51%)
Time from diagnosis to first HD-CT, months (IQR)	12 (8, 24)
Time from diagnosis to first HD-CT, *n* (%)	
3-6 months	280 (13%)
6-12 months	831 (38%)
>12 months	1093 (50%)
Histology	
Nonseminoma	746 (69%)
Seminoma	328 (31%)
Unknown	1130
Primary site, *n* (%)	
Retroperitoneal	305 (31%)
Gonadal	664 (69%)
Unknown	1235
IPFSG prognostic categories, *n* (%)	
Very low risk	18 (3.6%)
Low risk	52 (10%)
Intermediate risk	156 (31%)
High risk	191 (38%)
Very high risk	83 (17%)
Unknown	1704

HD-CT, high-dose chemotherapy; IPFSG, International Prognostic Factor Study Group; IQR, interquartile range.

months (95% CI 30.3-58.7) and 9.9 months (95% CI 8.5-12.4), respectively (Figure 2). The 2-year and 5-year OS were 55.6% (95% CI 53.1-58.3) and 46.8% (95% CI 44.0-49.7), respectively, while the corresponding PFS rates were 44.0% (95% CI 41.4-46.7) and 41.1% (95% CI 38.4-43.9), respectively. Worse OS and PFS rates were observed in nonseminoma compared with seminoma [median PFS: 7.4 months, 95% CI 6.6-8.9 compared with not reached [NR], 95% CI NR-NR; median OS: 25.3 months, 95% CI 18.4-36.4 compared with NR, 95% CI NR-NR; Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2026.108365], primary retroperitoneal tumors compared with TGCTs (median PFS: 7.2 months, 95% CI 6.2-9.4 compared with 26.9 months, 95% CI 12-NR; median OS: 16.9 months, 95% CI 12.9-24.1 compared with NR, 95% CI 55.7-NR; Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2026.108365), and less than three cycles compared with three cycles of HD-CT (median PFS: 7.2 months, 95% CI 6.2-8.4 compared with 19 months, 95% CI 12-58.7; median OS: 19.2 months, 95% CI 16.8-23.6 compared with NR, 95% CI 77-NR, all $P < 0.001$; Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2026.108365).

The multivariable Cox regression model confirmed that histotype (HR 0.47, 95% CI 0.34-0.64, $P < 0.001$), primary tumor site (HR 0.64, 95% CI 0.50-0.81, $P < 0.001$), and the number of treatment cycles (HR 0.56, 95% CI 0.45-0.71, $P < 0.001$) were significantly associated with OS (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2026.108365). In the multivariable Cox regression model addressing PFS, histotype (HR 0.39, 95% CI 0.29-0.51, $P < 0.001$), primary tumor site (HR 0.77, 95% CI: 0.62-0.96, $P = 0.018$), and the number of cycles (HR 0.67, 95% CI 0.54-0.82, $P = < 0.001$) also retained statistical significance (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2026.108365).

When patients were stratified according to TT, both Kaplan–Meier curves (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2026.108365) with log-rank test and the univariable Cox regression model (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2026.108365) did not show any significant difference in PFS and OS. However, when TT was analyzed as a continuous variable, restricted cubic spline analysis suggested a nonlinear association with both outcomes, characterized by an initial decrease in hazard followed by a progressive increase in the risk of death and disease progression at longer TT values (Figure 3).

Prognostic impact of time from diagnosis to first HD-CT dose across IPFSG prognostic groups

Kaplan–Meier curves showed no significant differences in OS or PFS between patients who received HD-CT within 12 months of diagnosis and those treated after 12 months, in either the low/intermediate- or high/very-high-risk groups (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2026.108365). When TT was modeled as a continuous variable, no statistically significant interaction was observed between TT and IPFSG risk group for PFS (interaction $P = 0.62$), indicating that the effect of TT on progression risk did not differ significantly by risk group (Figure 4B). By contrast, a significant interaction was observed for OS (interaction $P = 0.04$): in the low/intermediate-risk group, longer TT was associated with a progressively higher hazard of mortality, whereas this association was not apparent in the high/very-high-risk group (Figure 4A). Nevertheless, it is worth noting that, as shown in Table 1, the non–high-risk group was numerically dominated by intermediate-risk patients (156 of 226, 69%), with very-low- and low-risk patients together representing the minority (70 of 226, 31%); the observed OS interaction in this group is therefore likely driven predominantly by intermediate-risk patients and these findings should not be extrapolated to very-low/low-risk patients, who may warrant dedicated evaluation in future, larger series.

DISCUSSION

Salvage therapy in GCTs is a potentially curative treatment that should be considered in all patients with refractory or relapsed disease after first-line treatment. However, whether CD-CT is sufficient for all or some patients or whether HD-CT toxicity is justified by a true survival benefit, still needs to be demonstrated. At present, we have evidence that both approaches are effective and manageable when delivered in highly specialized centers. Because retrospective studies suggest a possible superiority of HD-CT, we aimed to report the contemporary, real-world outcomes of this strategy, considering changes in chemotherapy regimens and improvement in the management of

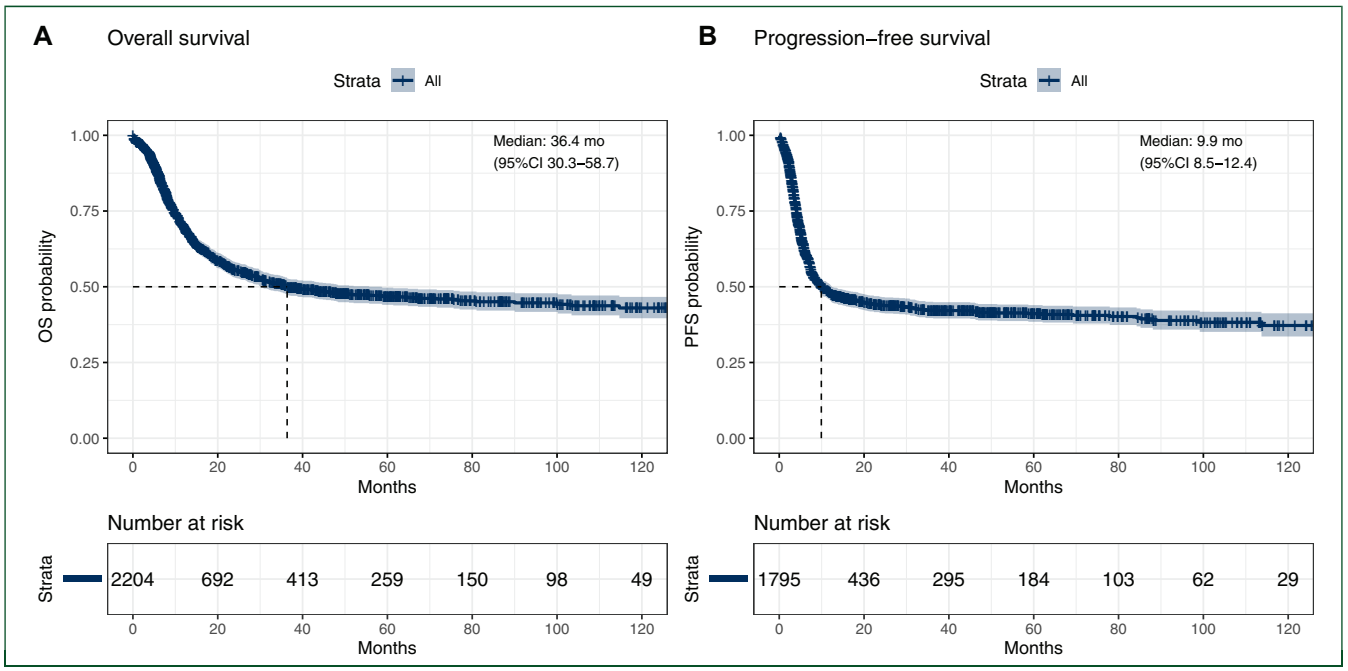


Figure 2. Kaplan–Meier curves depicting median OS (A) and PFS (B) in the entire cohort of 2204 patients treated with HD-CT. Median OS and PFS were 36.4 months (95% CI 30.3-58.7) and 9.9 months (95% CI 8.5-12.4), respectively.
CI, confidence interval; HD-CT, high-dose chemotherapy; OS, overall survival; PFS, progression-free survival.

patients over recent decades. Indeed, restricting our analysis to patients treated with HD-carboplatin–etoposide in the last 20 years ensures a more homogeneous population.

In our dataset, the largest ever published to our knowledge, the median OS from the first dose of HD-CT was >3 years with a median PFS of almost 10 months, but a 5-year PFS of 41.1%. The apparently short median PFS reflects the steep early decline in the PFS curve, followed by a long-term plateau, suggesting that although a subset of patients experiences early progression or lack of response, a substantial proportion achieves durable disease control after HD-CT. These results appear inferior compared with those reported for the TIP regimen (paclitaxel–ifosfamide–cisplatin; 5-year PFS of 66% and 5-year OS of 69%),[4] TI-CE

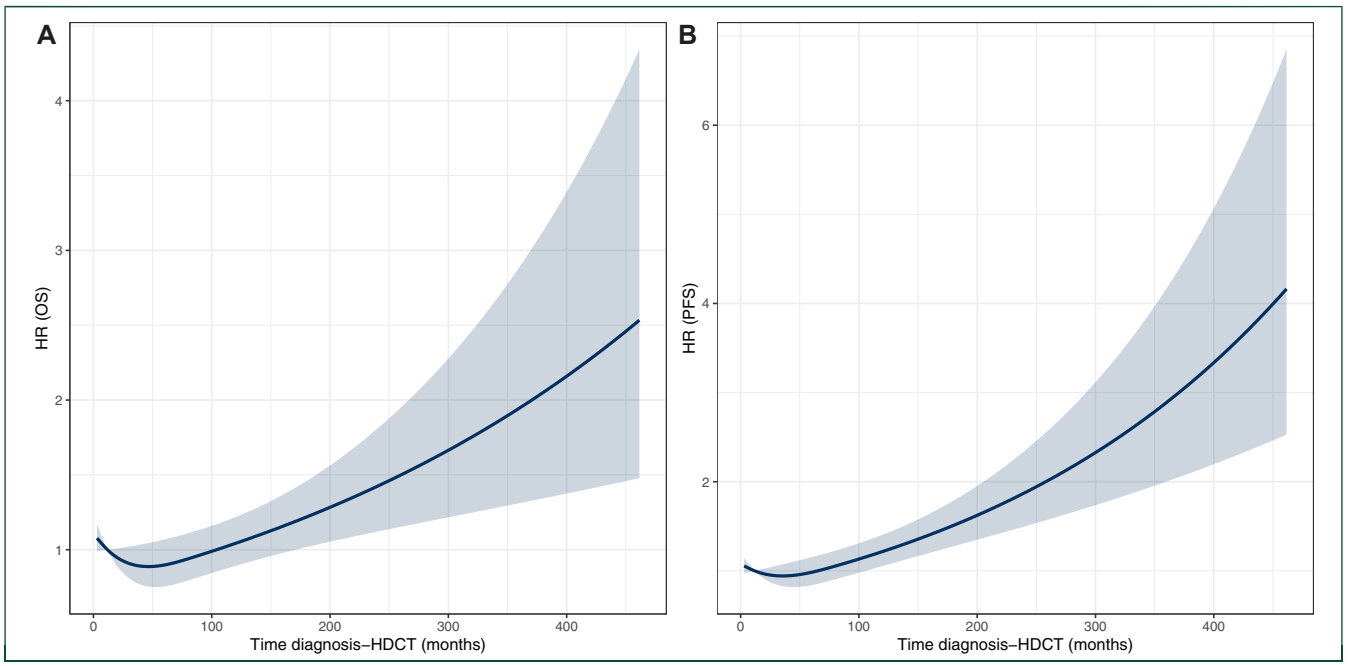


Figure 3. Spline-modeled hazard ratio for overall survival (A) and progression-free survival (B). Although the relationship appeared nonlinear, longer time intervals were generally associated with progressively higher hazards of death and disease progression beyond the early follow-up period. Shaded areas represent 95% CIs.
CI, confidence interval; HD-CT, high-dose chemotherapy.

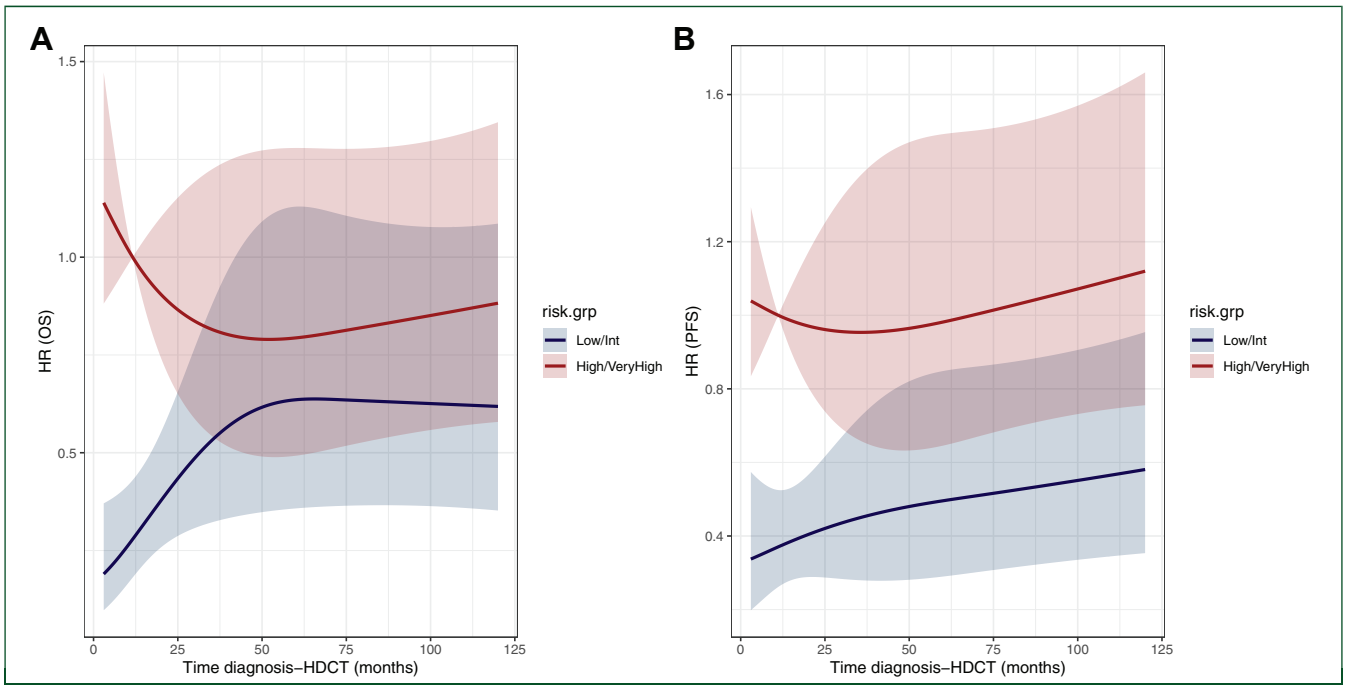


Figure 4. Spline-modeled hazard ratio for overall survival (A) and PFS (B) according to IPFSG category (red line, high/very high risk; blue line, very low/low/intermediate risk). When time from diagnosis to first HD-CT was analyzed as a continuous variable, longer time was associated with a progressively higher hazard of mortality in the very low/low/intermediate risk group, whereas no statistically significant interaction was observed between time and IPFSG risk group for PFS. CI, confidence interval; HD-CT, high-dose chemotherapy; IPFSG, International Prognostic Factor Study Group; PFS, progression-free survival.

(median PFS 22 months but 5-year OS of 52%),[5] and the IPFSG study (2-year PFS 49.6% and 5-year OS 53.2% for HD-CT group; 2-year PFS 27.8% and 5-year OS 40.8% for CD-CT group).[9] However, it is important to emphasize that our study has a shorter median follow-up and likely includes a population with a worse prognosis, given the higher proportion of patients classified as very high (17%) and high risk (38%) according to IPFSG compared with the other cited studies. Indeed, when examining survival according to IPFSG risk group, outcomes in our dataset are similar to those reported in the IPFSG analysis, with a 5-year OS of ∼30% in high- and very-high-risk patients. In this real-world context, selection bias cannot be controlled and it is reasonable that clinicians were more likely to refer patients with poor prognostic features for HD-CT. Moreover, in a recent SWENOTECA analysis, survival after HD-CT was comparable to our findings. Patients treated with HD-CT for progression within 3 months of first-line chemotherapy, likely representing a high/very-high-risk group, had a 5-year OS of 29%.[19]

When examining variables in the registry known to influence outcomes, we observed, as expected, that seminoma histology, a testicular primary, and receipt of a complete course of three cycles of HD-CT were associated with improved survival, consistent with previous reports.

Regarding the timing of HD-CT administration, available data indicate that HD-CT retains efficacy even when used as second or later salvage therapy, although survival declines substantially when it is delivered as a third or subsequent line.[7,20] In our dataset, the exact number of prior chemotherapy lines was not available. Instead, we relied on the interval from initial diagnosis to the first HD-CT dose as a pragmatic surrogate of treatment sequencing, an approach adopted in registry-based analyses when treatment history is incompletely captured. In the context of metastatic GCT, standard first-line cisplatin-based chemotherapy typically lasts ∼3-4 months and HD-CT is generally administered after disease progression or relapse following one or more conventional-dose regimens. Therefore, the interval between diagnosis and HD-CT provides a clinically plausible approximation of treatment trajectory, while acknowledging the inherent limitations of this proxy measure. In our analysis, the effect of TT on survival was not unequivocal. A correlation emerged only when TT was considered as a continuous variable, with longer TT associated with an increased risk of progression and death. Notably, when stratifying patients into very-low/low/intermediate-risk and high/very-high-risk groups, TT demonstrated a significant interaction with OS. In patients with non—high-risk disease, who in our cohort were predominantly classified as intermediate risk, longer TT was associated with a progressively higher risk of death, whereas this association was not apparent in the high/very-high-risk group. In the latter, the downward trend of the spline curve at longer TT intervals likely reflects data sparsity and survivor selection rather than a biologically meaningful effect.

These results seem to suggest that in the non—high risk population, in particular those with intermediate risk, receiving HD-CT earlier is associated with a lower risk of death. This finding may support offering HD-CT as initial salvage therapy rather than delaying it after CD-CT salvage therapy, to observe the highest benefit from HD-CT.

However, several major limitations of our study warrant caution when interpreting these results. Firstly, the absence of data on the number of prior therapy lines prevents us from clearly distinguishing patients who received later HD-CT because of late relapse from those who received preceding CD-CT salvage regimens. However, given that late relapses are uncommon, TT may nonetheless provide an approximative indication of the likely line of salvage therapy. Another important limitation is the availability of IPFSG risk group information for only 500 patients, which necessitated grouping patients into two broad categories, thereby missing differences among the individual prognostic groups. Moreover, although TT may represent a surrogate of treatment timing, it could also be influenced by underlying disease biology and other factors, including tumor aggressiveness, platinum sensitivity, and referral patterns, which may confound the observed association.

Conclusion

In this large contemporary cohort of patients with relapsed or refractory GCTs treated with HD-carboplatin—etoposide, survival outcomes were consistent with the established efficacy of HD-CT. Our findings seem to suggest that, particularly in patients with intermediate risk disease, earlier administration of HD-CT as salvage therapy may offer a survival advantage compared with delaying this approach. These observations reinforce the hypothesis that appropriate patient selection and timely referral for HD-CT are critical to maximizing benefit. Nevertheless, the absence of data on prior therapy lines limits definitive conclusions regarding the optimal sequencing of salvage treatments. Moreover, the observed association between treatment timing and survival may be confounded by differences in disease biology, prognosis, and other unmeasured clinical factors rather than reflecting a true effect of earlier HD-CT administration. Prospective evidence remains essential to clarify the comparative efficacy between HD-CT and CD-CT and to guide personalized decision making in the salvage setting.

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DISCLOSURE

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