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ORIGINAL ARTICLE

# Multicenter analysis of high-dose chemotherapy regimens for the treatment of patients with refractory or recurrent germ cell tumors

A. Chehrazi-Raffle[1*†], M. Zugman[1†], H. Ebrahimi[1], M. O. Shodiya[2], E. Maldonado[3], T. Othman[3], S. Jaime-Casas[1], R. B. Carrillo[4], X. Li[1], S. K. Pal[1], A. Tripathi[1], A. Zhumkhawala[1], R. Hoeg[5], C. Oliai[2], R. L. Olin[3], T. B. Dorff[1‡] & M. Mei[1‡]

[1]City of Hope Comprehensive Cancer Center, Duarte; [2]University of California, Los Angeles, Los Angeles; [3]University of California, San Francisco, San Francisco; [4]Instituto Nacional de Cancerología, Mexico City, Mexico; [5]University of California, Davis Comprehensive Cancer Center, Sacramento, USA

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**Background:** High-dose chemotherapy (HDCT) is an established salvage treatment for recurrent germ cell tumors (GCTs). Comparative analyses of contemporary carboplatin-based HDCT regimens are limited. This study provides a multicenter analysis of commonly used regimens.

**Patients and methods:** Data from four referral centers included patients treated with HDCT for recurrent GCTs between January 2010 and January 2024. Fisher's exact test and the Wilcoxon rank sum test were used for statistical analyses. Kaplan—Meier and log-rank tests assessed relapse-free survival (RFS) and overall survival (OS).

**Results:** Among 111 patients (median age 28.5 years), 76.6% had non-seminomatous GCT, and 43.2% had poor-risk disease per the International Germ Cell Cancer Collaborative Group (IGCCCG) classification. HDCT regimens included CE (50 patients; carboplatin and etoposide for two cycles) and TICE (32 patients; paclitaxel and ifosfamide, followed by carboplatin and etoposide for three cycles). HDCT was second-line in 26.1% and third-line or beyond in 73.9%. After 55.5 months' follow-up, no significant difference in RFS was observed [10.2 versus 5.9 months; hazard ratio (HR) 0.91, 95% confidence interval (CI) 0.54-1.51, $P = 0.706$]. TICE showed a trend toward longer OS (57.2 versus 19.8 months; HR 0.67, 95% CI 0.37-1.2, $P = 0.18$) and significantly improved OS in IGCCCG intermediate-/poor-risk patients (57.2 versus 14.0 months; HR 0.44, 95% CI 0.2-0.99, $P = 0.047$).

**Conclusions:** No significant difference in RFS or OS was observed between CE and TICE overall. However, TICE may offer more benefit to patients with higher-risk disease. Prospective studies are needed to validate these findings.

**Key words:** CE regimen, high-dose chemotherapy, prognostic models, relapsed germ cell tumors, TICE regimen

## INTRODUCTION

For nearly 40 years, high-dose chemotherapy (HDCT) has been a standard treatment for relapsed or refractory testicular germ cell tumors (GCTs).[1] Early efforts employing cyclophosphamide-based regimens were hampered by poor response rates and excessive toxicity.[2,3] Through refinements in chemotherapy dosing, stem cell collection, and supportive care measures, contemporary carboplatin-based regimens have yielded marked improvements in both clinical outcomes and treatment-related toxicity.[4-7]

While the efficacy and safety of HDCT in GCT is well defined, there remains some uncertainty in choosing between several HDCT regimens.[8] Researchers from Indiana University have reported single-center retrospective experiences using two courses of carboplatin 700 mg/m$^2$ plus etoposide 750 mg/m$^2$ given on days −5, −4, and −3 before peripheral infusion of stem cells (CE).[4,5] In contrast, researchers from the Memorial Sloan Kettering Cancer Center have prospectively examined two cycles of paclitaxel plus ifosfamide followed by three cycles of carboplatin area under the curve 7-8 mg/ml/min plus etoposide 400 mg/m$^2$ (TICE).[6,9,10] Although overall survival (OS) rates of 50%-66% have been reported from these single-center experiences and appear largely comparable, multicenter analyses comparing their efficacy are lacking.

To address the paucity of real-world data using contemporary HDCT regimens, we developed a multi-institutional database across four high-volume California cancer centers with the aim of examining practice patterns, patient outcomes, and previously established prognostic variables. In this article, we report the final results from this initiative.

*Correspondence to: Dr Alex Chehrazi-Raffle, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA 91010, USA. Tel: +1-626-218-4772

E-mail: achehraziraffle@coh.org (A. Chehrazi-Raffle).

@arafflemd, @mzugman, @EbrahimiHedyeh

†These authors contributed equally to this work.

‡Co-senior authors.

## PATIENTS AND METHODS

### Study design and population

This multicenter, retrospective cohort study was conducted across four high-volume cancer centers in California: City of Hope Comprehensive Cancer Center (COH), University of California Los Angeles (UCLA), University of California San Francisco (UCSF), and University of California Davis (UCD). The study included patients diagnosed with recurrent or refractory GCTs who underwent HDCT between 1 January 2010 and 1 January 2024. We included patients with histologically confirmed diagnosis of GCT (both seminomatous and non-seminomatous histologies), who received at least one cycle of HDCT. Clinical data were retrospectively abstracted from the electronic medical records of participating institutions. Information collected included patient demographics, tumor characteristics, tumor marker levels, and treatment details before and after HDCT. Patients with incomplete medical records or inadequate follow-up data were excluded.

The primary outcomes assessed were relapse-free survival (RFS) and OS. RFS was defined as the time after the date of last dose of HDCT to either relapse or last follow-up. OS was defined as the time after the last dose of HDCT to death from any cause or last follow-up.

### Statistical analysis

Demographic and clinical characteristics of the study population were summarized using descriptive statistics. Continuous variables were presented as means with standard deviations, or medians with ranges, and compared between groups either using the *t*-test or the Wilcoxon rank sum test. Categorical variables were summarized as frequencies and percentages and were compared using either Pearson's chi-square test or Fisher's exact test, as appropriate. RFS and OS were estimated using the Kaplan–Meier method, and survival curves were compared between treatment groups using the log-rank test.

Univariable and multivariable Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for RFS and OS, adjusting for potential confounders such as age, tumor histology, primary tumor site, tumor marker levels [alpha fetoprotein (AFP), human chorionic gonadotrophin ($\beta$HCG)], and different risk classification. The variables with significant associations in the univariable analysis ($P < 0.05$) were included in the multivariable models to account for confounding. All statistical analyses were conducted using R Statistical Software (version 4.3.1); two-sided *P*-values $<0.05$ were considered statistically significant.

## DATA AVAILABILITY

The authors declare that all relevant aggregate data supporting the findings of this study are available within the article. In accordance with the Health Insurance Portability and Accountability Act, we do not have institutional review board approval or patient consent to share individualized patient data, which contains potentially sensitive patient information and cannot be reported in a public data repository.

## RESULTS

### Patient characteristics

A total of 111 patients were identified across four high-volume centers in California. Of these, 50 patients received CE, 32 received TICE, and 29 were treated with other regimens. The latter group received high-dose carboplatin and etoposide chemotherapy, with carboplatin doses ranging from 187 mg/m$^2$ to 1500 mg/m$^2$ and etoposide doses ranging from 125 mg/m$^2$ to 1200 mg/m$^2$. Debulking regimens, which cytoreduce tumor load and assist with stem cell collection before HDCT, were defined as any cytotoxic chemotherapy that concluded within 30 days of the initiation of HDCT. Patient characteristics are presented by transplant type in Table 1.

The median age at diagnosis for the overall population was 28.5 years; the majority of patients were Latino (56.8%). The primary tumor site was classified as either mediastinal or non-mediastinal, with similar distribution across transplant types. Non-seminomatous GCTs (NSGCTs) were predominant, representing 76.6% of the population. Among patients with seminoma, 3 (9.4%) received TICE, 11 (22%) received CE, and 6 (20.7%) received other regimens. Late relapses, defined as disease recurrence occurring $>2$ years after first-line treatment, were rare, occurring in one patient (3%) in the CE cohort, three patients (6%) in the TICE cohort, and two patients (7%) in those receiving other regimens.

In terms of initial staging, the proportion of patients with poor-risk disease per the International Germ Cell Cancer Collaborative Group (IGCCCG) was similar between TICE (50%) and CE (44%). Among patients receiving other regimens, 10 (34.5%) had poor-risk disease. Tumor marker elevation at the time of HDCT, defined as $\beta$HCG $>1000$ IU/ml or AFP $>1000$ ng/ml, was similar across all cohorts ($P = 0.886$ and $P = 0.516$, respectively). Other key prognostic factors included the number and location of metastatic sites. Liver metastases were similar between TICE (21.9%) and CE (20.0%), whereas more than twice as many patients who received TICE had brain metastases at initial diagnosis compared with those who received CE (15.6% versus 6%, respectively). HDCT was administered as second-line therapy in 26.1% of the overall population and as third-line or more in 73.9%. Third-line treatment comprised 53.1% of TICE patients and 74% of CE patients.

### Clinical outcomes

The median follow-up from the date of the last transplant was 55.5 months, during which interval 59 relapse events and 74 deaths occurred. RFS estimates comparing TICE and CE showed non-significant statistical difference between the two regimens (HR 0.91, 95% CI 0.54-1.51, $P = 0.706$). Median RFS (mRFS) was 10.2 months (95% CI 5.0-49.0

**Table 1. Patient characteristics**

| | Overall ($N$ = 111) | CE ($n$ = 50) | TICE ($n$ = 32) | Others ($n$ = 29) | $P$ value |
|---|---|---|---|---|---|
| Institution | | | | | |
| COH | 32 (28.8%) | 14 (28.0%) | 18 (56.3%) | 0 (0%) | |
| UCD | 10 (9.0%) | 8 (16.0%) | 2 (6.3%) | 0 (0%) | |
| UCLA | 23 (20.7%) | 10 (20.0%) | 0 (0%) | 13 (44.8%) | |
| UCSF | 46 (41.4%) | 18 (36.0%) | 12 (37.5%) | 16 (55.2%) | |
| Age, years | | | | | 0.018 |
| Median (min-max) | 28.5 (14.0-58.0) | 31.0 (19.0-50.0) | 28.0 (18.0-58.0) | 26.0 (14.0-43.0) | |
| Missing | 1 (0.9%) | 1 (2.0%) | 0 (0%) | 0 (0%) | |
| Race | | | | | 0.489 |
| American Indian or Alaskan Native | 1 (0.9%) | 0 (0%) | 1 (3.1%) | 0 (0%) | |
| Asian | 8 (7.2%) | 4 (8.0%) | 3 (9.4%) | 1 (3.4%) | |
| Black | 1 (0.9%) | 0 (0%) | 0 (0%) | 1 (3.4%) | |
| White | 77 (69.4%) | 33 (66.0%) | 22 (68.8%) | 22 (75.9%) | |
| Missing | 24 (21.6%) | 13 (26.0%) | 6 (18.8%) | 5 (17.2%) | |
| Ethnicity | | | | | 0.569 |
| Non-Hispanic | 43 (38.7%) | 22 (44.0%) | 12 (37.5%) | 9 (31.0%) | |
| Hispanic | 63 (56.8%) | 26 (52.0%) | 19 (59.4%) | 18 (62.1%) | |
| Missing | 5 (4.5%) | 2 (4.0%) | 1 (3.1%) | 2 (6.9%) | |
| Primary site | | | | | 0.131 |
| Gonadal | 101 (91.0%) | 44 (88.0%) | 28 (87.5%) | 29 (100%) | |
| Mediastinal | 10 (9.0%) | 6 (12.0%) | 4 (12.5%) | 0 (0%) | |
| Histology | | | | | 0.502 |
| NSGCT | 85 (76.6%) | 39 (78.0%) | 24 (75.0%) | 22 (75.9%) | |
| Seminoma | 20 (18.0%) | 11 (22.0%) | 3 (9.4%) | 6 (20.7%) | |
| Missing | 6 (5.4%) | 0 (0%) | 5 (15.6%) | 1 (3.4%) | |
| IGCCCG risk | | | | | 0.972 |
| Good | 29 (26.1%) | 14 (28.0%) | 8 (25.0%) | 7 (24.1%) | |
| Intermediate | 11 (9.9%) | 5 (10.0%) | 4 (12.5%) | 2 (6.9%) | |
| Poor | 48 (43.2%) | 22 (44.0%) | 16 (50.0%) | 10 (34.5%) | |
| Missing | 23 (20.7%) | 9 (18.0%) | 4 (12.5%) | 10 (34.5%) | |
| AFP salvage, ng/ml | | | | | 0.886 |
| $<$1000 | 100 (90.1%) | 45 (90.0%) | 30 (93.8%) | 25 (86.2%) | |
| $\geq$1000 | 7 (6.3%) | 4 (8.0%) | 2 (6.3%) | 1 (3.4%) | |
| Missing | 4 (3.6%) | 1 (2.0%) | 0 (0%) | 3 (10.3%) | |
| $\beta$HCG salvage, U/ml | | | | | 0.516 |
| $<$1000 | 88 (79.3%) | 39 (78.0%) | 28 (87.5%) | 21 (72.4%) | |
| $\geq$1000 | 13 (11.7%) | 7 (14.0%) | 2 (6.3%) | 4 (13.8%) | |
| Missing | 10 (9.0%) | 4 (8.0%) | 2 (6.3%) | 4 (13.8%) | |
| Transplant line | | | | | $<$0.001 |
| Second line | 29 (26.1%) | 13 (26.0%) | 15 (46.9%) | 1 (3.4%) | |
| Third line or more | 82 (73.9%) | 37 (74.0%) | 17 (53.1%) | 28 (96.6%) | |
| Einhorn risk score | | | | | 0.267 |
| High | 43 (38.7%) | 21 (42.0%) | 10 (31.3%) | 12 (41.4%) | |
| Intermediate | 38 (34.2%) | 16 (32.0%) | 14 (43.8%) | 8 (27.6%) | |
| Low | 10 (9.0%) | 6 (12.0%) | 4 (12.5%) | 0 (0%) | |
| Missing | 20 (18.0%) | 7 (14.0%) | 4 (12.5%) | 9 (31.0%) | |
| IPFSG risk score | | | | | 0.004 |
| Very high | 36 (32.4%) | 21 (42.0%) | 13 (40.6%) | 2 (6.9%) | |
| High | 19 (17.1%) | 7 (14.0%) | 7 (21.9%) | 5 (17.2%) | |
| Intermediate | 25 (22.5%) | 8 (16.0%) | 8 (25.0%) | 9 (31.0%) | |
| Low | 21 (18.9%) | 7 (14.0%) | 4 (12.5%) | 10 (34.5%) | |
| Very low | 9 (8.1%) | 6 (12.0%) | 0 (0%) | 3 (10.3%) | |
| Missing | 1 (0.9%) | 1 (2.0%) | 0 (0%) | 0 (0%) | |
| Beyer risk score | | | | | 0.732 |
| Intermediate | 88 (79.3%) | 39 (78.0%) | 27 (84.4%) | 22 (75.9%) | |
| Poor | 20 (18.0%) | 11 (22.0%) | 5 (15.6%) | 4 (13.8%) | |
| Missing | 3 (2.7%) | 0 (0%) | 0 (0%) | 3 (10.3%) | |
| Lung metastases | | | | | 0.463 |
| No | 42 (37.8%) | 18 (36.0%) | 15 (46.9%) | 9 (31.0%) | |
| Yes | 64 (57.7%) | 29 (58.0%) | 16 (50.0%) | 19 (65.5%) | |
| Missing | 5 (4.5%) | 3 (6.0%) | 1 (3.1%) | 1 (3.4%) | |
| Brain metastases | | | | | 0.363 |
| No | 99 (89.2%) | 46 (92.0%) | 27 (84.4%) | 26 (89.7%) | |
| Yes | 10 (9.0%) | 3 (6.0%) | 5 (15.6%) | 2 (6.9%) | |
| Missing | 2 (1.8%) | 1 (2.0%) | 0 (0%) | 1 (3.4%) | |
| Liver metastases | | | | | 0.285 |
| No | 89 (80.2%) | 39 (78.0%) | 25 (78.1%) | 25 (86.2%) | |
| Yes | 19 (17.1%) | 10 (20.0%) | 7 (21.9%) | 2 (6.9%) | |
| Missing | 3 (2.7%) | 1 (2.0%) | 0 (0%) | 2 (6.9%) | |

*Continued*

**Table 1. Continued**

| | Overall ($N = 111$) | CE ($n = 50$) | TICE ($n = 32$) | Others ($n = 29$) | $P$ value |
|---|---|---|---|---|---|
| Bone metastases | | | | | 0.257 |
| No | 108 (97.3%) | 49 (98.0%) | 32 (100%) | 27 (93.1%) | |
| Yes | 1 (0.9%) | 0 (0%) | 0 (0%) | 1 (3.4%) | |
| Missing | 2 (1.8%) | 1 (2.0%) | 0 (0%) | 1 (3.4%) | |

AFP, alpha fetoprotein; βHCG, human chorionic gonadotrophin; COH, City of Hope Comprehensive Cancer Center; IGCCCG, International Germ Cell Cancer Collaborative Group; IPFSG, International Prognostic Factor Study Group; NSGCT, non-seminomatous germ cell tumors; UCD, University of California Davis; UCLA, University of California Los Angeles; UCSF, University of California San Francisco.

months) for the TICE cohort, 5.9 months (95% CI 4.2-34.0 months) for the CE cohort, and 5.0 months for patients who received other regimens (95% CI 4.0-50.3 months) (Figure 1A). Among patients with IGCCCG intermediate- or poor-risk disease, no difference was observed between TICE and CE (HR 0.58, 95% CI 0.29-1.16, $P = 0.124$). Within this subgroup, the mRFS was 10.2 months for TICE compared with 4.6 months for CE (Figure 2A).

However, we did observe a trend toward improved OS with TICE compared with CE (57.2 months versus 19.8 months, $P = 0.180$; Figure 1B). When stratifying patients with either IGCCCG intermediate- or poor-risk disease, patients who received TICE had significantly longer OS compared with CE (HR 0.44, 95% CI 0.2-0.99, $P = 0.047$; Figure 2B). When stratified by treatment line, we did not observe any difference in RFS or OS among patients who received HDCT in the second line versus third line or more (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105081).

An exploratory analysis of RFS2, defined as the time from the start of HDCT to second progression or death, was conducted among the 22 patients who received subsequent systemic therapy after HDCT. Median RFS2 was longer in the TICE group compared with the CE group (15.4 versus 9.6 months; HR 0.36, 95% CI 0.13-0.99, $P = 0.047$). (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.105081).

### *Risk factors and prognostic scores*

We carried out multivariable analyses to evaluate individual risk factors. Elevated AFP (>1000 ng/ml) or βHCG (>1000 U/ml) levels at the time of HDCT were negative prognostic markers. Primary mediastinal disease was associated with increased risk; pure seminoma histology was associated with reduced risk of death (Figure 3).

Patients were also classified using three previously established models designed to assess the prognosis of patients with GCTs in the salvage setting: Beyer, Einhorn, and the International Prognostic Factor Study Group (IPFSG) (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105081).[4,8,11] In the salvage setting, the Beyer score prognosticates patients as having either intermediate- or poor-risk disease. Using the Einhorn model, 75% of our cohort of patients who received TICE had intermediate- or high-risk disease compared with 74% of those who received CE, respectively. IPFSG also showed an evenly distributed risk pattern between patients who received TICE and those who received CE, with 63% of the TICE group and 56% of the CE group classified as having high- or very high-risk disease.

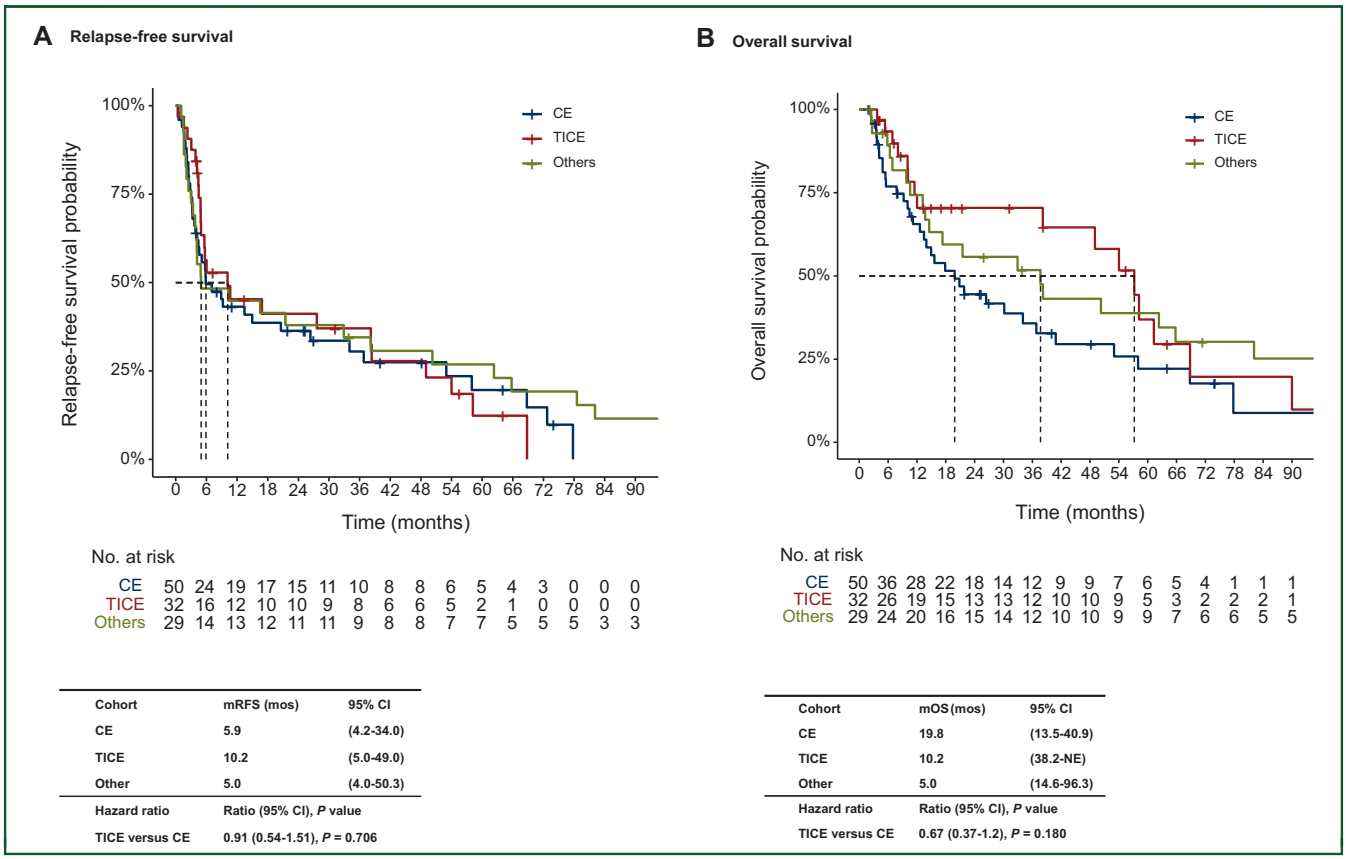
## DISCUSSION

For the first time, we carried out a multicenter retrospective analysis of outcomes and prognosis that compared contemporary HDCT regimens used for the treatment of recurrent GCTs. We found that elevated AFP and βHCG at the time of transplant were independently prognostic for worse RFS and OS. Additionally, though there was no difference in clinical outcomes between TICE and CE in the overall population, patients with IGCCCG intermediate- or poor-risk disease achieved improved OS from TICE. These findings suggest that TICE may be a more effective regimen for higher-risk patients than CE.

Prognostic factors for outcomes after HDCT in relapsed/refractory GCT have been studied in multiple previous retrospective analyses. Pooling data from 310 patients across four institutions treated between 1984 and 1993 with myriad HDCT regimens, Beyer et al. identified progressive disease before HDCT, the presence of a primary mediastinal NSGCT (PM-NSGCT), high levels of βHCG or AFP at the time of HDCT, absence of tumor marker normalization following first-line treatment, and platinum-refractory disease to be independent prognostic factors. Furthermore, patients could be stratified into good-, intermediate-, and poor-risk categories with 2-year failure-free survival rates of 51%, 27%, and 5%, respectively. However, most patients received only one round of HDCT.[11]

In their single-center study of 184 patients who were intended to receive two rounds of HDCT with CE between 1996 and 2004, Einhorn et al. found HDCT as third-line therapy or beyond, platinum-refractory disease, absence of tumor marker normalization following first-line treatment, or IGCCCG classification at first-line chemotherapy as factors associated with adverse disease-free survival. Elevated tumor markers at HDCT and Beyer score were not prognostic in this dataset.[4] A follow-up study of 364 patients treated with CE between 2004 and 2014 built upon these prognostic factors, reporting that elevated βHCG at the time of HDCT, IGCCCG intermediate- or poor-risk at initial diagnosis, and presence of PM-NSGCT or non-seminoma histology were also associated with worse progression-free survival (PFS).[5]

In their prospective phase I/II study involving 107 patients who received TICE between 1993 and 2006, Feldman




| Cohort | mRFS (mos) | 95% CI |
|---|---|---|
| CE | 5.9 | (4.2-34.0) |
| TICE | 10.2 | (5.0-49.0) |
| Other | 5.0 | (4.0-50.3) |
| **Hazard ratio** | **Ratio (95% CI), *P* value** | |
| TICE versus CE | 0.91 (0.54-1.51), *P* = 0.706 | |

| Cohort | mOS (mos) | 95% CI |
|---|---|---|
| CE | 19.8 | (13.5-40.9) |
| TICE | 10.2 | (38.2-NE) |
| Other | 5.0 | (14.6-96.3) |
| **Hazard ratio** | **Ratio (95% CI), *P* value** | |
| TICE versus CE | 0.67 (0.37-1.2), *P* = 0.180 | |

**Figure 1. HDCT outcomes by regimen.** Relapse-free survival. (B) Overall survival.
CE, carboplatin plus etoposide; CI, confidence interval; HDCT, high-dose chemotherapy; mOS, median overall survival; mRFS, median relapse-free survival; NE, not evaluable; TICE, paclitaxel and ifosfamide, followed by carboplatin and etoposide.

et al.[6] identified PM-NSGCT, HDCT as the third line of therapy or beyond, lung metastases, elevated βHCG at the time of HDCT, three or more metastatic sites, and IGCCCG intermediate- or poor-risk as poor prognostic factors. Furthermore, these investigators evaluated the prognostic utility of the Beyer and Einhorn scores for patients treated with TICE. While the Beyer score stratified patients effectively, the Einhorn score did not.

The most comprehensive prognostic model to date for initial salvage therapy was developed by the IPFSG.[8] Analyzing data from 1594 patients with relapsed/refractory GCT including patients who received both conventional dose chemotherapy as well as HDCT, seven clinical variables were independently associated with poor prognosis: PM-NSGCT, absence of tumor marker normalization following first-line treatment, high AFP, βHCG or lactate dehydrogenase at salvage therapy, progression-free interval of ≤3 months, and liver, bone, or brain metastases. Using a 10-point weight-ranked scoring system, patients were stratified into very low-, low-, intermediate-, high-, and very high-risk, with 2-year PFS rates of 75.1%, 51.0%, 40.1%, 25.9%, and 5.6%, respectively.

In the present study of 111 patients treated at four California tertiary-care centers between 2010 and 2024, we corroborated that AFP ≥1000 μg/l, βHCG ≥1000 IU/l, and IGCCCG poor-risk disease were associated with worse RFS and OS (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105081). This supports tumor markers and initial IGCCCG risk classification as validated prognostic variables. We also examined the Beyer, Einhorn, and IPFSG prognostic models using our multicenter cohort. All three models performed similarly, with higher scores corresponding to worse outcomes (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105081). Unfortunately, we were unable to compare TICE and CE directly due to the limited sample size of each subgroup. Our findings support the use of these prognostic models to guide decisions on treatment intensification with HDCT and highlight the need for larger multicenter studies to determine which regimens may be most effective for specific risk groups.

We observed poorer clinical outcomes than have been previously described. Prior studies of CE and TICE reported 2-year RFS rates of 57% and 48%, respectively[4,6]; our 2-year RFS rates were 36% (95% CI 25% to 53%) for CE and 41% (95% CI 26% to 64%) for TICE. One explanation is that our patient population had a significantly higher proportion of multiple relapses at the time of HDCT, which carries a 5-year OS rate of 17%.[12] Whereas receipt of HDCT in the third-line setting or beyond comprised 25%-27% in the aforementioned single-center studies, it accounted for 73.9% of

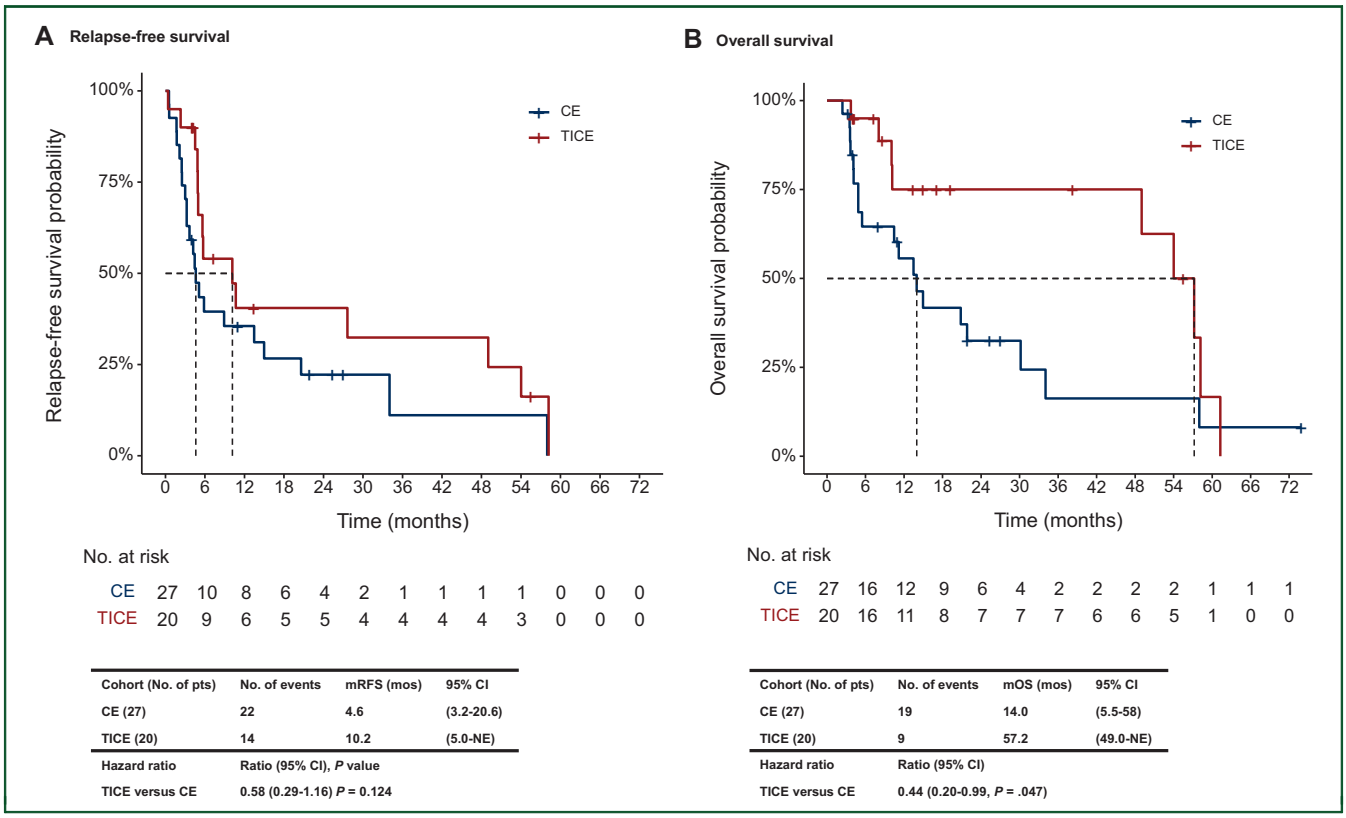



**Figure 2. CE versus TICE: IGCCCG intermediate- and poor-risk.** (A) Relapse-free survival. (B) Overall survival.
CE, carboplatin plus etoposide; CI, confidence interval; IGCCCG, International Germ Cell Cancer Collaborative Group; mOS, median overall survival; mRFS, median relapse-free survival; NE, not evaluable; TICE, paclitaxel and ifosfamide, followed by carboplatin and etoposide.

patients in our study. Longer follow-up of this cohort may determine whether a plateau in RFS or OS curves will emerge.

Another key finding from our study is that patients with IGCCCG intermediate- or poor-risk disease achieved a significantly prolonged OS with TICE as compared with CE.

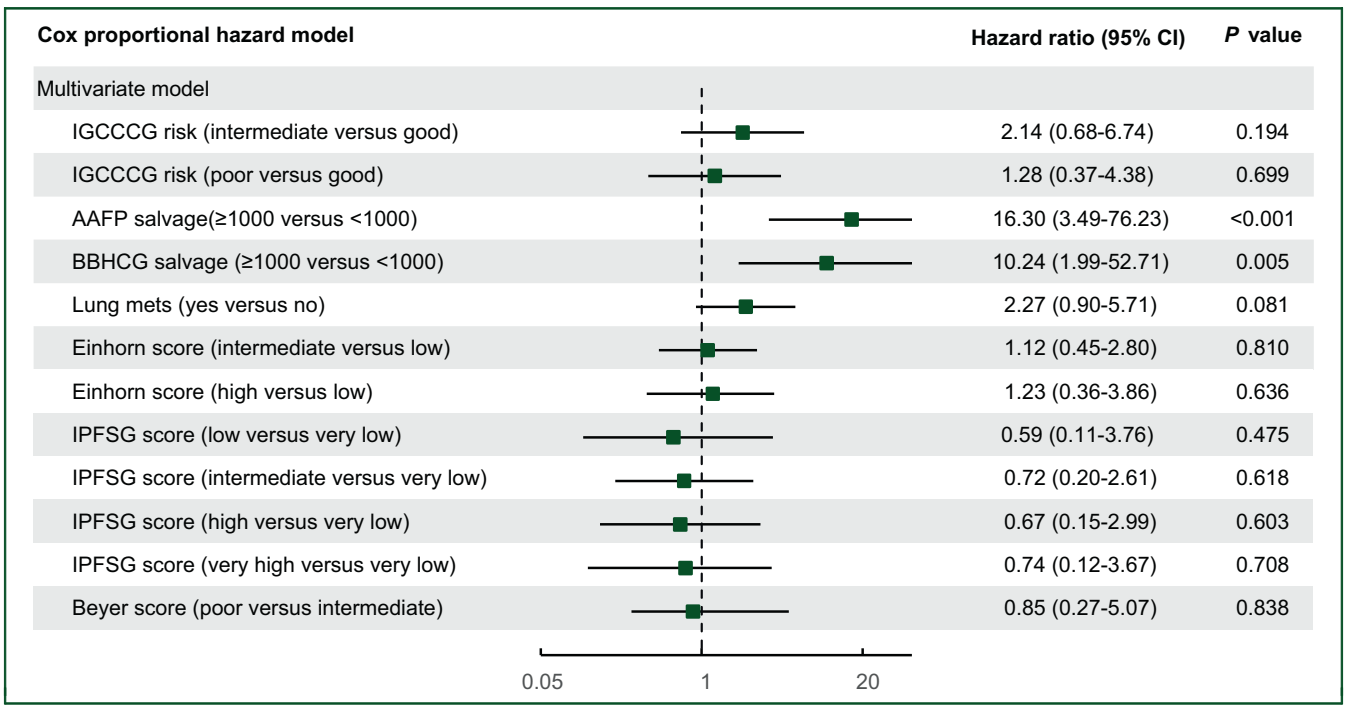



**Figure 3. Forest plot of multivariable analysis.**

Several distinctions between these regimens may explain this difference. Firstly, TICE delivers a higher cumulative dose of carboplatin due to both increased per-cycle dosing and the addition of a third cycle. Secondly, TICE has greater dose intensity, incorporating two cycles of paclitaxel and ifosfamide for tumor debulking and stem cell mobilization before HDCT. These factors could explain the improved survival observed in IGCCCG intermediate- or poor-risk patients, suggesting that a more intensified platinum dosing could be beneficial in this subgroup.

In addition, TICE achieved a significantly prolonged RFS2 compared with CE. This is consistent with the trend in OS between TICE and CE. It should be noted that the interpretation of RFS2 is constrained by the imbalance in the rate of subsequent therapy between each arm (37.5% in TICE versus 20% in CE). Nevertheless, this finding supports the broader survival advantage seen with TICE.

Our study has several limitations. The reliance on existing medical records introduces the possibility of incomplete or inaccurate data, which may affect the validity of our findings. Although we sought to mitigate selection bias by incorporating patients from four tertiary-care centers, patients were none the less all treated in California, which may limit the generalizability of the results. Additionally, CE was generally administered earlier in our dataset compared to TICE, introducing potential timing bias. Furthermore, our study is not equipped to help answer whether or not HDCT is the optimal choice in relapsed GCT as conventional dose chemotherapy may have therapeutic parity in this setting; the randomized TIGER trial will hopefully address this question (NCT02375204). Moreover, while the sample size was sufficient for some analyses, it was underpowered for detecting more subtle effects, particularly in subgroup analyses. Future analyses of these data with extended follow-up may help provide additional insights into long-term outcomes.

A key limitation of this study is the variation in prior chemotherapy regimens. For instance, 28/50 (56%) CE patients previously received paclitaxel and ifosfamide compared with only 7/32 (22%) TICE patients. Considering TICE also includes paclitaxel and ifosfamide, prior exposure to these agents may have dampened the efficacy of TICE in these patients. However, due to the limited size of these subgroups and overlap of agents between regimens, further adjustments were not feasible. Another limitation of this study is the lack of data on treatment-related toxicities and cause of death. As a result, we were unable to evaluate non-testicular cancer-related mortality, which has been directly linked to the number of platinum-based cycles,[12] or compare toxicity profiles between CE and TICE. Future studies incorporating long-term toxicity outcomes will be essential for a more comprehensive assessment of the risks and benefits of HDCT regimens.

### *Conclusion*

This study found no significant overall difference in outcomes between patients with refractory GCTs treated with CE and TICE regimens. However, among patients with higher-risk disease, those treated with TICE appeared to experience better outcomes, suggesting that TICE may offer particular benefit in this subgroup. While prognostic models proved useful for risk stratification, variation among them indicates that further refinement is necessary to standardize their application across clinical settings. Prospective studies are essential to clarify the clinical factors that are prognostic and predictive for optimizing treatment selection.

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## DISCLOSURE

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