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ORIGINAL REPORT

Brain Metastases in Patients With Germ Cell Tumors: Prognostic Factors and Treatment Options—An Analysis From the Global Germ Cell Cancer Group

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
To define characteristics, treatment response, and outcomes of men with brain metastases (BM) from germ cell tumors (GCT).

Patients and Methods
Data from 523 men with BM from GCT were collected retrospectively from 46 centers in 13 countries by using standardized questionnaires. Clinical features were correlated with overall survival (OS) as the primary end point.

Results
BM were present at initial diagnosis in 228 men (group A) and at relapse in 295 men (group B). OS at 3 years (3-year OS) was superior in group A versus group B (48% *v* 27%; $P < .001$). Multiple BM and the presence of liver or bone metastasis were independent adverse prognostic factors in both groups; primary mediastinal nonseminoma (group A) and elevations of α-fetoprotein of 100 ng/mL or greater or of human chorionic gonadotropin of 5,000 U/L or greater (group B) were additional independent adverse prognostic factors. Depending on these factors, the 3-year OS ranged from 0% to 70% in group A and from 6% to 52% in group B. In group A, 99% of patients received chemotherapy; multimodality treatment or high-dose chemotherapy was not associated with statistically improved survival in multivariable analysis. In group B, only 54% of patients received chemotherapy; multimodality treatment was associated with improved survival compared with single-modality therapy (hazard ratio, 0.51; 95% CI, 0.36 to 0.73; $P < .001$), as was high-dose compared with conventional-dose chemotherapy (hazard ratio, 0.41; 95% CI, 0.24 to 0.70; $P = .001$).

Conclusion
Men with BM from GCT have poor OS, particularly if additional risk factors are present. High-dose chemotherapy and multimodality treatment seemed to improve survival probabilities in men with BM at relapse.

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INTRODUCTION

In germ cell tumors (GCT), brain metastases (BM), either synchronous at initial diagnosis (group A) or metachronous at relapse (group B), are a defining feature of poor prognosis.[1,2] Because BM of GCT are rare, their optimal management remains controversial.[3,4] Reported retrospective series lack the power to robustly identify tumor or patient characteristics associated with outcome or to define optimal treatment strategies; some groups advocate chemotherapy alone,[5,6] multimodality treatment,[7-12] or even radiotherapy and surgery alone.[13]

Prospective trials are unlikely to be performed, so we retrospectively collected data on patients who had GCT with synchronous or metachronous BM with or without additional tumor sites among members of the Global Germ Cell Cancer Group. Here, we compare tumor and patient characteristics, treatments, and outcomes from this data collection with the following goals: to identify prognostic factors and to suggest management strategies for each of these two clinical scenarios.

PATIENTS AND METHODS

Patients

Data on 582 patients with GCT and BM at initial diagnosis or at relapse from 46 centers in 13 countries in the United States, Canada, Australia, and Europe were retrospectively collected from standardized detailed questionnaires and were reviewed by an international panel. Data were manually entered into an ACCESS database and were checked for plausibility and entry errors. In case of queries or data inconsistency, the principal investigators at the participating centers were contacted.

Patient Eligibility

Inclusion criteria for the study were as follows: Male sex; age 15 years or older; gonadal or extragonadal GCT either by histology or by unequivocal tumor marker (α-fetoprotein or human chorionic gonadotropin [HCG]) elevation in conjunction with other findings consistent with GCT diagnosis; BM present either at initial diagnosis or at relapse by computed tomography or magnetic resonance scanning with or without histologic confirmation; diagnosis of BM between Jan 1, 1990, and Dec 31, 2013; minimal follow-up of 2 years after diagnosis of BM unless deceased; and written consent by the principal investigator at participating centers to allow site visits and support verification of data entries, if requested.

Exclusion criteria included the following: BM diagnosis only post mortem; previous treatment for BM or malignant brain tumors; and missing data to an extent that did not allow inclusion in a prognostic factor analysis (eg, such as missing data on treatment outcome and survival). If repetitive and relevant queries on data quality occurred at a participating center, or if a participating center refused site visits for verification of data entry, all patients from this center were excluded from analysis. The study protocol was approved centrally by the ethics committee from the University of Marburg, Germany. Each center was required to obtain additional institutional approval.

Data from 59 patients were excluded from the current analysis for the following reasons: primary germ cell cancer of the brain (n = 27), follow-up for fewer than 2 years (n = 15), incomplete data (n = 10), no germ cell cancer histology (n = 2), treatment before 1990 (n = 2), female sex (n = 1), age younger than 15 years (n = 1), and death on the day of diagnosis of BM (n = 1).

Statistics

All statistical analyses were performed by a biostatistician (A.K.) from the coordinating center using STATA, version 11 (StataCorp LP, College Station, TX). Univariable descriptive statistics were performed with frequencies and percentages used for categoric variables and medians and ranges used for continuous variables.

The primary end point for the prognostic factor analysis was overall survival (OS), and progression-free survival (PFS) was a secondary end point. The Kaplan-Meier method was used to estimate survival rates, presented at 3 years. When applicable, median survival times as well as survival curves and smoothed estimates of the hazard rates also are provided.

For patients who received first-line treatment (group A), all survival-related end points were calculated from initiation of first-line treatment, whatever modality was chosen. For patients who had experienced relapse (group B), all survival-related end points were calculated from the initiation of the first day of salvage treatment, whatever modality was chosen.

PFS was calculated from the start of treatment and ended at the time of first disease progression or death as a result of progression. Patients with death as a result of causes other than progression were censored at the time of death. OS was calculated from the start of treatment and ended at the date of death. Patients alive at last follow-up were censored at the last known date alive.

Univariable analyses were performed with the log-rank test. Multivariable analyses were performed with the Cox proportional hazards regression model. Results that compared groups were presented with hazard ratios (HRs) and the associated 95% CIs. The proportional hazards assumptions were tested via Schoenfeld residuals.

Variables other than treatment with univariable significance of $P \leq .10$ were entered in the multivariable analysis. The results of the multivariable analysis were used to define a prognostic score that was based on a combination of variables with independent prognostic significance. Associations between treatment type and outcome were evaluated with the Cox model, adjusted for prognosis and compared within prognostic groups.

RESULTS

Of 582 patients, 523 (90%) fulfilled the entry criteria of the study and were considered eligible for the analysis. Details on characteristics, treatments, and outcomes in patients with synchronous BM at initial diagnosis (group A; n = 228) and metachronous BM at relapse (group B; n = 295 patients) are presented in Table 1. The median time from the previous response to the occurrence of metachronous BM in patients who experienced disease relapse from group B was 3 months (range, 0 to 74 months).

BM occurred almost exclusively in patients with nonseminoma histology. Although the locations of primary tumors between the two groups were similar, other relevant patient characteristics at initial diagnosis and at relapse were distinct. Among patients in group A, a significantly higher proportion had high HCG levels at presentation compared with patients from group B. More than half of patients (53%) in group A had initial values of HCG greater than 100,000 U/L. Only 17% of patients with BM at initial diagnosis had normal or moderate elevations of HCG of 1,000 U/L or less.

Significantly more patients in group A than in group B had multiple BM (67% *v* 56%; $P < .05$) and concurrent systemic disease (99% *v* 72%; $P < .05$). In particular, liver and/or bone involvement was significantly more common among patients in group A than in group B (46% *v* 25%; $P < .001$).

Almost all patients in group A had concurrent pulmonary metastases (94%) at initial presentation, and 47% of patients were asymptomatic with respect to their BM. This contrasts with a 62% rate of concurrent pulmonary metastases and a 30% rate of asymptomatic patients in group B ($P < .05$ for both).

Survival

PFS rates at 2 years were significantly higher in group A (29%; 95% CI, 23% to 35%) than in group B (21%; 95% CI, 16% to 26%; $P < .05$; Fig 1A). Relapses beyond 2 years were uncommon in either group (Appendix Fig A1A, online only). Progression in the brain after treatment occurred in 86 (54%) of 158 patients who had documented progression in group A and in 113 (49%) of 230 patients in group B (Appendix Table A1, online only). In group A, the 3-year OS was 48% (95% CI, 42% to 55%), and the median OS was 29.5 months. In group B, the 3-year OS was 27% (95% CI, 22% to 32%), and the median OS was only 8 months ($P < .001$; Fig 1B). Not all patients died as a result of uncontrolled BM. Only 66 (52%) of 128 patients in group A and 102 (45%) of 225 patients in group B died as a result of GCT with documented progression of BM. Deaths beyond 3 years were uncommon in either group (Appendix Fig A1B).

Multivariable Analysis and Prognosis in Group A

In group A, three variables were significantly associated with poor OS in the multivariable analysis. These were mediastinal primary site for patients with nonseminoma (HR, 1.66; 95% CI, 0.98 to 2.82), the presence of liver and/or bone metastases (HR, 2.11; 95% CI, 1.47 to 3.03), and the presence of multiple BM (HR, 1.88; 95% CI, 1.24 to 2.85; Table 2). Although OS decreased with increasing number of BM

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Group A: Brain Metastases at Diagnosis (n = 228)		Group B: Brain Metastases at Relapse (n = 295)		Total (N = 523)	
	No.	%	No.	%	No.	%
Age, years						
< 30	125	54.8	142	48.1	267	51
≥ 30	103	45.2	153	51.9	256	49
Primary tumor site						
Testis	197	86.4	245	83.1	442	84.5
Retroperitoneum	8	3.5	14	4.7	22	4.2
Mediastinum	17	7.5	32	10.8	49	9.4
Other	6	2.6	4	1.4	10	1.9
Histology						
Seminoma	9	4.0	14	4.7	23	4.4
Nonseminoma	216	95.0	280	94.9	496	94.8
Unknown	3	1.0	1	0.4	4	0.8
AFP, ng/mL						
≤ 10	100	43.9	128	43.4	228	43.6
> 10 to ≤ 1,000	61	26.7	49	16.6	110	21.0
> 1,000 to ≤ 10,000	19	8.3	16	5.4	35	6.7
> 10,000	13	5.7	6	2.0	19	3.6
Unknown	35	15.4	96	32.6	131	25.1
HCG, IU/L						
≤ 10	11	4.8	74	25.1	85	16.3
> 10 to ≤ 100	8	3.5	29	9.9	37	7.1
> 100 to ≤ 1,000	18	7.9	33	11.1	51	9.8
> 1,000 to ≤ 50,000	41	18.0	49	16.6	90	17.2
> 50,000 to ≤ 100,000	24	10.5	6	2.0	30	5.7
> 100,000	114	50.0	9	3.1	123	23.5
Unknown	12	5.3	95	32.2	107	20.4
Brain metastases						
Single	69	30.3	119	40.3	188	36.0
Multiple	141	61.8	149	50.5	290	55.4
Number unknown	18	7.9	27	9.2	45	8.6
Brain only	2	0.9	82	27.8	84	16.1
Brain and outside brain	226	99.1	213	72.2	439	83.9
Metastatic site						
Lung	215	94.3	184	62.4	399	76.3
Mediastinum	1	0.4	43	14.6	44	8.4
Abdomen	135	59.2	93	31.5	228	43.6
Bone	14	6.1	32	10.8	46	8.8
Liver	96	42.1	57	19.3	153	29.3
Liver and/or bone	104	45.6	75	25.4	179	34.2
Clinical symptoms						
Any symptom	121	53.0	208	70.5	329	62.9
Seizures	31	13.6	59	20.0	90	17.2
Headache	58	25.4	93	31.5	151	28.9

Abbreviations: AFP, α-fetoprotein; HCG, human chorionic gonadotropin.

in univariable analysis, use of a higher cutoff or multiple categories did not increase the discriminatory power of the multivariable model. Because the regression model coefficients were similar, one point was assigned for each of these three variables, and a score that ranged from 0 to 3 was obtained by summing the number of points for each patient.

Thus, a total of four prognostic groups were identified: low risk (score, 0; 16% of patients; 3-year OS, 71%), intermediate risk (score, 1; 51% of patients; 3-year OS, 54%), high risk (score, 2; 29% of patients; 3-year OS, 30%), and very high risk (score, 3; 4% of patients; 3-year OS, 0%; Table 2; Fig 2A).

Multivariable Analysis and Prognosis in Group B

Three variables were significantly associated with poor OS in multivariable analysis in patients from group B (Table 3): multiple BM (HR, 2.00; 95% CI, 1.40 to 2.87), liver and/or bone metastases (HR, 1.92; 95% CI, 1.29 to 2.84), and at least one elevated tumor marker, defined as an α-fetoprotein of 100 ng/mL or greater or an HCG of 5,000 U/L or greater (HR, 2.11; 95% CI, 1.48 to 3.02). Similar to group A, an increasing number of BM did not change the multivariable prognostic score, despite inferior survival. Although one third of patients in group B had missing marker values (n = 103; 35%), this important variable was retained in the model, because patient characteristics and prognostic scores were similarly distributed among patients with and without missing data (3-year OS for patients with missing data *v* full data: 28% *v* 26%; HR, 0.92; 95% CI, 0.70 to 1.22; $P = .57$). In group B, patients with isolated BM at relapse were more often treated with either surgery or radiotherapy alone but had similar

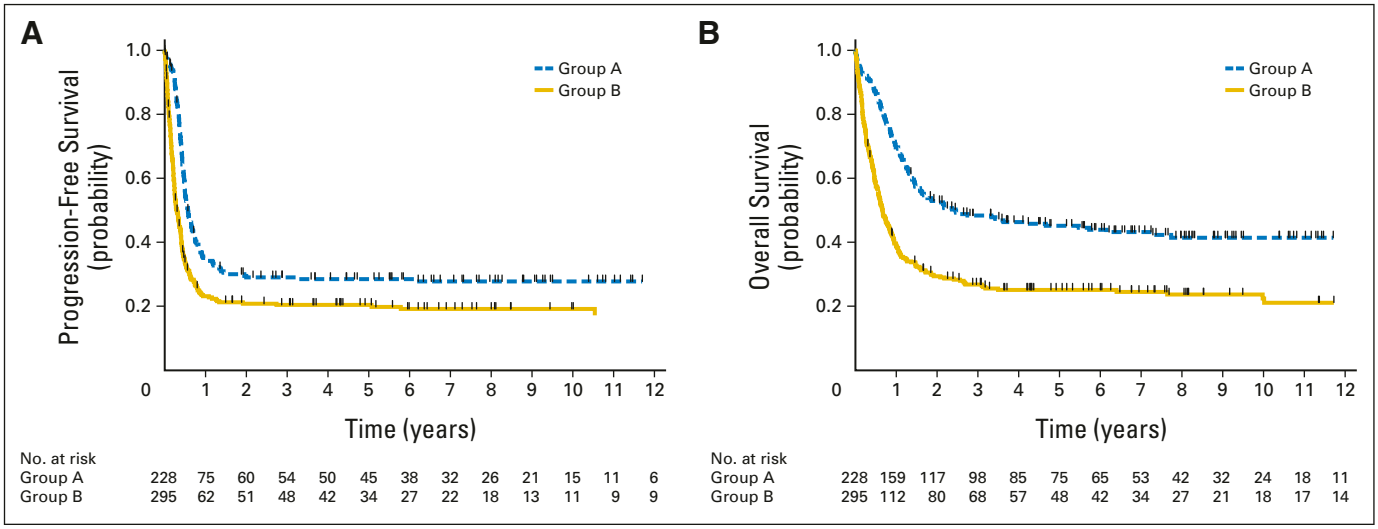

Fig 1. (A) Progression-free survival in patients with brain metastases at initial diagnosis (group A) and at relapse (group B). (B) Overall survival in patients with brain metastases at initial diagnosis (group A) and at relapse (group B).

outcomes to patients who experienced relapse with BM and systemic metastases (data not shown).

Similar to group A, a prognostic score was calculated for each patient in group B by assigning each adverse factor a score of 1, which resulted in a score sum that varied from 0 to 3. Because the outcomes for patients with score values of 2 or 3 were equally poor (6% and 5% 3-year OS, respectively), these two groups were combined to result in three prognostic groups: low risk (score, 0; 22% of patients; 3-year OS, 52%), intermediate risk (score, 1; 41% of patients; 3-year OS, 30%) and high risk (score, 2 or 3; 37% of patients; 3-year OS, 7%; Table 3; Fig 2B).

Treatments and Outcomes in Group A

Single-modality treatment was used in 103 patients (45%), and multimodality treatment was used in 125 patients (55%). Chemotherapy was administered in almost all patients across the four prognostic groups (99%). In contrast, neurosurgical resection varied by prognostic group and was more frequently used in patients with low risk (41%) versus intermediate risk (21%), high risk (7%), or very high risk (0%; $P < .001$; Appendix Tables A2 and A3, online only). Neurosurgical resections were not associated with improved OS in the multivariable analysis (adjusted HR, 0.81; 95% CI, 0.46 to 1.39; $P = .44$).

An uneven distribution across the prognostic groups was also observed for the use of radiation therapy in patients with low risk (44%), intermediate risk (52%), high risk (36%), and very high risk (22%; $P < .10$; Appendix Table A3). Whole-brain irradiation in 92 (92%) of 100 patients was not associated with a significant improvement in OS in multivariable analysis (adjusted HR, 0.77; 95% CI, 0.53 to 1.12; $P = .17$).

As a result, in group A, improved outcome with multimodality treatment versus single-modality treatment was significant in the univariable analysis (HR, 0.57; 95% CI, 0.40 to 0.80; $P < .001$), but this benefit lost significance after adjustment for prognostic group classification in the multivariable analysis (HR, 0.71; 95% CI, 0.49 to 1.03; $P = .07$; Appendix Fig A2, online only). There was also no benefit of improved OS associated with the use of high-dose chemotherapy in univariable analysis (HR, 0.86; 95% CI of HR, 0.46 to 1.59; $P = .62$), although this treatment was used infrequently in patients from group A, which limited the potential of this analysis (Appendix Table A2).

Table 2. OS According to Significant Variables in Patients With Synchronous Metastases at Initial Diagnosis (group A)

	Multivariable Analysis		
Prognostic Variable	HR (95% CI)	*P*	Score
Primary site		.059	
Testis/retroperitoneum	1		0
Mediastinum/other	1.66 (0.98 to 2.82)		+1
Liver and/or bone		< .001	
No liver/bone	1		0
Liver or bone	2.11 (1.47 to 3.03)		+1
No. of brain metastases		.003	
Single	1		0
Multiple	1.88 (1.24 to 2.85)		+1
Prognostic score*	3-Year OS Probability		
Low risk (n = 32)	1	.707	0
Intermediate risk (n = 108)	1.70 (0.89 to 3.25)	.543	1
High risk (n = 61)	3.31 (1.71 to 6.40)	.295	2
Very high risk (n = 9)	6.98 (2.87 to 16.96)	0	3

Abbreviations: HR, hazard ratio; OS, overall survival.
*Eighteen patients were not classified because of missing data.

Treatments and Outcomes in Group B

Compared with group A, fewer patients in group B received chemotherapy either alone or in combination with other therapies (99% *v* 58%; $P < .05$). Instead, significantly more patients in group B underwent surgery alone, radiation therapy alone, or surgery in combination with radiation therapy (Appendix Table A4, online only). This applied particularly to patients with isolated metachronous BM at relapse without other systemic metastatic sites. Chemotherapy was more frequently given as high-dose chemotherapy in group B than in group A (56 [19%] of 295 patients in group B *v* 22 [10%] of 228 patients in group A; $P < .05$). Whole-brain irradiation was administered in 177 (89%) of 199 patients. Overall, a greater variability of treatments was observed in group B than in group A (Appendix Table A4).

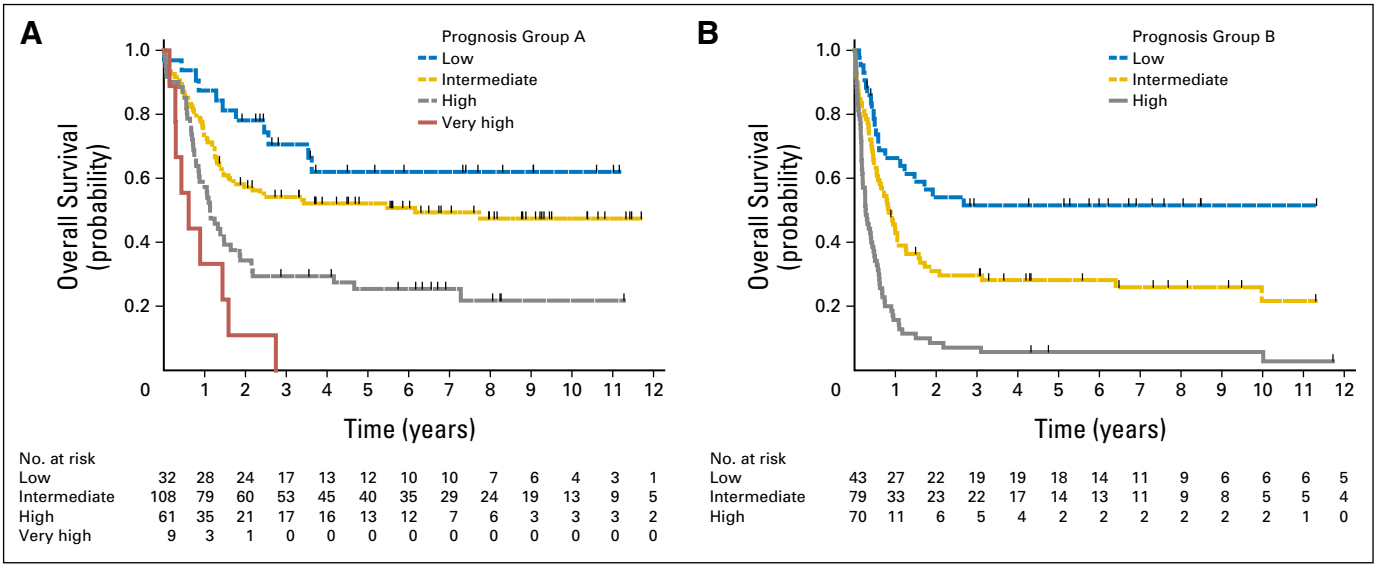

Fig 2. (A) Overall survival (OS) according to prognosis in patients with synchronous metastases at initial diagnosis (group A). (B) OS according to prognosis in patients with metachronous metastases at relapse (group B).

Radiation therapy and chemotherapy were used with similar frequency throughout the prognostic groups. Similar to group A, surgery was more frequently used in patients in group B with low risk (53%) than with intermediate (35%) and high (16%) risks (Appendix Table A5, online only).

Chemotherapy (HR, 0.64; 95% CI, 0.49 to 0.83; $P < .001$), surgery (HR, 0.55; 95% CI, 0.41 to 0.72; $P = .001$), radiation therapy (HR, 0.70; 95% CI, 0.53 to 0.92; $P = .01$), and high-dose chemotherapy (HR, 0.51; 95% CI, 0.34 to 0.77; $P = .001$) were all associated with significantly improved OS in univariable analysis. In multivariable analysis stratified by prognostic groups, only the use of multimodality treatment (HR, 0.52; 95% CI, 0.37 to 0.73; $P < .001$) and high-dose chemotherapy (HR, 0.41; 95% CI, 0.24 to 0.69; $P < .001$) remained significant (Fig 3).

Table 3. OS According to Significant Variables in Patients With Metachronous Metastases at Relapse (group B)

	Multivariable Analysis		
Prognostic Variable	HR (95% CI)	*P*	Score
No. of brain metastases		< .001	
Single	1		0
Multiple	2.00 (1.40 to 2.87)		+1
Liver and/or bone		< .001	
No liver/bone	1		0
Liver or bone	1.92 (1.29 to 2.84)		+1
AFP and HCG		< .001	
Both low*	1		0
At least one high	2.11 (1.48 to 3.02)		+1
Prognostic score†	3-Year OS Probability		
Low risk (n = 43)	1	.516	0
Intermediate risk (n = 79)	1.97 (1.20 to 3.25)	.297	1
High risk (n = 70)	4.46 (2.70 to 7.37)	.071	2-3

NOTE. A total of 103 patients were not classified because of missing data.
Abbreviations: AFP, α-fetoprotein; HCG, human chorionic gonadotropin; HR, hazard ratio; OS, overall survival.
*AFP ≤ 100 ng/mL and HCG ≤ 5,000 IU/L.
†The 3-year OS prognostic score for patients with missing data versus full data was 0.278 versus 0.261 (HR, 0.924; 95% CI, 0.701 to 1.217; $P = .57$).

DISCUSSION

Little is known about the presentation, prognostic factors, treatment, or outcome of patients with BM from GCT.[3,4] We demonstrated that

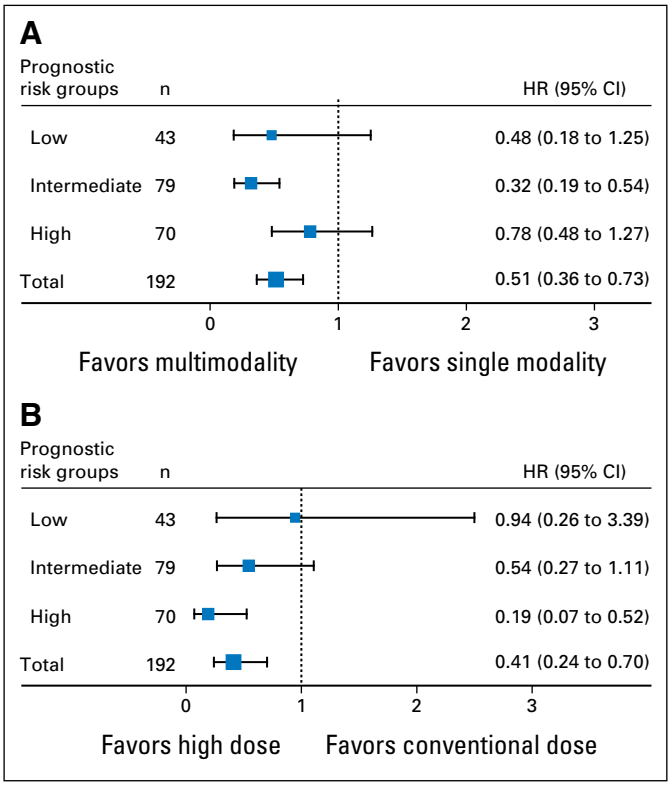

Fig 3. Results of multivariable analysis of treatments in patients with metachronous brain metastases at relapse (group B): (A) multimodality versus single-modality treatment and (B) high-dose versus conventional-dose chemotherapy. HR, hazard ratio.

greater than 50% of patients with either synchronous BM at the time of initial diagnosis or metachronous BM at relapse experience disease progression and die within 1 year after the diagnosis of BM and that approximately half of those patients died as a result of systemic progression rather than uncontrolled BM. Patients who present with adverse prognostic factors in addition to BM, and particularly those who experience relapse with metachronous BM, have worse outcomes.

The absence of symptoms did not exclude even widespread metastatic brain disease in either group; almost half of the patients who presented with BM and one third of patients who experienced relapse with BM were asymptomatic. BM was associated with nonseminoma histology, with a high frequency of pulmonary or liver and/or bone metastases, and with high serum levels of HCG. BM therefore may be more frequent in patients with a high systemic burden of disease, particularly those with lung metastases and high HCG levels or those who experience relapse after cisplatin-based chemotherapy, whereas the likelihood of BM in the absence of these features is low.

Our results demonstrated significant differences between patients who present with synchronous BM at initial diagnosis versus those who experience relapse. Patients with synchronous BM at initial diagnosis tend to have a higher burden of systemic disease than those who experience relapse in the brain. Yet, despite this higher burden of disease, these patients still have better prognoses than previously treated patients, which suggests that chemotherapy resistance is a critically important driver of outcome.

In contrast, multivariable analysis showed that the number of BM and the presence of liver and/or bone metastases were significantly associated with a poor outcome in both groups of patients, which points toward similarities in the factors that determine outcome in these otherwise-distinct groups of patients. The large number of patients in the present analysis allowed us to develop well-defined and discriminatory prognostic models for patients who presented with synchronous BM at initial diagnosis as well as in those who had metachronous BM at relapse; these models provide accurate estimates of the likelihood of cure and survival in these rare but important clinical scenarios.

Treatment guidelines for untreated metastatic GCT are straightforward and focus heavily on cisplatin-based combination treatment.[3] Existing guidelines are much less clear for patients with GCT and BM, for which management usually is based on individual or institutional preferences. This may in part explain the large heterogeneity of treatments found in the present analysis. The retrospective nature, selection bias, disproportional representation of treatment frequencies, and other potentially confounding factors limit the assessment of treatment strategies applied in patients from this data collection. Nevertheless, because we identified well-defined prognostic subgroups, a few important observations about treatment strategies can be made.

First, almost all patients who presented with synchronous BM at initial diagnosis received chemotherapy. Patients with better prognostic features were more likely to be offered additional radiotherapy or neurosurgical resections. However, despite trends in favor of multimodality treatment, multivariable analysis in the present data set did not support the general use of neurosurgery and/or radiation therapy in addition to chemotherapy, particularly not for patients with low risk. On the basis of these results, we suggest that chemotherapy should remain the standard of care in patients who present with synchronous BM at initial diagnosis to avoid additional toxicity from multimodality treatment, whereas additional radiation therapy and/or neurosurgery may be used in particular clinical circumstances according to individual decisions. The number of patients treated with stereotactic radiation was too small to assess the impact of this modality. Similarly, although we did not find a benefit from high-dose chemotherapy versus conventional-dose chemotherapy in multivariable analysis of patients with synchronous BM at initial diagnosis, the numbers of patients treated with this intensive systemic approach as first-line therapy were too small to draw definite conclusions.

Second, the greater variability in the management of patients who experienced relapse with metachronous BM may in part reflect the lack of evidence for their optimal treatment.[3,4] Our analysis provided a broad overview of current management practices. In univariable analysis, all treatments evaluated in patients with metachronous BM resulted in improved OS. However, only the use high-dose chemotherapy and multimodality treatment were associated with a superior outcome in the multivariable analysis, particularly in patients with intermediate and poor risks. This contrasts with patients who had synchronous BM at initial diagnosis, in whom high-dose chemotherapy and multimodality treatment were not significantly associated with improved OS. Therefore, on the basis of the current analysis, the application of the latter two strategies may be important to maximize the outcome only for patients with GCT who experience relapse with metachronous BM.

The current analysis is associated with all the shortcomings of a retrospective series, which include selection bias, reporting bias, missing data, a diversity of treatment approaches and regimens, as well as other potential confounders of outcome. Nevertheless, this large series describes prognostic factors and supports decision making in a clinical scenario that previously lacked robust data.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

Cox proportional hazards regression model: a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

prognostic factor: a measurable patient characteristic that is associated with the subsequent course of disease (whether or not therapy is administered). The identification of a prognostic factor does not necessarily suggest a cause-and-effect relationship. However, within a suitable outcome model, the measurement of a prognostic factor contributes to an estimate of an outcome probability (eg, the probability of disease-free survival within a given time interval).

prognostic model: a combination of patient, tumor, and treatment characteristics that predict the outcome of individual patients.

progression-free survival: time from random assignment until death or first documented relapse, categorized as either locoregional (primary site or regional nodes) failure or distant metastasis or death.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Brain Metastases in Patients With Germ Cell Tumors: Prognostic Factors and Treatment Options—An Analysis From the Global Germ Cell Cancer Group

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Table A1. Patients With Progression of Brain Metastases, Among All Patients Who Experienced Progression, According to Treatment Modality

	No. (%) of Patients			
	Group A		Group B	
Treatment	No Progression With BM	Progression With BM	No Progression With BM	Progression With BM
CT alone	34 (44)	43 (56)	11 (46)	13 (54)
CT + RT	25 (46)	29 (54)	34 (53)	30 (47)
CT + surgery	8 (47)	9 (53)	6 (33)	12 (67)
CT + RT + surgery	5 (56)	4 (44)	7 (50)	7 (50)
RT alone	—	1 (100)	43 (68)	20 (32)
Surgery alone	—	—	6 (33)	12 (67)
Surgery + RT	—	—	10 (34)	19 (66)
Total	72 (46)	86 (54)	117 (51)	113 (49)

Abbreviations: BM, brain metastases; CT, chemotherapy; RT, radiotherapy.

Table A2. Univariable Analysis of OS According to Treatment in Patients With Synchronous Metastases at Initial Diagnosis in Group A

Treatment	No. of Patients (n = 228)	No. of Events (n = 128)	3-Year OS Probability	HR (95% CI)	*P*
Combination*					.012
Only CT	102	68	0.342		
CT then surgery	11	5	0.614		
CT then RT	49	24	0.549		
CT then surgery then RT	1	1	0		
Surgery then CT	15	6	0.733		
Surgery then RT then CT	6	2	0.667		
Surgery then RTCT	6	2	0.667		
Only RT	1	1	0		
RT then CT	12	8	0.486		
RTCT	24	11	0.486		
RTCT then surgery	1	0	—		
Surgery†					
No	188	112	0.444		
Yes	40	16	0.670	0.581 (0.34 to 0.98)	.04
RT†					
No	128	79	0.412		
Yes	100	49	0.577	0.697 (0.49 to 1.00)	.05
CT†					
Conventional	204	116	0.484		
High dose	22	11	0.475	0.857 (0.46 to 1.59)	.62
Treatment modality					
Single	103	69	0.339		
Multiple	125	59	0.604	0.559 (0.39 to 0.79)	< .001

Abbreviations: CT, chemotherapy; HR, hazard ratio; OS, overall survival; RT, radiation therapy; RTCT, radiation therapy and chemotherapy.
*Detailed information was missing in two patients.
†Detailed information was missing in one patient.

Table A3. Distribution of Treatments Within Prognostic Groups in Patients With Brain Metastases at Initial Diagnosis (group A)

Variable	No. (%) of Patients by Prognostic Group			
	Low (n = 32)	Intermediate (n = 107)	High (n = 61)	Very High (n = 9)
Combination				
Only chemotherapy	6	41	36	7
CT then surgery	4	4	2	—
CT then RT	6	29	11	1
CT then surgery then RT	—	1	—	—
Surgery then CT	8	6	1	—
Surgery then RT then CT	—	6	—	—
Surgery then RTCT	1	4	1	—
Only RT	—	—	—	—
RT then CT	4	5	3	—
RTCT	3	10	7	1
RTCT then surgery	—	1	—	—
Surgery (*P* < .001)				
No	19 (59)	85 (79)	57 (93)	9 (100)
Yes	13 (41)	22 (21)	4 (7)	—
RT (*P* = .10)				
No	18 (56)	51 (48)	39 (64)	7 (78)
Yes	14 (44)	56 (52)	22 (36)	2 (22)
CT (*P* = .12)				
Conventional	32 (100)	93 (87)	54 (89)	9 (100)
High dose	—	14 (13)	7 (11)	—
Combined modality treatment (*P* < .001)				
Only chemotherapy	6 (19)	41 (38)	36 (59)	7 (78)
Combined modality	26 (81)	66 (62)	25 (41)	2 (22)

NOTE. Nineteen patients were not classified.
Abbreviations: CT, chemotherapy; RT, radiation therapy; RTCT, radiation therapy and chemotherapy.

Table A4. Univariable Analysis of OS According to Treatments in Patients With Metachronous Metastases in Group B

Treatment	No. of Patients (n = 295)	No. of Events (n = 225)	3-Year OS Probability	HR (95% CI)	*P*
No treatment or palliative care	22	22	0.091		
Combination					
Only chemotherapy	30	22	0.188		
CT then surgery	6	4	0.333		
CT then RT	23	17	0.228		
CT then surgery then RT	4	2	0.500		
Only surgery	18	16	0.167		
Surgery then CT	20	12	0.450		
Surgery then RT	34	22	0.401		
Surgery then RT then CT	14	8	0.643		
Surgery then RTCT	6	3	0.500		
Only RT	49	44	0.125		
RT then CT	34	27	0.235		
RTCT	31	21	0.323		
RTCT then surgery	1	1	0.000		
Surgery					
No	189	155	0.196		
Yes	106	70	0.399	0.545 (0.41 to 0.73)	< .001
RT					
No	96	78	0.226		
Yes	199	147	0.290	0.696 (0.53 to 0.92)	.001
CT					
No	123	104	0.201		
Yes	172	121	0.316	0.640 (0.49 to 0.83)	< .001
CT type					
Conventional	108	84	0.235		
High dose	56	32	0.464	0.512 (0.34 to 0.77)	.001
Treatment modality					
Single	119	106	0.141		
Multimodality	176	119	0.355	0.43 (0.33 to 0.57)	< .001

Abbreviations: CT, chemotherapy; HR, hazard ratio; OS, overall survival; RT, radiation therapy; RTCT, radiation therapy and chemotherapy.

Table A5. Distribution of Treatments Within Prognostic Groups in Patients With Brain Metastases at Relapse (group B)

Treatment	No. (%) of Patients by Prognostic Group			
	Low (n = 43)	Intermediate (n = 79)	High (n = 70)	Missing (n = 103)
No treatment of brain metastases	—	4	9	9
Combination				
Only chemotherapy	7	10	7	6
CT then surgery	2	3	1	—
CT then RT	3	12	3	5
CT then surgery then RT	2	1	1	—
Only surgery	1	4	1	12
Surgery then CT	3	6	1	10
Surgery then RT	10	4	4	16
Surgery then RT then CT	4	6	1	3
Surgery then RTCT	1	3	—	2
Only RT	2	11	20	16
RT then CT	4	7	9	14
RT then CT then surgery	—	1	1	1
RTCT	4	7	11	9
RTCT then surgery	—	—	1	—
Surgery				
No	20 (47)	51 (65)	59 (84)	59 (57)
Yes	23 (53)	28 (35)	11 (16)	44 (43)
RT				
No	13 (30)	27 (34)	19 (27)	37 (36)
Yes	30 (70)	52 (66)	51 (73)	66 (64)
CT				
No	13 (30)	23 (29)	34 (49)	53 (51)
Yes	30 (70)	56 (71)	36 (51)	50 (49)
CT type				
Conventional	22 (76)	35 (65)	25 (76)	26 (54)
High dose	7 (24)	19 (35)	8 (24)	22 (46)
Multimodality treatment				
Single modality	10 (23)	29 (37)	37 (53)	43 (42)
Multimodality	33 (76)	50 (63)	33 (47)	60 (58)

NOTE. A total of 103 patients were not classified.
Abbreviations: CT, chemotherapy; RT, radiation therapy; RTCT, radiation therapy and chemotherapy.

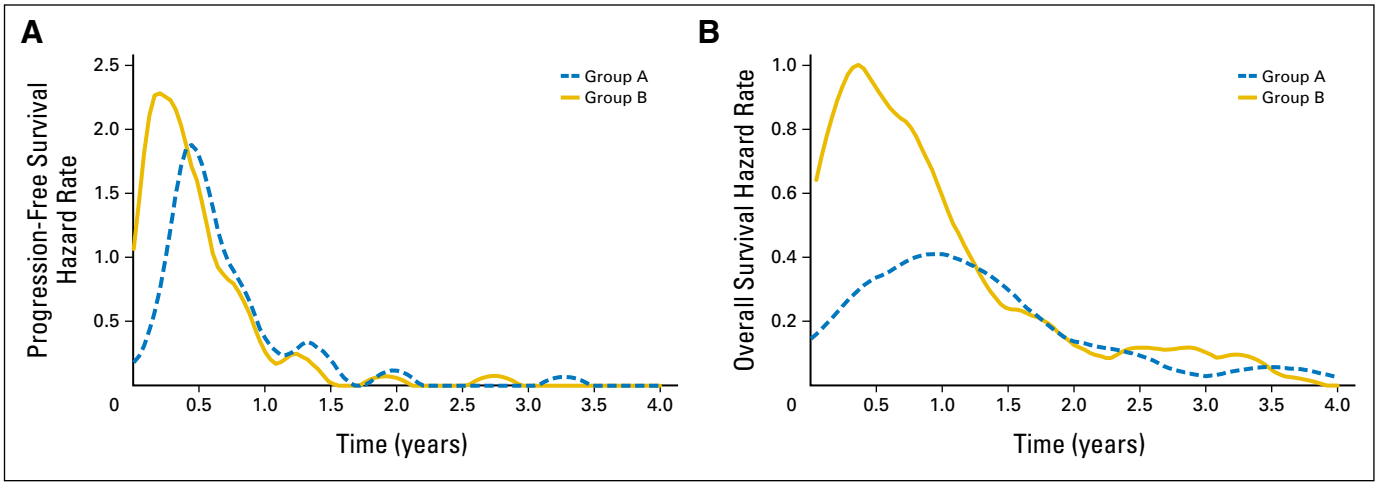

Fig A1. (A) Hazard rate for progression in patients with brain metastases at initial diagnosis (group A) and at relapse (group B). (B) Hazard rate for death in patients with brain metastases at initial diagnosis (group A) and at relapse (group B).

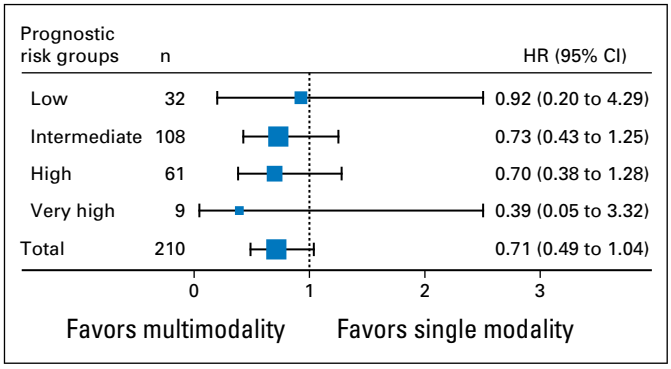

Fig A2. Multivariable results of multimodality treatment in patients with synchronous brain metastases at initial diagnosis (group A). HR, hazard ratio.