ORIGINAL RESEARCH

DOI: 10.37047/jos.2021-87403

Retrospective Analysis of Testicular Germ Cell Tumor Patients with Brain Metastases: A Single-Center Experience

Musa Barış AYKAN[a], Gül Sema YILDIRAN[a], Ramazan ACAR[a], Nazlıcan İĞRET[a], Birol YILDIZ[a], İsmail ERTÜRK[a], Nuri KARADURMUŞ[a]

[a]Department of Medical Oncology, University of Health Sciences Gülhane Faculty of Medicine, Ankara, Türkiye

ABSTRACT Objective: We evaluated the survival characteristics of testicular germ cell tumor (GCT) patients with brain metastases (BM). **Material and Methods:** In this retrospective cross-sectional study, patients with relapsed or refractory GCT and BM were evaluated. The characteristic clinical features of the patients, their systemic treatments, local treatments applied to BM, and follow-up periods were recorded. The primary endpoint was to assess survival after detection of synchronous and metachronous BM. The secondary endpoint was determined as overall survival (OS). **Results:** Twenty-five patients were included in this study with median age and interquartile range (IQR) of 30.24 and 7.92, respectively. Stage IIIC was detected at first diagnosis in 72% of the patients. The most commonly used local BM treatment was the combination of surgery and radiotherapy (60%). The objective response rate (complete response plus partial response) after local BM treatment was 60%. The median OS in the whole group was 24.75 (IQR: 25.97) months. The median OS (IQR) in the synchronous BM group was significantly different than that in the metachronous BM group [33.51 (18.13) vs. 9.97 (7.52), 95% confidence interval of 6.7 to 40.3 months, p=0.013]. There was no difference in the median OS between the groups [median (IQR)=36.39 (25.35) months vs. 23.70 (35.68) months, p=0.672]. **Conclusion:** The patients with GCTs presenting with BM during diagnosis were in a better condition than those who developed BM at relapse. However, no significant difference was found in OS. This may indicate shorter survival times for the patients who relapse, as the tumor is resistant to systemic therapy.

Keywords: Testicular germ cell tumor; testicular neoplasms; central nervous system neoplasms

Germ cell tumors (GCTs) are especially common in men between the ages of 20 and 40 years.[1] Generally, surgery and, when necessary, systemic chemotherapy are performed for treatment. It is a chemosensitive tumor. Owing to effective systemic treatment protocols, especially cisplatin-based chemotherapy protocols, successful clinical results can often be obtained even in the advanced stage.[2] Long-term remission can be achieved with high-dose chemotherapy (HDC) in relapsing or refractory GCTs.[3]

The poor risk criteria recommended by the International Germ Cell Cancer Collaborative Group (IGCCCG) are used to define the group with a generally poor prognosis of GCTs. Poor risk criteria include elevated serum tumor markers and the presence of mediastinal primary and non-pulmonary metastases.[4] Regardless of whether it is detected as synchronous at diagnosis or metachronous at relapse, brain metastasis (BM) is a rare clinical condition among non-pulmonary visceral metastases and has a poor prognosis even when detected alone.[5]

Management in cases with BM is often controversial. Retrospective case studies on this subject generally do not report significant endpoints and descriptive results. The combination of surgery, radiotherapy, and systemic chemotherapy is often required in cases of GCTs with BM. However, the effectiveness of these treatment approaches differs among patients due to clinical and radiological characteristics.

Correspondence: Musa Barış AYKAN
Department of Medical Oncology, University of Health Sciences Gülhane Faculty of Medicine, Ankara, Türkiye
E-mail: musabarisaykan@gmail.com

Peer review under responsibility of Journal of Oncological Sciences.

Received: 05 Dec 2021 ***Received in revised form:*** 24 Feb 2022 ***Accepted:*** 12 Mar 2022 ***Available online:*** 31 Mar 2022

Based on the abovementioned information, we first examined the clinical characteristics of the patients with GCTs and BM and the modalities used for treatment before and after BM. As a general oncological feature, a survival difference in patients with metastases during the first diagnosis and at relapse is expected. Therefore, we also compared the synchronous BM and metachronous BM groups regarding survival and other clinical features.

MATERIAL AND METHODS

INCLUSION/EXCLUSION CRITERIA

We retrospectively reviewed the medical records of outpatients and inpatients with relapsed/refractory GCTs from a tertiary clinic from January 2017 through June 2021. The inclusion criteria were age ≥18 years, with histologically confirmed advanced testicular cancer, and BM during the diagnosis of GCT or after relapse/refractory disease. The exclusion criteria were age <18 years and insufficient clinical data.

The age of the patient, the localization and histological characteristics of the primary malignancy and stage at the time of diagnosis, the symptoms associated with this condition before the detection of BM, the period in which BM was detected (synchronous vs. metachronous), and the way of detection (solitary vs. multiple) were recorded. The metastasis status of the lungs, liver, bones and lymph nodes, the serum tumor marker status, the IGCCCG risk group, whole systemic treatments, and the characteristics of treatments specific to BM (surgery, radiotherapy, and chemotherapy) were evaluated. The response to systemic treatments and treatments for BM were recorded. The time from the first diagnosis to BM (for cases with BM in metachronous), overall survival, and survival after BM was recorded. The patients were further divided into 2 groups according to the synchronous or metachronous detection of BM. Survival after BM was computed as the time from the date of detection of BM to the date of last examination or date of death. Overall survival was computed from the date of initial diagnosis to the date of death from any cause or the date of the last examination. The primary endpoint of the study was to demonstrate the overall survival of the whole group after BM. Then, it was used to determine the difference between the overall survival according to synchronous or metachronous BM. The local ethics committee approved the study protocol (Health Sciences University Gülhane Training and Research Hospital Clinical Research Ethics Committee, approval number: 2021/59, date: September 29, 2021). All procedures in this study were conducted following the Declaration of Helsinki.

RESPONSE CRITERIA

Complete remission was defined as the disappearance of all clinically and radiologically detectable lesions and the normalization of tumor markers. Reduction in tumor burden greater than 20% was defined as partial response. Tumor growth greater than 20% was defined as progressive disease. Any other response was classified as stable disease.

STATISTICAL ANALYSIS

Descriptive data are presented as a percentage. The Kolmogorov-Smirnov test was conducted to determine whether the continuous variables followed a normal distribution. Normally distributed continuous data were expressed as the mean±standard deviation, and data that were not normally distributed were expressed as the median with the interquartile range (IQR). The differences between groups according to distribution and type of variables were determined by performing chi-square tests, Student's t-tests, or Mann-Whitney U tests. Statistically significant differences were considered at $p<0.05$. All statistical analyses were performed using the SPSS 22.0 software (SPSS Inc., Chicago, Illinois).

RESULTS

The final sample included 25 patients. The median age (IQR) of the group at initial diagnosis was 30.24±7.92 years, and the most-common localization of the primary tumor was the testicles (100%). Patients were often identified in Stage IIIC at the time of initial diagnosis (72%). Most patients had a metachronous BM presentation (72%). Moreover, in most patients, multiple metastatic lesions with BM were detected (60%). During diagnosis, the serum

tumor marker levels at S3 were detected in 36% of the patients. Based on the IGCCCG risk classification evaluation, the majority of the patients were included in the "poor" risk group (68%). Lung metastasis is the most common visceral metastasis (84%) other than BM. The bleomycin, cisplatin, and etoposide regimen is the most preferred protocol in first-line systemic therapy (84%). The objective response rate (complete response plus partial response) in first-line systemic therapy is 88%. A relapsed refractory disease occurred in 98% of the patients, necessitating second-line treatment. Paclitaxel, ifosfamide, and cisplatin regimen is the most preferred protocol in second-line systemic therapy (100%). HDC is the most preferred approach in third-line systemic therapy (90%) (Table 1). Headaches (44%) and seizures (40%) were the most common causes of admission to the hospital before BM. For the specific treatment of BM, dual local therapy (surgery and radiotherapy) is the most common approach (60%). The objective response rate is 60% after BM-specific treatment. The most common method of radiotherapy is intensity-modulated radiation therapy (IMRT) (70%). After local treatment of BM, more than 2 types of systemic chemotherapy were administered in 56% of the patients. The interval between first diagnosis and BM in patients with metachronous BM was 10.93 (38.25) months. After the diagnosis of BM, the patients with synchronous BM survived significantly longer than the patients with metachronous BM (33.51±18.13 months vs. 9.97±7.52 months, 95% confidence interval: 6.7 to 40.3 months, p=0.013). There was no difference in the median overall survival between the groups [36.39 (25.35) months vs. 23.70 (35.68) months, p=0.672] (Table 2 and Figure 1).

DISCUSSION

BM are the most common intracranial tumors in adults. BM are often seen in the lungs, breasts, kidneys, and melanomas, but metastases from GCTs to the brain in adults are rare. They also represent a poor prognostic feature.[6] During the first diagnosis, patients with GCTs may present with BM as an indicator of systemic disease. However, BM may occur as a relapse, either independently or with other visceral metastases, after the control of local or systemic disease.[5] Due to this rare occurrence, there is a lack of data and, therefore, an absence of a general treatment approach.[7] The differences in the treatment approach and survival between synchronous and metachronous BM presentation have also been debated for a long time.[8] Considerable differences in the inclusion criteria and the small sample size preclude the generalization of the results of the reported case studies. Patients with synchronous and metachronous BM were included in this study. We found a significant difference in survival between the synchronous and metachronous BM groups.

Relapse-free survival following first-line chemotherapy is considered to be 70% or more in men with advanced-stage testicular GCTs at good risk. GCTs that relapse following first-line chemotherapy require additional treatment, mainly with platinum-based chemotherapeutic protocols.[9,10] In our study, 18 patients had poor-risk characteristics based on the IGCCCG criteria. Additionally, a significant number of the patients had high levels of serum tumor markers. An important indicator of prognosis in GCTs is a high level of serum tumor markers.[11] Serum tumor markers were in the highest category, i.e., S3 [S3: lactate dehydrogenase >10×upper limit of normal or human chorionic gonadotropin (mIU/mL) >50,000 or alpha fetoprotein (ng/mL) >10,000], in nine patients during initial diagnosis. This was a common characteristic of the resistant clinical course and poor prognostic feature of our patients.

Multiple BM were found in 60% of the patients. Feldman et al. also reported this rate as 55.4% for all groups in their study, and multiple BM was reported as a poor prognostic feature.[12] The presence of single/solitary BM suggests better survival than the presence of multiple BM.[8,13] The presence of multiple BM is important as the treatment approach is shifted from surgery to radiotherapy. This is the main factor that complicates the management of these cases.

Upon examining our cases for visceral metastases, we found that 28% of the patients had liver metastases. Liver metastasis is the most common

TABLE 1: The demographic and disease and treatment related characteristics of the patients.

Features	Synchronous (n=7)	Metachronus (n=18)	Total (n=25)
Age, mean (SD), years	30.85 (9.11)	30 (7.68)	30.24 (7.92)
Histology, n (%)			
- Non -seminoma	7 (100)	18 (100)	25 (100)
Clinical stage (AJCC, 8th), n (%)			
- I	0 (-)	2 (11)	2 (8)
- IIIA	0 (-)	2 (11)	2 (8)
- IIIB	0 (-)	3 (17)	3 (12)
- IIIC	7 (100)	11 (61)	18 (72)
Serum tumor markers, n (%)			
- S0	0 (-)	3 (17)	3 (12)
- S1	2 (28)	5 (28)	7 (28)
- S2	2 (28)	4 (22)	6 (24)
- S3	3 (43)	6 (33)	9 (36)
IGCCCG risk groups, n (%)			
- Good risk	0 (-)	6 (33)	6 (24)
- Intermediate risk	0 (-)	2 (11)	2 (8)
- Poor risk	7 (100)	10 (56)	17 (68)
Presentation of brain metastases, n (%)			
- Solitary	4 (57)	6 (33)	10 (40)
- Multiple	3 (43)	12 (67)	15 (60)
Visceral metastasis, n (%)			
- Lung	5 (71)	16 (89)	21 (84)
- Liver	2 (29)	5 (28)	7 (28)
- Bone	0 (-)	3 (17)	3 (12)
First line chemotherapy, n (%)			
- BEP	5 (71)	16 (89)	21 (84)
- EP	1 (14)	2 (11)	3 (12)
- VIP	1 (14)	0 (-)	1 (4)
Best objective response after first line chemotherapy, n (%)			
- Complete response	2 (28)	9 (50)	11 (44)
- Partial response	4 (57)	7 (38)	11 (44)
- Stable disease	1 (14)	1 (6)	2 (8)
- Progressive disease	0 (-)	1 (6)	1 (4)
Second line chemotherapy, n (%)			
- TIP	6 (86)	18 (100)	24 (96)
Best objective response after second line chemotherapy, n (%)			
- Complete response	3 (50)	7 (39)	10 (42)
- Partial response	2 (33)	8 (44)	10 (42)
- Stable disease	1 (17)	2 (11)	3 (12)
- Progressive disease	0 (-)	1 (5)	1 (4)
Third line chemotherapy, n (%)			
- GEMPOX	1 (17)	1 (7)	2 (5)
- HDC	5 (83)	13 (93)	18 (90)
Best objective response after first line chemotherapy, n (%)			
- Complete response	4 (67)	5 (36)	9 (45)
- Partial response	1 (17)	3 (21)	4 (20)
- Stable disease	0 (-)	0 (-)	0 (-)
- Progressive disease	1 (17)	6 (43)	7 (35)

SD: Standard deviation; AJCC: The American Joint Committee on Cancer; S1: Lactate dehydrogenase (LDH) <1.5×upper limit of normal (ULN) and human chorionic gonadotropin (hCG) (mIU/mL) <5,000 and alpha fetoprotein (AFP) (ng/mL) <1,000; S2: LDH 1.5 to 10×ULN or hCG (mIU/mL) 5,000 to 50,000 or AFP (ng/mL) 1,000 to 10,000; S3: LDH>10×ULN or hCG (mIU/mL) >50,000 or AFP (ng/mL) >10,000; IGCCCG: The International Germ Cell Cancer Collaborative Group; BEP: Bleomycin, cisplatin, etoposide; EP: Cisplatin, etoposide; VIP: Ifosfamide, etoposide, cisplatin; TIP: Paclitaxel, ifosfamide and, cisplatin; GEMPOX: Gemcitabine, paclitaxel and oxaliplatin; HDC: High-dose chemotherapy.

non-pulmonary metastasis site in advanced GCTs.[14] Liver, brain, and bone metastases represent a poor prognostic feature in GCTs.[15,16]

Considering that our cases consisted of patients with synchronous or metachronous BM receiving multi-line therapy, it was not surprising to en-

TABLE 2: Clinical, treatment-related and survival characteristics of brain metastases.

Features	Synchronous (n=7)	Metachronus (n=18)	Total (n=25)
Associated symptom before detection of BM, n (%)			
- Seizure	2 (29)	8 (44)	10 (40)
- Headache	5 (71)	6 (33)	11 (44)
- Plegia	0 (-)	2 (11)	2 (8)
- Loss of vision	0 (-)	1 (6)	1 (4)
- None	0 (-)	1 (6)	1 (4)
Local treatment of BM, n (%)			
- Surgery only	0 (-)	2 (11)	2 (8)
- Radiotherapy only	1 (14)	7 (39)	8 (32)
- Surgery plus radiotherapy	6 (86)	9 (50)	15 (60)
Modality of radiotherapy, n (%)			
- IMRT	6 (86)	10 (56)	16 (70)
- WBRT	1 (14)	6 (33)	7 (30)
Best objective response after local treatment of BM, n (%)			
- Complete response	6 (86)	6 (33)	12 (48)
- Partial response	1 (14)	2 (11)	3 (12)
- Stable disease	0 (-)	6 (33)	6 (24)
- Progressive disease	0 (-)	4 (22)	4 (16)
Number of chemotherapy lines after BM, n (%)			
- None	0 (-)	5 (28)	5 (20)
- 1 line	1 (14)	5 (28)	6 (24)
- 2 lines	1 (14)	6 (33)	7 (28)
- 3 lines	5 (71)	2 (11)	7 (28)
Interval between first diagnosis and BM, median (IQR), months	- (-)	10.93 (38.25)	- (-)
Survival after BM, mean (SD), months	33.51 (18.13)	9.97 (7.52)	13.81 (18.21)
Overall survival, median (IQR), months	36.39 (25.35)	23.70 (35.68)	24.75 (25.97)

BM: Brain metastasis; IMRT: Intensity-modulated radiation therapy; WBRT: Whole-brain radiotherapy; IQR: Interquantile range; SD: Standard deviation.

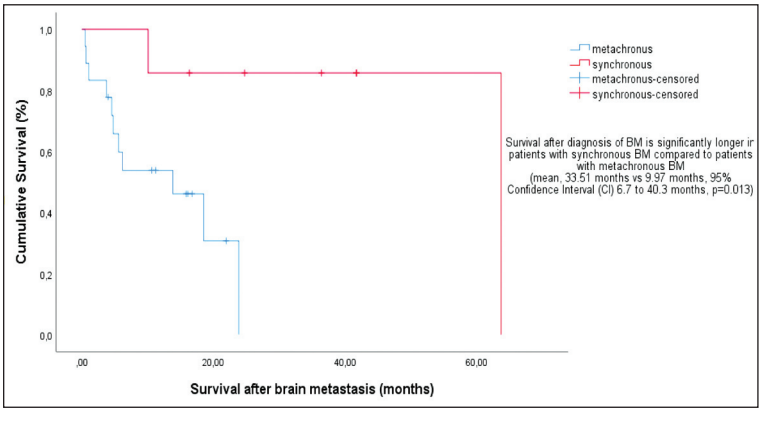

FIGURE 1: Analysis plot of survival after synchronized or metachronous presentation of brain metastasis. BM: Brain metastasis.

counter liver metastases so frequently. Lung metastases were also detected in more than half of our patients.

Platinum-based chemotherapy protocols constitute the basic systemic treatment approach in GCTs.[17] All patients received cisplatin-based chemotherapy protocols in first-line and second-line systemic therapy. In the third-line systemic therapy, 90% of the patients received HDC therapy, which increases the chances of successful treatment in advanced stages. Kalra et al. reported that the chance of cure increases with HDC and other multimodality therapy in GCT patients with active BM.[18] In our patients, the objective response rate (complete response rate plus partial response rate) was 65% after third-line treatment.

In most of the patients, symptoms suggesting BM were detected, but it was not confirmed in some of the cases. Central nervous system imaging should be performed not only for symptomatic patients but also in cases presenting with visceral metastasis and elevated serum tumor marker levels or presenting with relapse.[13]

For treating BM, radiotherapy was performed in 92% of our patients. This rate was reported as 68% in a study by Girones et al. IMRT can be applied to eligible patients with BM.[19] IMRT was performed in 70% of our cases. However, previous studies mostly used whole-brain radiotherapy. This is probably because the IMRT technique was not well-known when those studies were conducted.[13,20] Most patients receive another form of treatment (radiotherapy or surgery) besides chemotherapy. Due to the nature of the treatment selection for the cases, it is difficult to determine which combination of modalities might be the most suitable for these patients. We argue that applying only a single treatment modality may lead to a worse endpoint. Surgery and radiotherapy significantly improve the condition of the patients who develop BM before or after platinum-based induction regimens. A complete response was obtained in 48% of our patients after local BM treatment.

In metachronous BM patients, the median (IQR) duration was 10.93 (38.25) months between the first diagnosis and the date of BM diagnosis. Boyle et al. reported this duration as 8.25 months (3-17.5 months).[13] Also, after diagnosis of BM, the synchronous BM group showed higher survival than the metachronous BM group. Patients with GCTs presenting with BM during diagnosis tend to do better than patients who develop BM at relapse. We argue that patients with synchronous BM during the first diagnosis have a higher burden of systemic disease than those who experience relapses in the brain. However, despite this higher disease burden, these patients have a better prognosis after diagnosis of BM than the previously treated patients with subsequent resistance to chemotherapy, which is considered to be an important cause. However, no significant difference was found in overall survival. As a general oncological notion, this may suggest poor survival in cases that present as relapsed, as the tumor is resistant to systemic therapy. The similarity in overall survival suggested that although the brain was controlled with effective BM-specific treatment approaches, systemic disease burden and resistance to treatment made survival similar in most cases.

This study had several limitations. First, although the study was conducted in a reference center for GCTs, the number of patients was limited probably because it was a single-center study. Although a significant difference in survival after BM was found between groups, the small sample size prevented us from obtaining definitive results. Second, because this was a retrospective study, the results might have low accuracy and some bias. Third, the study had a cross-sectional design. Therefore, the results cannot be assumed to be causal.

CONCLUSION

In conclusion, the patients treated with current sequential systemic treatment procedures and radiotherapeutic techniques were evaluated in this study. BM management in GCT patients requires a multidisciplinary approach. Large, systemic analyses and prospective trials investigating optimal management of these patients are still lacking. The rarity of this clinical condition makes it difficult to conduct large clinical trials, but such studies are needed to optimize the treatment of these patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Musa Barış Aykan;* ***Design:*** *Musa Barış Aykan;* ***Control/Supervision:*** *Nuri Karadurmuş;* ***Data Collection and/or Processing:*** *Nazlıcan İğret;* ***Analysis and/or Interpretation:*** *İsmail Ertürk;* ***Literature Review:*** *Ramazan Acar;* ***Writing the Article:*** *Gül Sema Yıldıran;* ***Critical Review:*** *Birol Yıldız;* ***References and Fundings:*** *Nazlıcan İğret;* ***Materials:*** *Musa Barış Aykan.*

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33. Erratum in: CA Cancer J Clin. 2021;71(4):359. [Crossref] [PubMed]
2. Carver BS, Serio AM, Bajorin D, et al. Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. J Clin Oncol. 2007;25(35):5603-5608. [Crossref] [PubMed]
3. Yildiz B, Pinar Aral I, Balyemez U, et al. What is the optimal high-dose treatment following autologous stem cell transplantation in relapsed or refractory germ cell cancer: a retrospective comparison of high-dose ICE and high-dose CE. J BUON. 2020;25(2):1136-1140. [PubMed]
4. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol. 1997;15(2):594-603. [Crossref] [PubMed]
5. International Prognostic Factors Study Group, Lorch A, Beyer J, Bascoul-Mollevi C, et al. Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. J Clin Oncol. 2010;28(33):4906-4911. [Crossref] [PubMed]
6. Wen PY, Loeffler JS. Management of brain metastases. Oncology (Williston Park). 1999;13(7):941-954, 957-961; discussion 961-962, 9. [PubMed]
7. Beyer J, Albers P, Altena R, et al. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. Ann Oncol. 2013;24(4):878-888. [Crossref] [PubMed] [PMC]
8. Hardt A, Krell J, Wilson PD, et al. Brain metastases associated with germ cell tumors may be treated with chemotherapy alone. Cancer. 2014;120(11):1639-1646. [Crossref] [PubMed]
9. Culine S, Kramar A, Théodore C, et al; Genito-Urinary Group of the French Federation of Cancer Centers Trial T93MP. Randomized trial comparing bleomycin/etoposide/cisplatin with alternating cisplatin/cyclophosphamide/doxorubicin and vinblastine/bleomycin regimens of chemotherapy for patients with intermediate- and poor-risk metastatic nonseminomatous germ cell tumors: Genito-Urinary Group of the French Federation of Cancer Centers Trial T93MP. J Clin Oncol. 2008;26(3):421-427. [Crossref] [PubMed]
10. Motzer RJ, Nichols CJ, Margolin KA, et al. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. J Clin Oncol. 2007;25(3):247-256. [Crossref] [PubMed]
11. Barlow LJ, Badalato GM, McKiernan JM. Serum tumor markers in the evaluation of male germ cell tumors. Nat Rev Urol. 2010;7(11):610-7. [Crossref] [PubMed]
12. Feldman DR, Lorch A, Kramar A, et al. Brain metastases in patients with germ cell tumors: prognostic factors and treatment options--an analysis from the Global Germ Cell Cancer Group. J Clin Oncol. 2016;34(4):345-351. [Crossref] [PubMed] [PMC]
13. Boyle HJ, Jouanneau E, Droz JP, Fléchon A. Management of brain metastases from germ cell tumors: a single center experience. Oncology. 2013;85(1):21-26. [Crossref] [PubMed]
14. Wood MJ, Thomas R, Howard SA, Braschi-Amirfarzan M. Imaging of metastatic germ cell tumors in male patients from initial diagnosis to treatment-related toxicities: a primer for radiologists. AJR Am J Roentgenol. 2020;214(1):24-33. [Crossref] [PubMed]
15. Pico JL, Rosti G, Kramar A, et al; Genito-Urinary Group of the French Federation of Cancer Centers (GETUG-FNCLCC), France; European Group for Blood and Marrow Transplantation (EBMT). A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. Ann Oncol. 2005;16(7):1152-1159. [Crossref] [PubMed]
16. McCaffrey JA, Mazumdar M, Bajorin DF, Bosl GJ, Vlamis V, Motzer RJ. Ifosfamide- and cisplatin-containing chemotherapy as first-line salvage therapy in germ cell tumors: response and survival. J Clin Oncol. 1997;15(7):2559-2563. [Crossref] [PubMed]
17. Einhorn LH. Curing metastatic testicular cancer. Proc Natl Acad Sci U S A. 2002;99(7):4592-4595. [Crossref] [PubMed] [PMC]
18. Kalra M, Adra N, Hanna N, Abonour R, Einhorn LH. High-dose chemotherapy plus peripheral blood stem cell transplantation for patients with relapsed germ cell tumors and active brain metastases. Cancer. 2020;126(6):1202-1207. [Crossref] [PubMed]
19. Girones R, Aparicio J, Roure P, et al; Spanish Germ Cell Cancer Group (SGCCG). Synchronous versus metachronous brain metastasis from testicular germ cell tumors (TGCT): an analysis from the Spanish Germ Cell Cancer Group data base. Clin Transl Oncol. 2014;16(11):959-965. [Crossref] [PubMed]
20. Nonomura N, Nagahara A, Oka D, et al. Brain metastases from testicular germ cell tumors: a retrospective analysis. Int J Urol. 2009;16(11):887-893. [Crossref] [PubMed]