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Original Article

Effectiveness of craniotomy and long-term survival in 35 patients with gestational trophoblastic neoplasia with brain metastases: a clinical retrospective analysis

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ABSTRACT

Objective: To investigate the clinical characteristics, treatments, and prognostic factors among patients with gestational trophoblastic neoplasia (GTN) exhibiting brain metastases who underwent craniotomy.
Methods: Thirty-five patients with GTN who had brain metastases and subsequently underwent craniotomies between January 1990 and December 2018 at Peking Union Medical College Hospital were identified using the GTN database. Their clinical manifestations, treatments, outcomes, and prognostic factors were retrospectively analyzed.
Results: All 35 patients underwent decompressive craniotomy, hematoma removal, and metastatic tumor resection combined with multiagent chemotherapy. Eighty percent (28/35) achieved complete remission, 11.4% (4/35) achieved partial remission, and 8.6% (3/35) had progressive disease. Not counting 2 patients who were lost to follow-up, 81.8% of the patients (27/33) were alive after a median follow-up of 72 months. The 5-year overall survival rate was 80.4%. Univariate analysis revealed that a history of chemotherapy failure (p=0.020) and a >1-week interval between craniotomy and chemotherapy commencement (p=0.027) were adverse risk factors for survival. Multivariate analysis showed that previous chemotherapy failure remained an independent risk factor for poor survival (odds ratio=11.50; 95% confidence interval=1.55–85.15; p=0.017).
Conclusion: Decompressive craniotomy is a life-saving option if metastatic hemorrhage and intracranial hypertension produce a risk of cerebral hernia in patients with GTN who have brain metastases. Higher survival rates and improved prognoses can be achieved through perioperative multidisciplinary cooperation and timely standard postoperative chemotherapy.

Keywords: Gestational Trophoblastic Neoplasia; Brain Metastases; Craniotomy; Drug Resistance; Survival

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Synopsis
Decompressive craniotomy is a life-saving option for patients with GTN at risk of cerebral hernia. Craniotomy combined with timely standard chemotherapy could help improve survival in certain patients. Previous chemotherapy failure is an independent risk factor for poor survival.

INTRODUCTION

Gestational trophoblastic neoplasia (GTN) are rare gynecological malignancies that encompass invasive moles, choriocarcinomas, placental site trophoblastic tumors, and epithelioid trophoblastic tumors. With the development of effective chemotherapeutic agents, nearly all patients with GTN can expect to be cured if treated properly. The overall survival rate of low-risk patients is close to 100% while that of high-risk patients is >90% owing to integrated chemotherapy-based treatments [1]. However, early hematogenous metastases may occur given the vasophilic and destructive features of GTN. Brain metastasis is considered one of the reasons for treatment failure, and is a predictor of poor prognosis [2].

Brain metastases arising from GTN are not rare; their reported incidence rates range from 3% to 28% [3-5]. Patients can have asymptomatic intracranial tumors or present with transient neurological prodromes; intracranial hypertension caused by hemorrhaging can also be the primary symptom [6]. Multi-agent systematic chemotherapy and intrathecal methotrexate injection are recommended for treating brain metastases [1,7]. It has also been reported that intravenous administration of high-dose methotrexate (1 g/m^2) facilitates drug transport across the blood-brain barrier to improve outcomes [5], and some medical facilities also choose systematic chemotherapy combined with whole brain radiation, stereotactic radiotherapy, or gamma-knife radiotherapy [5,7-9]. With improvements in treatment strategies, the mortality rates in patients with brain metastasis have decreased from 50%–75% to 14.8%–29.7%; however, it remains significantly higher than that of patients with GTN overall [5,7,10,11]. Cerebral hernia secondary to intracranial metastatic hemorrhage and hypertension remains a major cause of death.

Previous studies at our hospital demonstrated that the overall survival of patients with GTN who have life-threatening intracranial hypertension or cerebral hernia can be improved by performing emergency decompressive craniotomy and metastatic tumor resection followed by multiagent chemotherapy [12]. In this study, the medical records of patients with GTN who had brain metastases and subsequently underwent craniotomy were reviewed with the aim of determining the effectiveness of this type of surgical intervention on their prognoses. The patients' clinical characteristics, treatments, and prognostic factors were retrospectively analyzed.

MATERIALS AND METHODS

1. Patients

Patients were identified using the Peking Union Medical College Hospital GTN database, and medical records were reviewed to extract information on their diagnoses, treatments, and outcomes. A total of 146 patients with GTN who had brain metastases were admitted to the Department of Obstetrics and Gynecology at Peking Union Medical College Hospital between January 1990 and December 2018. Thirty-five of them (23.9%) underwent craniotomy, and were

thus retrospectively analyzed. This study was approved by the ethics committee of Peking Union Medical College Hospital, and written informed consent was obtained from all participants.

2. Assessments

The initial assessment before treatment consisted of medical history, physical examination, complete blood count, biochemistry, serum β-human chorionic gonadotropin (β-hCG) level, chest radiography or chest computed tomography (CT), abdomino-pelvic CT if brain metastasis was detected, pelvic sonography or pelvic magnetic resonance imaging (MRI), and brain CT or MRI. All patients were diagnosed and scored according to the International Federation of Gynecology and Obstetrics (FIGO) 2000 staging system [13].

3. Treatments

All 35 patients underwent craniotomies. Among them, 26 underwent emergency decompressive craniotomy, hematoma removal, and metastatic tumor resection owing to intracranial hemorrhage caused by brain metastases; these included 18 and 8 patients who had been diagnosed with choriocarcinoma before and after craniotomy, respectively. The remaining 9 patients underwent craniotomy owing to intracranial tumors of unknown origin, and were diagnosed with choriocarcinoma based on postoperative pathology. Additional surgeries were performed as necessary to remove drug-resistant lesions in the lung and uterus.

All the patients received multi-agent chemotherapy, including FAV (5-fluorouracil/floxuridine, actinomycin D, and vincristine), FAEV (5-fluorouracil/floxuridine, actinomycin D, etoposide, and vincristine), EMA/CO (etoposide, methotrexate, and actinomycin D/cyclophosphamide and vincristine), EMA/EP (etoposide, methotrexate, and actinomycin D/etoposide and cisplatin), and others [1,14-16]. In addition to systemic chemotherapy, patients with intracranial hypertension received an intrathecal injection of methotrexate (12.5–15 mg per round with a total of 25–45 mg per course). Intrathecal injection was stopped when the cerebrospinal fluid β-hCG decreased to normal levels (<5 mIU/mL) . After craniotomy, 2 patients received additional intensity modulated radiotherapy for tumor bed and adjacent area, with a dose of 45 Gy in 15 or 25 fraction.

Intravenous 20% mannitol and glycerin fructose were administered perioperatively to patients with neurological symptoms such as headache and vomiting that were caused by intracranial hypertension; glucocorticoid dehydration was also administered to decrease intracranial pressure when necessary. Meanwhile, corresponding sedation, analgesia, and hemostasis treatments were used to control bleeding, decrease intracranial pressure, and alleviate cerebral crisis.

4. Evaluation of efficacy and toxicity

Serum β-hCG levels were monitored weekly; cerebrospinal fluid β-hCG was monitored every week or cycle, with imaging performed every 2–3 cycles to determine treatment efficacy. Complete remission (CR) was defined as normal β-hCG levels (<5 mIU/mL) maintained for 4 consecutive weeks, partial remission (PR) as a decrease of >50% in β-hCG levels, and progressive disease (PD) as plateaued or increased β-hCG levels after at least 2 courses of treatment. Chemoresistance referred to either a plateau (<50% decrease) or an increase in serum β-hCG levels after at least two consecutive cycles of chemotherapy. Recurrence referred to elevated serum β-hCG levels in the absence of pregnancy after CR. Complete blood count and biochemistry were measured weekly, and other adverse effects were recorded. Toxicities were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

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JOURNAL OF GYNECOLOGIC ONCOLOGY

5. Statistical analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS version 23.0; IBM Corp., Armonk, NY, USA). Fisher's exact probability test was used to compare the qualitative variables. A logistic regression model was used to perform multivariate analysis. The Kaplan-Meier method was used to draw survival curves, which were then compared using the log-rank test. A p-value <0.05 was considered statistically significant.

RESULTS

1. Clinical characteristics

The mean age of the 35 patients was 28.6±5.9 years (range, 21–45 years). The median gravidity was 2 (range, 1–7), and the median parity was 1 (range, 0–3). Pretreatment serum β-hCG levels were elevated, with a median of 13,381.4 IU/L (range, 285.3–3,751,260.0 IU/L) before admission. All 35 patients with brain metastases also had lung metastases; their detailed clinical information is shown in **Table 1**. Patients were diagnosed with brain metastases based on CT or MRI findings (**Figs. 1** and **2**). The mean brain metastasis diameter was 4.0±1.3 cm (range 0.7–6 cm); the detailed features of these brain metastases and their symptoms are described in **Table 2**. All the patients were classified as stage IV. Eight patients were transferred to our hospital after experiencing chemoresistance (n=5) or recurrence (n=3) at

Table 1. Clinical characteristics of 35 patients with GTN who had brain metastases

Clinical characteristics	Category	Cases (n=35)
Age (yr)	<40	33 (94.3)
	≥40	2 (5.7)
Antecedent pregnancy	Mole	7 (20.0)
	Abortion*	9 (25.7)
	Term	19 (54.3)
Interval from index pregnancy (mo)	<4	7 (20.0)
	4–6	5 (14.3)
	7–12	5 (14.3)
	>12	18 (51.4)
Serum β-hCG, IU/L	$<10^3$	8 (22.9)
	$>10^3$–10^4	7 (20.0)
	$>10^4$–10^5	9 (25.7)
	$>10^5$	11 (31.4)
Largest tumor size including uterus (cm)	<3	21 (60.0)
	3–5	7 (20.0)
	≥5	7 (20.0)
Sites of metastases (lung and brain excluded)	None	24 (68.6)
	Kidney	7 (20.0)
	Liver and adrenal gland	1 (2.9)
	Intestine and vulva	1 (2.9)
	Bone	1 (2.9)
	Vagina	1 (2.9)
Number of metastases†	1–4	33 (94.3)
	5–8	2 (5.7)
Previous failed chemotherapy	No	27 (77.1)
	Yes	8 (22.9)
FIGO scores	7–12	14 (40.0)
	>12	21 (60.0)

Values are presented as number (%).
β-hCG, β-human chorionic gonadotropin; GTN, gestational trophoblastic neoplasia; FIGO, International Federation of Gynecology and Obstetrics.
*Including 1 case of ectopic pregnancy; †Lung metastases larger than 3 cm on chest CT or any size on chest X-ray can be counted for the number of metastases.

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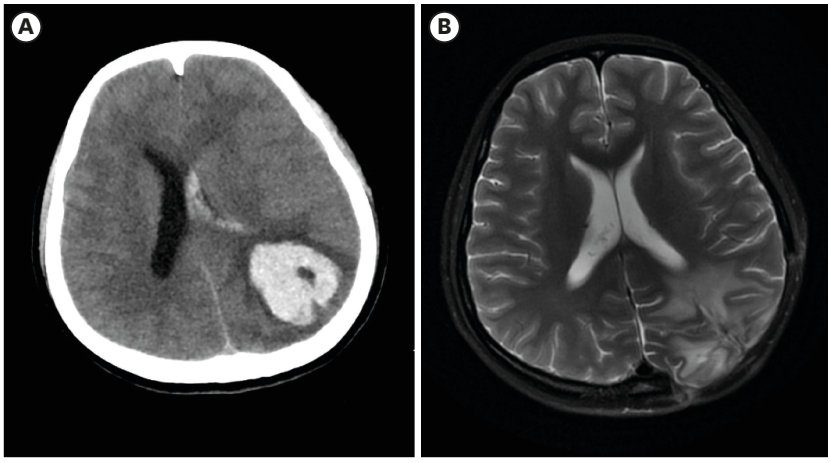

Fig. 1. Gestational trophoblastic neoplasia with cerebral metastasis. (A) Before craniotomy, computed tomography showed left parietal-occipital metastatic tumor with cerebral hemorrhage ruptured into left lateral ventricle, peritumoral edema, left lateral ventricle compression, and midline shift. (B) One month after craniotomy, T2-weighted magnetic resonance image showed encephalomalacia at left parietal-occipital lobe. Bilateral ventricles were symmetric without midline shift.

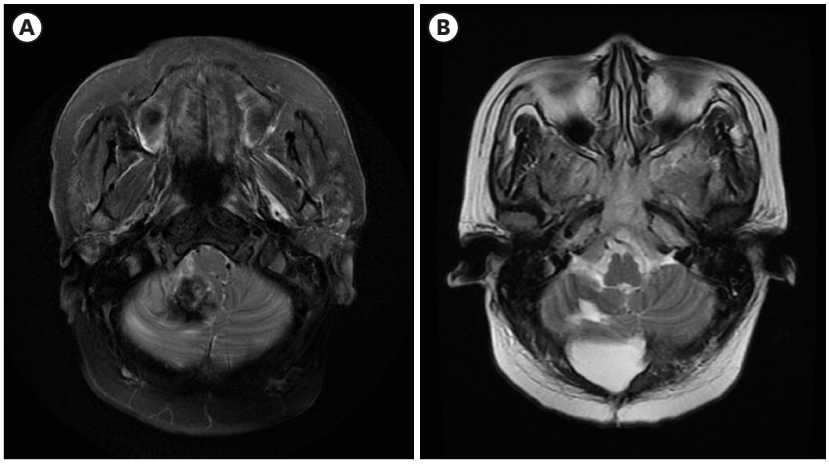

Fig. 2. Gestational trophoblastic neoplasia with cerebellar metastasis. (A) Before craniotomy, T2-weighted MR image showed hemorrhagic metastatic tumor at the right cerebellar hemisphere with peritumoral edema, compression of medulla and the fourth ventricle, midline shift. (B) One month after craniotomy, T2-weighted MR image showed postoperative cystic lesion at the right cerebellar hemisphere, with normal medulla and the fourth ventricle. MR, magnetic resonance.

another hospital, and the remaining 27 received primary chemotherapy at our hospital. The median FIGO score evaluated before craniotomy was 13 (range, 8–21). All 35 patients had high-risk disease, including 21 (60%) who had a FIGO score >12. After craniotomy, 6 patients underwent pulmonary lobectomies owing to persistent pulmonary lesions, and 1 underwent a hysterectomy owing to a drug-resistant uterine lesion. All 35 patients received a mean 9.8 courses of multi-agent combination chemotherapy (range, 2–25 courses), among whom 15 received a mean of 1.5 courses of chemotherapy before craniotomy (range, 1–4). Moreover, 33 patients were administered an intrathecal injection of methotrexate.

2. Efficacy

Among 35 patients, 28 (80.0%) achieved CR, 4 (11.4%) achieved PR, and 3 (8.6%) experienced PD. Follow-up at outpatient clinics and via telephone interviews for the 32 survivors (CR or PR) continued until November 2020. Not counting 2 surviving patients

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Table 2. Features and related symptoms of brain metastases of the 35 patients

Features and symptoms	Category	Cases (n=35)
Number of brain metastases	Solitary	21
	Multiple	14
Location of brain metastases	Frontal lobe	13
	Temporal lobe	9
	Parietal lobe	8
	Occipital lobe	6
	Cerebellum	3
	Basal ganglia	1
Side of brain metastases	Left	13
	Right	17
	Both	5
Symptoms	Headache and vomiting	34
	Hemiplegia	9
	Loss of consciousness	7
	Convulsion	6
	Aphasia	1
	Sensory impairment	1
	Hearing loss	1
	Urinary incontinence	1
	Ataxia	1

(6.3%) who were lost to follow-up, the median monitoring time for the remaining 30 patients was 72 months (range, 5–204 months).

While 1 of the 28 patients who achieved CR was lost to follow-up, the remaining 27 were followed for 20–204 months. Twenty-three of these patients did not experience relapse, although 4 of them relapsed 1–2 months after their most recent chemotherapy. Among those who relapsed, 1 patient received second-line chemotherapy and achieved CR, relapsed again, and then regained CR after combined chemoradiotherapy for a drug-resistant pulmonary lesion; this patient had no recurrence during the subsequent 127 months of follow-up. Two patients received salvage chemotherapy (EMA/CO or EMA/EP) and immunotherapy after recurrence, and remained under treatment. The last patient underwent resection of a pulmonary drug-resistant lesion combined with salvage chemotherapy and achieved CR after recurrence, but later experienced a second recurrence and died 60 months after her craniotomy.

Among the four patients who achieved PR, 1 died of septic shock secondary to grade 4 neutropenia, while the other 3 abandoned treatment. One of these remaining 3 patients was lost to follow-up after discharge, another achieved CR during the follow-up period as her β-hCG levels normalized, and the third died of disease progression after 5 months of follow-up.

The 3 patients who experienced PD died. As such, among the 33 patients in the entire cohort with available treatment and follow-up data, 27 (81.8%) survived and 6 (18.2%) died. The clinical characteristics of the six died patients are shown in **Table S1**.

3. Fertility outcomes and long-term complications

Six patients got pregnant 3–4 years after remission, 3 of whom had term deliveries with healthy newborns. Neurological symptoms disappeared in 22 patients after treatment; however, the remainder experienced intermittent seizures (n=2), dyskinesia (n=1), left visual field defect (n=1), and intermittent symptoms of intracranial hypotension (n=1) during the follow-up period.

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4. Identifying prognostic factors using univariate and multivariate analyses

Univariate analysis of potential prognostic variables among the 33 patients with available follow-up and treatment outcome data revealed that a history of chemotherapy failure (p=0.020) and a prolonged interval (i.e., >1 week) between craniotomy and chemotherapy (p=0.027) were risk factors for poor prognosis (**Table 3**). Multivariate analysis showed that a history of chemotherapy failure was an independent risk factor for survival (odds ratio=11.50; 95% confidence interval [CI]=1.55–85.15; p=0.017). The 5-year overall survival rate of all patients who underwent craniotomy in this study was 80.4%; that of patients with a history of previous chemotherapy failure was significantly lower than that of patients receiving primary treatment (41.7% vs. 92.0%, p=0.007) (**Fig. 3**).

DISCUSSION

Brain metastasis from GTN is a poor prognostic factor, especially when cerebral herniation caused by intracranial hemorrhage and hypertension occurs. It still remained unclear whether craniotomy can improve the survival of such patients. In this study, 35 patients with GTN who underwent craniotomy and received multi-agent chemotherapy over a 29-year period were retrospectively investigated; this was the largest study of craniotomy performed for patients with GTN who have brain metastases to date.

The overall survival for GTN patients with brain metastases have increased from 46% (1962–1995) to 64% (1995–2009) [17]. In 2015, Savage et al. [5] reported a cohort of 27 GTN patients with brain metastases, five of whom required emergency neurosurgery. Twenty-three (85%) patients were long term survivors but four patients died. Our center has reported a

Table 3. Univariate analysis of prognostic variables (n=33)

Variables	Category	Alive	Death	Odds ratio (95% confidence interval)	p-value
Age (yr)	<40	25 (80.6)	6 (19.4)	0	1.000
	≥40	2 (100)	0 (0)		
Antecedent pregnancy	Mole	4 (66.7)	2 (33.3)	0.478 (0.161–1.422)	0.398
	Abortion	6 (75.0)	2 (25.0)		
	Term	17 (89.5)	2 (10.5)		
Interval from index pregnancy (mo)	≤12	14 (82.4)	3 (17.6)	1.077 (0.184–6.319)	1.000
	>12	13 (81.3)	3 (18.8)		
Serum β-hCG (IU/L)	$<10^5$	18 (78.3)	5 (21.7)	0.400 (0.040–3.955)	0.640
	$\geq 10^5$	9 (90.0)	1 (10.0)		
Renal metastases	No	22 (84.6)	4 (15.4)	2.200 (0.311–15.548)	0.584
	Yes	5 (71.4)	2 (28.6)		
Metastases (lung and brain excluded)	No	19 (82.6)	4 (17.4)	1.187 (0.180–7.843)	1.000
	Yes	8 (80.0)	2 (20.0)		
Number of metastases	1–4	25 (80.6)	6 (19.4)	0	1.000
	5–8	2 (100.0)	0 (0.0)		
FIGO score	<12	7 (87.5)	1 (12.5)	1.750 (0.173–17.686)	1.000
	≥12	20 (80.0)	5 (20.0)		
Craniotomy in our center	No	14 (70.0)	6 (30.0)	0	0.060
	Yes	13 (100.0)	0 (0.0)		
Previous failed chemotherapy	No	23 (92.0)	2 (8.0)	11.500 (1.553–85.154)	0.020
	Yes	4 (50.0)	4 (50.0)		
Interval from craniotomy to chemotherapy (wk)	>1	13 (68.4)	6 (31.6)	0	0.027
	≤1	14 (100.0)	0 (0.0)		
Intrathecal MTX injection	Yes	25 (80.6)	6 (19.4)	0	1.000
	No	2 (100.0)	0 (0.0)		

Values are presented as number (%).
β-hCG, β-human chorionic gonadotropin; FIGO, International Federation of Gynecology and Obstetrics.

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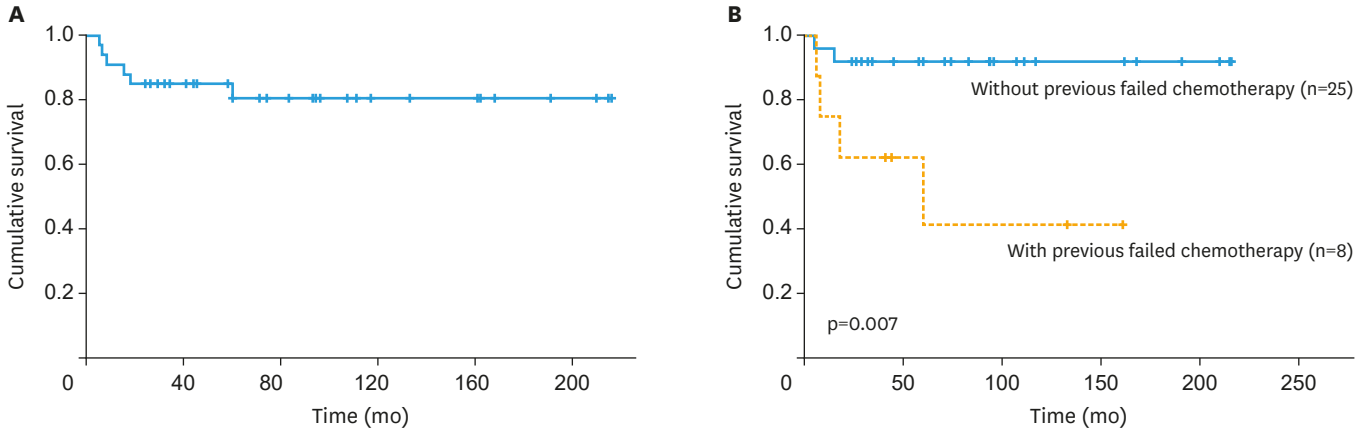

Fig. 3. Kaplan-Meier curve for (A) overall survival of 33 patients with gestational trophoblastic neoplasia who had brain metastases and subsequently underwent craniotomy, (B) Survival of patients without versus with previous failed chemotherapy.

5-year survival rate (OS) of 71.1% in 109 patients [7]. Gavanier et al. [18] reported 21 patients with GTN brain metastases in a French Reference Centre, and found that the 5-year overall survival rate was 69.8% (95% CI=44.3–85.3) and 81.5% (95% CI=52.3–93.7, after excluding early deaths). The survival rate of our study was similar to those of previous literatures, which provided evidence for the conclusion that craniotomy could temporarily save the lives and create opportunity to receive curative chemotherapy.

GTN treatment generally involves chemotherapy. Although surgical resection of metastatic tumors is not the preferred intervention for patients with brain metastases, craniotomy remains highly effective in certain individuals. Owing to the rarity of craniotomies for GTN (performed in 14.7%–20.6% of patients with brain metastases), few retrospective studies with small sample sizes have been performed to date [18-20]. Among the 109 patients with GTN at our hospital who had brain metastases, 62.5% (5/8) of early deaths were attributed to intracranial hemorrhage and cerebral hernia. Twenty-six patients died after primary treatment, of whom 22 (84.6%) died of intracranial hemorrhage, cerebral hernia, or multiple organ failure [7]. Intracranial hypertension with cerebral hernia is the most common direct cause of death in patients with GTN who have brain metastases. In the current study, 26 patients underwent emergency craniotomy for intracranial hemorrhage and hypertension; most were in critical condition and rapidly deteriorated following their admission. Without prompt craniotomy, life-threatening cerebral herniation can develop. The mortality rate was reduced to 18.2% (6/33) when performing craniotomy combined with timely and standard postoperative chemotherapy; this rate is similar or even better than that of patients who did not undergo craniotomy [7]. Therefore, when intracranial hypertension due to metastatic hemorrhage occurs and conservative treatment becomes futile, hematoma removal and metastatic tumor resection via decompressive craniotomy should be readily performed regardless of intracranial tumor size and quantity. The aim should be to remove the intracranial hematoma, reduce intracranial pressure, and create an opportunity for standard chemotherapy administration.

Gentle chemotherapy during the perioperative period is recommended to avoid early mortality owing to poor general performance and unstable vital signs. The preferred regimen at our facility is actinomycin D plus etoposide for 3 days with 9–12-day rest intervals, while cisplatin plus etoposide for 2 days, repeated weekly, is administered at other centers

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[1,2,21], without increased risk of subsequent resistance [22]. Once the patient's general status improves after 1–3 cycles, full-dose chemotherapy can be administered. Having received multidisciplinary cooperative supportive treatment, no patients died during the perioperative period in our study. After long-term follow-up, only 5 of the 33 patients (15.1%) developed long-term postoperative complications such as epilepsy, dyspraxia, and visual field defects. Additionally, fertility and pregnancy outcomes were not affected by craniotomy. Taken together, craniotomy appears to be generally safe when combined with perioperative multidisciplinary cooperative treatment plus timely standard postoperative chemotherapy.

Although craniotomy can temporarily save the lives of patients with brain metastasis and allow the administration of chemotherapy, timely standard systemic chemotherapy combined with intrathecal injection remain the most important modalities for improving outcomes. In this study, both univariate and multivariate analyses showed that a history of chemotherapy failure was a negative risk factor for prognosis. The 5-year overall survival was significantly lower in patients with previous chemotherapy failure than in those who underwent primary treatment (41.7% vs. 92.0%). Therefore, more attention should be paid to the timely diagnosis of GTN and administration of standard initial chemotherapy, which are the keys to avoiding drug resistance and improving prognosis. Notably, a long interval between craniotomy and chemotherapy was also a poor prognostic factor.

Chemotherapy is the foundation of GTN treatment and should be administered as soon as possible after diagnosis. This is also the case for patients who undergo emergency surgery. The benefit of perioperative chemotherapy was determined based on our previous experience, but postoperative recovery might be delayed by chemotherapy owing to unstable vital signs. However, chemotherapy should be performed as soon as possible after vital signs stabilize. Our study showed that the mortality rate of patients who commenced chemotherapy more than 1 week after craniotomy was 31.6%, which was significantly higher than that of patients who started chemotherapy earlier (i.e., <1 week). Therefore, chemotherapy should be administered as early as possible within 1 week after surgery.

Furthermore, the possibility of brain metastasis in patients with GTN should be considered if women of reproductive age present with intracranial tumors or hemorrhaging of unknown origin, especially with menopause, abnormal uterine bleeding, or menstrual abnormalities. It has been reported that 50% of intracranial tumor hemorrhages are caused by metastatic tumors, such as those arising from GTN [3]. In this study, 17 patients who initially presented with intracranial hemorrhaging or intracranial tumors underwent craniotomy at another hospital before choriocarcinoma was diagnosed via postoperative pathology. Thus, menstrual and reproductive history should be investigated carefully for women of child-bearing age, and serum β-hCG should be measured to rule out GTN and preclude unnecessary delays in achieving a diagnosis and performing craniotomy.

A limitation of this study was its retrospective design, which potentially introduced selection bias. Patients who underwent emergency craniotomy were likely to have more serious conditions generally, whereas those who were in extremely critical conditions may have abandoned treatment and subsequently succumbed early to their disease. It was not possible to perform a prospective study of craniotomy because of the rarity of GTN with brain metastases. Another limitation was the small sample size given the aforementioned rarity. Finally, the improved prognosis due to craniotomy cannot be generalized to all the GTN patients with brain metastases, owing to absence of a non-craniotomy group to compare.

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In conclusion, treatment should not be withheld from patients with GTN who have brain metastases and present with intracranial metastatic hemorrhage and hypertension, even when on the verge of cerebral herniation. Improved prognosis can be achieved through perioperative multidisciplinary cooperation and timely standard postoperative chemotherapy.

SUPPLEMENTARY MATERIAL

Table S1

The clinical characteristics of 6 died patients

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REFERENCES

1. Ngan HY, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. Update on the diagnosis and management of gestational trophoblastic disease. Int J Gynaecol Obstet 2018;143 Suppl 2:79-85.
PUBMED | CROSSREF
2. Kong Y, Yang J, Jiang F, Zhao J, Ren T, Li J, et al. Clinical characteristics and prognosis of ultra high-risk gestational trophoblastic neoplasia patients: a retrospective cohort study. Gynecol Oncol 2017;146:81-6.
PUBMED | CROSSREF
3. Suresh TN, Santosh V, Shastry Kolluri VR, Jayakumar PN, Yasha TC, Mahadevan A, et al. Intracranial haemorrhage resulting from unsuspected choriocarcinoma metastasis. Neurol India 2001;49:231-6.
PUBMED
4. Evans AC Jr, Soper JT, Clarke-Pearson DL, Berchuck A, Rodriguez GC, Hammond CB. Gestational trophoblastic disease metastatic to the central nervous system. Gynecol Oncol 1995;59:226-30.
PUBMED | CROSSREF
5. Savage P, Kelpanides I, Tuthill M, Short D, Seckl MJ. Brain metastases in gestational trophoblast neoplasia: an update on incidence, management and outcome. Gynecol Oncol 2015;137:73-6.
PUBMED | CROSSREF
6. Piura E, Piura B. Brain metastases from gestational trophoblastic neoplasia: review of pertinent literature. Eur J Gynaecol Oncol 2014;35:359-67.
PUBMED
7. Xiao C, Yang J, Zhao J, Ren T, Feng F, Wan X, et al. Management and prognosis of patients with brain metastasis from gestational trophoblastic neoplasia: a 24-year experience in Peking union medical college hospital. BMC Cancer 2015;15:318.
PUBMED | CROSSREF
8. Soper JT, Spillman M, Sampson JH, Kirkpatrick JP, Wolf JK, Clarke-Pearson DL. High-risk gestational trophoblastic neoplasia with brain metastases: individualized multidisciplinary therapy in the management of four patients. Gynecol Oncol 2007;104:691-4.
PUBMED | CROSSREF
9. Ghaemmaghami F, Behtash N, Memarpour N, Soleimani K, Hanjani P, Hashemi FA. Evaluation and management of brain metastatic patients with high-risk gestational trophoblastic tumors. Int J Gynecol Cancer 2004;14:966-71.
PUBMED | CROSSREF
10. Altintaş A, Vardar MA. Central nervous system involvement in gestational trophoblastic neoplasia. Eur J Gynaecol Oncol 2001;22:154-6.
PUBMED
11. Neubauer NL, Strohl AE, Schink JC, Lurain JR. Fatal gestational trophoblastic neoplasia: an analysis of treatment failures at the Brewer Trophoblastic Disease Center from 1979–2012 compared to 1962–1978. Gynecol Oncol 2015;138:339-42.
PUBMED | CROSSREF
12. Yang JJ, Xiang Y, Yang XY, Wan XR. Emergency craniotomy in patients with intracranial metastatic gestational trophoblastic tumor. Int J Gynaecol Obstet 2005;89:35-8.
PUBMED | CROSSREF

13. Ngan HY, Bender H, Benedet JL, Jones H, Montruccoli GC, Pecorelli S, et al. Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. Int J Gynaecol Obstet 2003;83 Suppl 1:175-7.
PUBMED | CROSSREF
14. Deng L, Zhang J, Wu T, Lawrie TA. Combination chemotherapy for primary treatment of high-risk gestational trophoblastic tumour. Cochrane Database Syst Rev 2013;(1):CD005196.
PUBMED | CROSSREF
15. Feng F, Xiang Y, Wan X, Geng S, Wang T. Salvage combination chemotherapy with floxuridine, dactinomycin, etoposide, and vincristine (FAEV) for patients with relapsed/chemoresistant gestational trophoblastic neoplasia. Ann Oncol 2011;22:1588-94.
PUBMED | CROSSREF
16. Lybol C, Thomas CM, Blanken EA, Sweep FC, Verheijen RH, Westermann AM, et al. Comparing cisplatin-based combination chemotherapy with EMA/CO chemotherapy for the treatment of high risk gestational trophoblastic neoplasia. Eur J Cancer 2013;49:860-7.
PUBMED | CROSSREF
17. Neubauer NL, Latif N, Kalakota K, Marymont M, Small W Jr, Schink JC, et al. Brain metastasis in gestational trophoblastic neoplasia: an update. J Reprod Med 2012;57:288-92.
PUBMED
18. Gavanier D, Leport H, Massardier J, Abbas F, Schott AM, Hajri T, et al. Gestational trophoblastic neoplasia with brain metastasis at initial presentation: a retrospective study. Int J Clin Oncol 2019;24:153-60.
PUBMED | CROSSREF
19. Bakri Y, Berkowitz RS, Goldstein DP, Subhi J, Senoussi M, von Sinner W, et al. Brain metastases of gestational trophoblastic tumor. J Reprod Med 1994;39:179-84.
PUBMED
20. Semple PL, Denny L, Coughlan M, Soeters R, Van Wijk L. The role of neurosurgery in the treatment of cerebral metastases from choriocarcinoma: a report of two cases. Int J Gynecol Cancer 2004;14:157-61.
PUBMED | CROSSREF
21. Yang J, Xiang Y, Wan X, Feng F, Ren T. Primary treatment of stage IV gestational trophoblastic neoplasia with floxuridine, dactinomycin, etoposide and vincristine (FAEV): A report based on our 10-year clinical experiences. Gynecol Oncol 2016;143:68-72.
PUBMED | CROSSREF
22. Alifrangis C, Agarwal R, Short D, Fisher RA, Sebire NJ, Harvey R, et al. EMA/CO for high-risk gestational trophoblastic neoplasia: good outcomes with induction low-dose etoposide-cisplatin and genetic analysis. J Clin Oncol 2013;31:280-6.
PUBMED | CROSSREF