Management of liver and brain metastases in ultra-high-risk patients with gestational trophoblastic neoplasia: a single-center experience

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Abstract

Objective To report our recent experience managing ultra-high-risk gestational trophoblastic neoplasia (GTN) patients with liver and brain metastases. Design A retrospective review of data from a national gestational trophoblastic disease centre. Setting The Obstetrics & Gynecology Hospital of Fudan University, Shanghai, China. Sample Total of 298 GTN patients recruited from January 2014 to December 2017. Main outcome measures The CR rate and drug-resistance rate after initial treatment of ultra-high-risk GTN patients with liver or brain metastases. Methods The clinical characteristics and treatment and prognosis outcomes in 11 ultra-high-risk GTN patients with liver or brain metastases were performed by descriptive analyses. The prognostic factors for death in all GTN patients were identified by Cox proportional hazards regression. Survival analysis were used to analyze survival time between GTN patients stratified according to liver or brain metastases. Results. The CR rate and drug-resistance rate after initial treatment of ultra-high-risk GTN patients with liver or brain metastases was 0% and 90.9% respectively, but the 5-year OS rate was 81.8% (n=11). Liver metastases (hazard ratio [HR]: 34.05; 95% confidence interval [CI]: 1.65–703.7; P=0.02) and brain metastases (HR: 49.19; 95% CI: 5.6–432.1; P<0.01) were independently significant risk factors for death in all GTN patients. Conclusions. Liver and brain metastases were found to be independently significant risk factors for death in all GTN patients. The drug-resistance rate with initial treatment was 90.9% in ultra-high-risk GTN patients with liver or brain metastases.

Introduction

Gestational trophoblastic neoplasia (GTN) is a type of curable neoplasm and the rate of overall survival (OS) following standardized chemotherapy is greater than 90% [1-4]. Low-risk GTN patients (International Federation of Obstetrics and Gynecology [FIGO] score [?]6) should be treated with a single agent, with a rate of OS approaching 100%. High-risk GTN patients (FIGO score [?]7) require multi-agent chemotherapy, with a survival rate of approximately 90%[5, 6]. The FIGO Cancer Report 2021 divides GTN patients with FIGO score [?]7 into a high-risk subgroup (7 [?]FIGO score [?]12) and ultra-high-risk subgroup (FIGO score >12, as well as patients with liver, brain, or extensive metastases), and the latter do poorly when treated with first-line multiple-agent chemotherapy[6]. Most high-risk GTN patients develop many metastases of any type over months or years after the causative pregnancy [4]. The long-term survival is only 27% when there is metastasis to the liver, 70% with brain metastases, and 10% with both sites of metastasis [4, 7]. The presence of liver, brain, or kidney metastases (relative risk [RR] 4.99, 95% confidence interval [CI] 1.96–12.71) is the strongest risk factor for death in patients with GTN [2, 8].

There is limited available information about liver or brain metastases in GTN owing to its rarity [7, 9-12]. Randomized controlled trials (RCTs) on GTN are scarce because of the low prevalence of this disease and its highly chemo-sensitive nature[11, 13]. Optimal treatment strategies for patients with liver or brain metastases

have not been identified. Hence, we carried out a retrospective analysis and report the clinical characteristics, treatment details, outcome, and prognosis in the management of ultra-high-risk GTN patients with liver or brain metastases at our center.

Methods

Study design and sample

We conducted a retrospective analysis including a total of 313 patients with GTN who were diagnosed and treated at the Hospital of Obstetrics and Gynecology, Fudan University in Shanghai, China from January 2014 to December 2017. Placental site trophoblastic tumor (PSTT) and extrauterine epithelioid trophoblastic tumors (ETT) are insensitive to chemotherapy and usually require adjuvant surgery[14]; these have distinct biological behaviors with typical GTN[15]. Twelve patients with pathologically confirmed PSTT and three with ETT were excluded, leaving 298 GTN patients for analyses, including 233 (78.2%, 233/298) low-risk GTN (FIGO score [?]6) and 47 (15.8%, 47/298) high-risk GTN (FIGO score 7–11), and 18 (6.0%, 18/298) ultra-high-risk GTN (FIGO >12, as well as patients with liver, brain, or extensive metastases) (Figure 1). The clinical characteristics, treatment details, outcomes, and prognoses of these 298 patients with GTN were retrieved from the medical records in our hospital. Ethical approval was obtained from the Ethics Committee of Hospital of Obstetrics and Gynecology, Fudan University, Shanghai, China.

Treatment

All patients were evaluated upon admission at our institution and underwent examination, blood routine testing, serum biochemistry, pre-therapy serum human chorionic gonadotrophin (hCG) assays, brain magnetic resonance imaging (MRI), pelvis MRI, chest X-ray, and computed tomography (CT) scans of the chest and abdomen. Brain MRI or CT was also performed if patients had neurological symptoms during treatment. Patients were prospectively assigned a FIGO stage and risk score[6].

Chemotherapy was delivered according to standard protocols. First-line multiple-agent chemotherapy was the EMA-CO regimen (etoposide, methotrexate, actinomycin-D/cyclophosphamide, vincristine). For patients who did not respond to the EMA-CO regimen, salvage chemotherapy regimens were considered, including EMA-EP (etoposide, methotrexate, actinomycin-D/etoposide, cisplatin) and TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide). Two to four consolidation courses were given after normalization of serum β-hCG. Furthermore, intrathecal methotrexate (12.5 mg [6]) was injected on day 8, combined with systemic EMA-CO or EMA-EP chemotherapy for GTN patients with brain metastases, until normalization of the serum and cerebrospinal fluid (CSF) β-hCG. To minimize long-term toxicity, patients did not receive whole-brain radiotherapy as part of their routine management.

Diagnostic criteria

We confirmed post-molar GTN using 2021 FIGO criteria[6]. The presence of metastases in GTN patients was also detected using tools for investigation according to 2021 FIGO criteria[6] as follows: (1) chest X-ray is appropriate for diagnosing lung metastases and can be used for counting the number of lung metastases to evaluate the risk score; (2) lung CT may not be used for the risk score; (3) liver metastases may be diagnosed using CT scan or MRI; (4) brain metastases may be diagnosed using MRI or CT scan.

Definition of variables

The following data were collected from the electronic and paper medical records: age, antecedent pregnancy, interval from antecedent pregnancy to chemotherapy, pre-therapy serum β-hCG, tumor size including uterus, metastases (lung, kidney, liver, brain, other), number of metastases, previous chemotherapy failure, FIGO stage, and FIGO score. Details of pre-therapy CSF hCG (only for brain metastases), as well as treatment and outcome for GTN patients with liver or brain metastases, were also abstracted from the medical records. Serum β-hCG level <5 IU/L was set as the cutoff for a normal value in this study; this was determined using a kit (Beckman Coulter, Inc., Chaska, MN USA). Early death was defined as death occurring within four weeks of treatment initiation.

Follow-up

Patients who were alive were followed up either through telephone interviews or at outpatient clinics until June 2022 (the last follow-up time for the entire cohort) or death.

Efficacy evaluation

The treatment efficacy was evaluated from three aspects, complete remission (CR), drug resistance, and relapse. CR was defined as normalization of β-hCG levels for at least three consecutive weeks. Relapse was defined as elevated serum β-hCG level after CR without any evidence of pregnancy. Drug-resistance was defined as serum β-hCG level decreasing >10% over two courses of chemotherapy.

Statistical analysis

The associations of prognostic factors with death were assessed using the chi-squared test for univariate analysis and analyzed with Cox proportional hazards regression for multivariate analysis (considering the time from chemotherapy initiation to the last follow-up time or death) to establish the hazard ratio (HR) of death in 298 GTN patients. Only positive variables in univariate analysis were enter into the multifactor model, except for FIGO stage and FIGO score. Descriptive analyses were performed for clinical characteristics, treatment, and prognosis information of 11 ultra-high-risk GTN patients with liver or brain metastases. The rates of CR after initial treatment and resistance to initial treatment in ultra-high-risk GTN patients were compared between those with and without liver or brain metastases using the chi-squared test. Survival time was compared in 298 GTN patients stratified according to liver or brain metastases using the log-rank test. Survival time was compared in 18 high-risk GTN patients stratified according to having/not having liver or brain metastases was compared by the log-rank test. A secondary analysis of longer-term survival was performed at six years (72 months), which was the median follow-up time for the entire cohort. There were no missing values. P -values <0.05 were considered to be statistically significant. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

During the period January 2014 to December 2017, 11 ultra-high-risk GTN patients with liver or brain metastases received first-line multiple-agent chemotherapy treatment at the Hospital of Obstetrics and Gynecology, Fudan University, Shanghai, China, including one patient with concomitant liver and brain metastases. Liver and brain metastases accounted for 1.3% (4/298) and 2.7% (8/298) of 298 GTN patients, respectively, including one patient with concomitant liver and brain metastases.

Clinical characteristics

As shown in Table 1, 70 (23.5%) GTN patients were older than 40 years. Antecedent pregnancy was molar pregnancy in 227 (76.2%) GTN patients. The interval from antecedent pregnancy to chemotherapy was [?]12 months in 10% of cases. Pre-therapy serum β-hCG was $>10^5$ IU/L in 9.7% of patients. More than 8 metastases were observed in 14.8% of cases and 8.4% of the patients had previously had two- or multiple-agent chemotherapy failure. Tumor size including uterus was more than 5 cm in 9.7% of patients.

Liver and brain metastases were observed in 1.3% and 2.7% of patients, respectively. Lung metastases was found in 60.1% of patients, followed by kidney metastases in 0.3%. According to the FIGO 2021 staging system, 37.9% of GTN cases were classified as stage I, 1.7% as stage II, 56% as stage III, and 4.4% as stage IV. A total of 18 patients were defined as the ultra-high-risk group according to the FIGO Cancer Report 2021 (ultra-high-risk subgroup: FIGO score >12, as well as patients with liver, brain, or extensive metastases)[6].

Chemotherapy

Ten patients received first-line EMA-CO treatment, and one was treated with EMA-EP chemotherapy. TP/TE, BEP, and EMA-EP were the most common used salvage chemotherapy regimens for GTN patients with liver or brain metastases. All GTN patients with brain metastases (n=8) received a combination of

systemic chemotherapy (EMA-CO or EMA-EP) and intrathecal injection of methotrexate (Table 2). A further two to four courses of consolidation chemotherapy were administered to patients with normalization of serum and CSF β-hCG levels (Table 2).

Adjuvant surgery and radiotherapy

A total of eight patients with liver or brain metastases underwent adjuvant surgery to extirpate drug-resistant lesions. The surgical procedure included pulmonary lobectomy (n=5), resection of drug-resistant lesions in the liver (n=1), uterus (n=1), and ophthalmologic surgery (n=1), respectively. Local interventional surgery was performed in three patients to manage bleeding. Of the 11 GTN patients with liver or brain metastases, 8 (8/11, 72.7%) received 11 adjuvant surgical treatments.

No patients received whole-brain radiation therapy but three patients had stereotactic radiotherapy for residual brain metastases at the end of treatment (Table 2).

Treatment outcome

The initial chemotherapy drug-resistance rate was 90.0% (10/11) in 11 ultra-high-risk GTN patients with liver or brain metastases. Ultimately, of the 11 ultra-high-risk GTN patients with liver or brain metastases, nine were long-term survivors and two patients died. As detailed in Table 2, of the patients who died, one had early death within four weeks after treatment initiation for cerebral hernia and multiple organ failure. Another patient died despite receiving optimal standard dose chemotherapy after developing severe bone marrow failure 23 months from the initial chemotherapy (Table 2).

The CR rate after initial treatment was 11.1% and the drug-resistance rate with initial treatment was 72.2% in 18 ultra-high-risk GTN patients. There was a significantly lower CR rate (0% vs. 28.6%,P <0.01) and higher drug-resistance rate (90.0% vs 42.9%, P <0.01) after initial treatment in ultra-high-risk GTN patients with liver or brain metastases. (n=18) (Table 3).

Overall survival (OS)

The CR rate after initial treatment of all 298 GTN patients approached 88.4% and the 5-year OS rate of all 298 GTN patients was 98.7%, with a median follow-up time of six years (range: 62–82 months; IQR: 20 months) (Figures 2, 3). The CR rate after initial treatment in ultra-high-risk patients approached 11.1% and the 5-year OS rate was 77.8% (n=18). The CR rate after initial treatment in ultra-high-risk patients with liver or brain metastases approached 0% and the 5-year OS rate was 81.8% (n=11).

Survival time was significantly shorter among patients with than in those without brain and liver metastases (P <0.01, log-rank test; Figures 2, 3).

Prognostic factors

Univariate analysis of prognostic factors revealed that liver metastases (P <0.01) and brain metastases (P <0.01) were associated with death in GTN patients. Other prognostic factors including non-molar pregnancy (P<0.05), interval from antecedent pregnancy to chemotherapy >12 months (P<0.01), pre-therapy serum β-hCG $>10^5$ (P<0.01), tumor size including uterus [?]5 cm (P<0.01), >8 metastases (P<0.01), history of failed multidrug chemotherapy failure (P<0.01), FIGO III and IV stage (P<0.01), and FIGO score >13 (P<0.01).

Multivariate analysis (excluding FIGO stage and FIGO score) revealed that liver metastases (HR: 34.05; 95% CI: 1.65–703.7;P <0.05) and brain metastases (HR: 49.19; 95% CI: 5.6–432.1; P <0.01) were independently significant risk factors for death in all patients with GTN (Table 1).

Discussion

The current study found that liver or brain metastases were exceptionally rare, which is consistent with previous reports[6, 9, 10].However, early death and a dramatically high drug-resistance rate with initial treatment remains a critical problem in ultra-high-risk GTN patients with liver and brain metastases.

We found that liver or brain metastases accounted for 1.3% and 2.7% in all GTN patients, respectively, which is supported by previous reports from China[9, 10], France[12], and the United Kingdom (UK) [7, 11]. At Peking Union Medical College Hospital, GTN patients with liver metastases reportedly accounted for 1.9%[9] and brain metastases accounted for 3.4% of patients [10], respectively. Similarly, the incidence of liver metastases was only 1.8% (38/2100) of all GTN patients in the Charing Cross GTN database from 1975 to 2007[16] and the incidence of brain metastases in GTN patients was only 1.7% (21/1251) in a 17-year retrospective study in France[12]. The difference between studies in Asia and Europe could be owing to differences in prevalence, discrepancies between hospital-based and population-based data, or disparities in the availability of central pathology review. The reason for the rare prevalence of liver or brain metastases might be related to sensitivity to chemotherapy in patients with GTN.

However, liver metastases (HR: 34.05; 95% CI: 1.65–703.7;P =0.02) and brain metastases (HR: 49.19; 95% CI: 5.6–432.1;P =0.01) were found to be independently significant risk factors for death in GTN patients in our study. Similar findings have been reported, showing that the presence of liver or brain metastases is a strong indicator of a poor outcome in GTN [5, 7, 9], such as cerebral hemorrhage [12], neurological sequelae[12], less than 40% 5-year survival rate[7] and early death [2]. The survival rate of GTN patients with brain metastases is only 35%–70%[10, 17], and 27%–48% [7, 16] for liver metastases. Additionally, we found a significantly lower CR rate (0% vs. 28.6%, P <0.01) and higher drug-resistance rate (90.0% vs 42.9%, P <0.01) after initial treatment between the subgroups with and without liver or brain metastases in ultra-high-risk GTN patients. Hence, this confirms that liver or brain metastases is a crucial risk factor for ultra-high-risk GTN patients, which can lead to poorer outcome than ultra-high-risk GTN patients without liver or brain metastases.

In this study, one ultra-high-risk patients with concomitant liver and brain metastases had early death only four days after treatment initiation (before adequate chemotherapy could be given). The patient died from cerebral hernia and multiple organ failure. Similarly, other studies have reported that early death remains a critical problem in GTN patients with liver and brain metastases. One study found that early death was significantly associated with ultra-high-risk GTN, occurring in 13.8% of these patients [2]. Many deaths happened soon after admission for hemorrhage or metabolic results of overwhelming disease[4]. When deaths within four weeks were excluded, survival in patients with brain metastases (86%) was equivalent to that for other patients [18]. Similarly, in 37 patients with liver metastases treated between 1977 and 2005, OS increased to 48% at five years. However, when early deaths were excluded, survival was 68% in a UK study [16]. For GTN patients with liver or brain metastases and massive disease, starting with standard first-line multidrug chemotherapy may cause sudden tumor collapse with severe bleeding, metabolic acidosis, myelosuppression, septicemia, and multiple organ failure, any or all of which can result in early death[6]. To minimize early deaths in patients with very advanced disease, starting chemotherapy with low-dose induction EP chemotherapy (etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 on days 1 and 2) before commencing EMA-CO may help to reduce tumor edema[4] and can remarkably reduce the early death rate from 7.8% to 0.7%[19]. Additionally, EP chemotherapy can enable a more gradual reduction in tumor bulk during the initial weeks of treatment to minimize the risk of early death [19]. Several series have also suggested that the use of low-dose induction etoposide and cisplatin may benefit GTN patients with a FIGO score [?]13 [2, 6, 12, 20, 21], especially if their increased risk score is due to a large tumor burden or metastases to the brain, liver, or extensive metastases[6, 14] owing to hemorrhagic sequelae at the tumor sites[22].

Ten patients among 11 ultra-high-risk GTN patients with liver or brain metastases were treated with EMA-CO as first-line chemotherapy in our study. The results were consistent with previous studies, showing that the most commonly used multiple-agent chemotherapy for high-risk GTN worldwide remains the EMA-CO protocol [6, 11, 14, 19, 23-25], which is considered to have the best effectiveness-to-toxicity ratio[13]. The cumulative 5-year survival rate of patients given EMA-CO is between 75% and 90% [4, 19]. The OS rate was 86.2% in all GTN patients after EMA-CO and 85.4% in the high-risk group in a UK study [19]. However, Bolze et al. reported that the 5-year death rate approached 38.4% in patients with FIGO score [?]13 treated with EMA-CO, with or without low-dose EP[20].Furthermore, a Cochrane review found that 20% of patients do not achieve a complete response with EMA-CO therapy[6], and most can ultimately be salvaged with TP/TE or EP-EMA [6, 12, 21, 26].

In this study, the drug-resistance rate reached 90.9% with initial treatment in ultra-high-risk GTN patients with liver or brain metastases. A retrospective series in India including 82 high-risk GTN patients suggested that the resistance or relapse rate was only 31 (37.8%) after EMA-CO therapy [27]. This discrepancy might be owing to differences in study participants because the study in India only reported the drug-resistance rate with initial treatment in high-risk GTN patients rather than ultra-high-risk patients. The extremely high drug-resistance rate with initial treatment in GTN patients with liver or brain metastases in our study suggests that the combination of chemotherapy with adjuvant immunological therapy or surgery is needed, in comparison with chemotherapy alone, as initial treatment [28]. Immunological reactions might be involved in the development of GTN from complete hydatidiform mole (CHM)[29]. Recent work suggests that checkpoint immunotherapies represent an important new approach for the management of drug-resistant GTN [2, 3, 5, 8]. Additionally, poly (ADP-ribose) polymerase inhibitors (PARP) and anti-angiogenesis agents are novel treatments for drug-resistant GTN [15].

In the present study, adjuvant surgical procedures were performed in eight (72.7%) ultra-high-risk GTN patients with liver or brain metastases as a component of their therapy, among whom six ultimately achieved long-term survivors. Similarly, several studies have found that adjuvant surgery might be an effective choice for high-risk GTN patients[5, 6, 10-12, 15, 21, 30], which is in accordance with our results. Previous studies have confirmed that surgery not only reduces the tumor burden but also removes isolated chemoresistant lesions, such as in the lung or brain [2, 3, 5, 31, 32]. Hence, surgery (RR 0.336, 95% CI 0.177–0.641, P =0.001) is a protective factor in the prognosis of ultra-high-risk GTN patients[5]. Generally, nearly 50% of GTN patients with high-risk disease require some surgical intervention to achieve a cure[33]. Hysterectomy can be considered with uncontrolled uterine bleeding and laparotomy might be needed to stop bleeding in organs such as the liver, gastrointestinal tract, kidneys, and spleen[6, 21, 31]. To decrease the early death rate, neurosurgery is needed if there is bleeding into the brain or increased intracranial pressure [6, 11, 12, 21]. However, with the availability of uterine artery embolization, hysterectomy can often be avoided [31]. Additionally, selective angiographic embolization is used to control hemorrhage from multiple liver metastases[30].

In our study, no patients had whole-brain radiation therapy, but three patients had stereotactic radiotherapy for residual brain metastases at the end of treatment. The strategy for treating GTN patients with brain metastases at our center is intravenous multidrug chemotherapy and intrathecal methotrexate. Stereotactic radiotherapy was used for 37.5% (3/8) GTN patients with brain metastases for residual brain metastases at the end of treatment. However, concomitant whole-brain radiotherapy has rarely been used at our center owing to intellectual impairment in patients over the long term. Our results are consistent with those of previous studies showing that radiotherapy plays a limited role in the treatment of brain [6, 12, 21] and liver metastases[7] in GTN patients. An observational study performed at Peking Union Medical College Hospital found that only 0.9% (2/109) of GTN patients with brain metastases received brain irradiation during 1990–2013 because this can induce long-term intellectual impairment in patients who are cured [10]. However, some centers may administer whole-brain radiotherapy (3000 cGy in 200 cGy daily fractions) concurrent with chemotherapy or use stereotactic or gamma knife radiation to treat existing or residual brain metastases after chemotherapy [6]. Neubauer et al. recommended an approach using whole-brain irradiation combined with systemic multi-agent chemotherapy to treat patients with brain metastases; however, their reported OS was only 50%[34]. In the UK, only one of 46 GTN patients with liver metastases received liver irradiation between 1958 and 1994[7].

Although this study was limited owing to its retrospective design and relatively small sample size, we reported our experience in the management of ultra-high-risk GTN patients with liver or brain metastases. Early death and the remarkably high drug-resistance rate to initial chemotherapy remain two critical problems in GTN patients with liver or brain metastases. We speculate that the combination of chemotherapy with adjuvant immunological therapy or surgery, compared with chemotherapy alone, as initial treatment may improve patient prognosis. RCTs are needed to confirm our hypothesis. Furthermore, starting chemotherapy with low-dose induction EP chemotherapy before commencing EMA-CO might be helpful in these patients. Further work is essential to explore optimal treatment strategies in this patient population. Specialized multidisciplinary teams and tertiary specialist centers are critical to the management of GTN.

Conflicts of Interest

The authors report no conflict of interest.

Authorship contribution statement

Xin Lu initiated the study concept. Yanhong Ming conducted project administration, statistical analysis, data curation and editing writing. Yu Cheng and Xingran Wang conducted data curation, statistical analysis and drafted the manuscript. Wenzhi Li and Hailin Yu made significant contribution to the data analysis, and critically revised the manuscript. Tingting Zhu, Jinjuan Chen and Fenghua Ma coordinated the study and revised the manuscript. All authors read and approved the final manuscript.

Details of ethics approval

Ethical approval was obtained from the Ethics Committee of Hospital of Obstetrics and Gynecology, Fudan University, Shanghai, China.

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Table 1. Univariate and multivariate analysis of risk factors for prognosis in all patients with gestational trophoblastic neoplasia (n=298)

*Chi-squared test, **Cox proportional hazards regression.

NED, no evidence of disease.

Only positive variables in univariate analysis were entered in the multifactor model, excluding FIGO stage and FIGO score.

Table 2. Clinical characteristics, treatment, and prognosis information of GTN patients with liver or brain metastases (n=11)

Abbreviation: EMA: etoposide, methotrexate, dactinomycin; EP: etoposide/cisplatin; CO: cyclophosphamide/vincristine; FA:5-fluorouracil (5-FU), dactinomycin: β-hCG, β-human chorionic gonadotropin; TC: paclitaxel/carboplatin (Q3 weeks); TP: paclitaxel/cisplatin (Q3 weeks); TP/TE: paclitaxel, cisplatin/paclitaxel, etoposide; BEP: bleomycin, etoposide, cisplatin; MAC: methotrexate, dactinomycin, cyclophosphamide; GP: gemcitabine, cisplatin; ICE: ifosfamide, etoposide, cisplatin; FAV: floxuridine, actinomycin D, vincristine; IT MTX: intrathecal methotrexate; FIGO, International Federation of Gynecology and Obstetrics; CSF: cerebrospinal fluid; Early death: Death occurring within 4 weeks of treatment initiate; DOD, dead of disease; NED, no evidence of disease.

Table 3 Comparison of treatment outcomes of ultra-high-risk GTN patients for liver or brain metastases (n=18)

Ultra-high-risk GTN patients: FIGO score >12, as well as patients with liver, brain, or extensive metastases.

* Chi-squared test, $P<0.05$ indicates statistical significant

Figure 1 Patient population flow chart

Figure 2 Kaplan–Meier curve for overall survival in 298 patients with gestational trophoblastic neoplasia stratified according to having/not having brain metastases (*P<0.01, log-rank test*)

Figure 3 Kaplan–Meier curve for overall survival in 298 patients with gestational trophoblastic neoplasia stratified according to having/not having liver metastases (*P<0.01, log-rank test*

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