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Original Article

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Prognostic Scoring and Outcome of Gestational Trophoblastic Disease Patients

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Abstract

Background: Gestational trophoblastic neoplasia (GTN) uses prognostic scores to predict the development of resistance to single-agent chemotherapy. Requiring combination chemotherapy, high-risk patients are defined as those with an International Federation of Gynecology and Obstetrics (FIGO) score ≥ 7. Treatment at a specialized center based on an appropriate and prompt diagnosis is needed for the reduction of untimely death as well as to improve the survivability of patients. This study aimed to study for classifying definitions of low-risk, high-risk, and ultra-high-risk prognostic scores. Also, the outcomes of gestational trophoblastic patients and brain metastasis have been observed.

Methods: The study was observational design. The medical records of 56 gestational trophoblastic patients who visited the Buddhachinaraj Phitsanulok Hospital between 2012 and 2022 were collected and reviewed. The patients had been classified into three groups: low-risk, high-risk, and ultra-high-risk. The low-risk was stage I - III with a score < 7, while the high-risk was defined as FIGO stage II-III with a score ≥ 7. Also, a risk score ≥ 13 was defined as ultra-high risk.

Results: Among the 56 patients in this study, 47 patients were at low-risk, accounting for 83.9%, while nine patients were at high-risk (16.1%). No patient had a score of more than 12, defined as ultra-high-risk. All patients had been alive for at least 10 years after diagnosis with brain metastasis stage IV. The incidence of high-risk GTN patients was displayed in 9/56 (16.1%) with lung and brain metastasis. The high-risk score of GTN with brain metastasis showed an incidence rate of GTN patients among 1/56 (1.78%). The ultra-high-risk group was not presented.

Conclusions: Multimodality treatment has benefits for stage IV patients and high-risk groups. However, ultra-high-risk patients with a prognostic score higher than 12 or ≥ 13 have slightly increased mortality rates. A high-risk group FIGO stage IV with brain metastasis is alive in this study.

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Introduction

Hydatidiform moles develop commonly during the reproductive years of females. After molar evacuation, approximately 15% of patients present with locally invasive gestational trophoblastic neoplasia (GTN) [1]. The incidence of gestational trophoblastic disease (GTD) in Southeast Asia is 1 in 500 pregnancies. Management of GTD includes uterine evacuation and β-human chorionic gonadotropin (hCG) follow-up, which results in a high survival rate. GTD risk is associated with low socioeconomic status and vitamin A deficiency, typically affecting Southeast Asian women who have a high rate of malignancy [2]. The post-molar GTN diagnosis criteria consist of the following: 1) histologic diagnosis of choriocarcinoma; 2) persistence of hCG 6 months after a molar pregnancy; 3) plateaued hCG for 21 days; and 4) the increment of hCG level by about 10% or more for at least three values over 14 days. GTN involves a group of placental trophoblastic cells, which include invasive hydatidiform moles, choriocarcinomas, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) [3, 4]. The mortality rate for the invasive mole is 15%, while choriocarcinoma is 100%. GTN classification uses the staging of the International Federation of Gynecology and Obstetrics (FIGO) 2002, with the modified World Health Organization (WHO) scoring system. Low-risk GTN is defined as FIGO stages I - III with a score < 7, while a high-risk GTN is defined as FIGO stages II - III with a score ≥ 7. However, a risk score ≥ 13 is defined as ultra-high-risk GTN, which has a high mortality rate [5, 6]. Chemotherapy can promote a survival rate approaching 100% for single-agent chemotherapy, which is used in the treatment of low-risk GTN.

Multiagent chemotherapy is used in treatment for high-risk GTN with an approximately 90% survival rate. Nevertheless, multiple-agent chemotherapy is a treatment with or without adjuvant radiotherapy, surgery for excision of the resistance foci of disease in brain metastasis, classified as stage IV. Mostly, multiagent chemotherapy is classified as EMA-CO (etoposide, methotrexate, and dactinomycin alternated weekly with cyclophosphamide and vincristine). A retrospective study was presented to assess survival outcomes and brain metasta-

Table 1. Characteristics of Gestational Trophoblastic Patients

Characteristic	Total cases (n = 56)
Age at diagnosis (years), median	32.5
< 40 years, n (%)	40 (71.4)
> 40 years, n (%)	16 (28.6)
Median time between last pregnancy and start treatment (month)	1
Median hCG level before treatment (mIU/mL)	12,490
FIGO score, n (%)	
< 7	47 (83.9)
7 - 12	9 (16.1)
Antecedent pregnancy, n (%)	
Molar pregnancy	56 (100)
Pretreatment hCG level (mIU/mL), n (%)	
< 1,000	7 (12.5)
> 1,000 - 10,000	21 (37.5)
> 10,000 - 1,000,000	17 (30.36)
> 100,000	11 (19.64)
Operation, n (%)	
Suctional curettage	51 (91)
Hysterectomy	5 (9)
Histopathology, n (%)	
Hydatidiform mole	52 (92.8)
Choriocarcinoma	2 (3.6)
Placental site trophoblastic tumor (PSTT)	2 (3.6)
Site of metastasis, n (%)	
Lung	15 (26.78)
Brain	1 (1.78)
Treatment, n (%)	
Actinomycin-D	48 (85.7)
Methotrexate-folinic acid	2 (3.6)
EMA-CO	6 (10.7)

FIGO: International Federation of Gynecology and Obstetrics; EMA-CO: etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine; hCG: human chorionic gonadotropin.

sis with multimodality treatment.

Materials and Methods

The Buddhachinaraj Phitsanulok Hospital is a tertiary care center in the lower part of the northern region of Thailand. The referral center has been divided into 12 areas where primary or secondary care hospitals have referred to the tertiary care center, whereas Buddhachinaraj Phitsanulok Hospital is a referral center in Area 2. There are five provinces in Area 2 including Phetchaboon, Tak, Sukhothai, Uttaradit, and Phitsanulok. GTN women have been referred to the tertiary care hospital center, Buddhachinaraj Phitsanulok Hospital. Fifty-six medical records between 2012 and 2022 were reviewed. Classification of GTN, as well as the FIGO/WHO scoring system, was based on prognostic factors and GTN FIGO staging. A score of less than 7 is a low-risk GTN, while a score of 7 or more is a high-risk GTN, as shown in Table 1.

This observational study described the consequences of GTN and the ultra-high-risk group scores > 12 or a brain, liver extensive metastasis by a modified WHO risk scoring system. The study obtained approval from the Institutional Review Board (IRB) of Buddhachinaraj Phitsanulok Hospital (ethical reference number: 078/65) and was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Fifty-six gestational trophoblastic neoplastic patients were diag-

nosed at a median age of 32.5 years. Forty patients were aged less than 40 years, or 71.4%. Thirteen patients formed a subgroup aged 20 or less, and 31 patients were between 20 and 39 years old. Twelve patients were aged 40 years or older. All patients had a median time of 1 month between the last pregnancy and the start of treatment. The median β-hCG level before treatment was 12,490 mIU/mL. The majority of patients (47 patients, or 83.9%) were low-risk GTN, while nine patients (16.1%) were high-risk GTN. No patients had a score of more than 12. All patients had antecedent pregnancy of molar pregnant with no previous abortion or term pregnancy. Seven patients (12.5%) had pre-treatment β-hCG levels less than 1,000 mIU/mL, while 21 patients (37.5%) had β-hCG levels between 1,000 and 10,000 mIU/mL. Seventeen patients (30.36%) had β-hCG levels between 10,000 and 1,000,000 mIU/mL. As well, 11 patients (19.64%) had β-hCG levels of more than 1000,000 mIU/mL. Fifty-two patients were diagnosed with hydatidiform moles, and four patients had choriocarcinoma and PSTT, with two patients in each group.

Fifty-one patients had suctional curettage, while five patients had hysterectomy. Fifteen patients had lung metastasis with GTN stage III. However, one brain metastasis presented with seizures, and alteration of consciousness at a secondary care unit. The presenting symptoms included abnormal vaginal bleeding in two patients, while 53 patients were asymptomatic. In a review of treatment with single-agent chemotherapy, actinomycin-D was mostly used in 48 patients, and two patients were prescribed methotrexate-folinic acid (MTX-FA). Multiple-agent chemotherapy was prescribed for six patients with EMA-CO. All 56 patients are alive, as shown in Table 1.

A review of severe symptoms of generalized tonic-clonic seizures for 2 min was carried out on a 19-year-old woman in October 2014. She had no medical history. Ultrasonography showed a vesicular pattern with a 4 × 3 × 2 cm content appearance. Computed tomography (CT) with a contrast of the brain showed a left parietal hemorrhage of 4.2 × 5 × 6.4 cm. The Glasgow coma scale (GSC) was E4 V2 M5, which was described as spontaneous eye opening, incomprehensible sounds, and localized pain to response. The pupils were 3 mm, reactive to light in both eyes, and all motor responses were grade IV. The patient had been referred to a tertiary care center of Buddhachinaraj Phitsanulok Hospital. The endotracheal tube intubation was done. Her last period was 2 months ago, without contraception. Serum β-hCG exceeded 581,302 mIU/mL (normal range 0 - 3 mIU/mL). A neurosurgeon conducted a craniotomy and removal of a blood clot from the left frontal lobe with tissue biopsy, with blood loss of 50 mL intraoperatively. Tissue from the brain and a fraction of the blood clot in the vagina had been sent to a pathologist. Clinicopathology revealed extensive atypical cells correlated to choriocarcinoma. She was diagnosed with metastatic choriocarcinoma of the brain. In the meantime, a radiation therapy physician had given a total brain radiotherapy dose of 3 Gy/day for 10 fractions. Multiagent chemotherapy of EMA-CO was given continuously for six cycles. Recent surveillance showed a normal β-hCG level.

Discussion

Locally invasive GTN develops in about 15% of patients after evacuation, while GTN exhibits the histology of hydatidiform mole, choriocarcinoma, PSTT, and ETT after molar evacuation or hysterectomy. However, metastatic GTN occurs in 4% of patients after complete evacuation of a mole. The main metastasis sites are the lungs (80%), vagina (30%), pelvis (20%), liver (10%), and brain (10%). Mostly, this study found lung metastasis with low-risk GTN in FIGO stage III. Nevertheless, the low-risk score was revealed at 83.9%, while the high-risk score was 16.1%. There were no ultra-high-risk scores of ≥ 13, though this study showed one brain metastasis. Thus, the prognostic scoring system can reliably predict the potential for resistance to chemotherapy [1-5].

This study showed the limitations of a retrospective study design which did not show a high risk of FIGO scores ≥ 7 in stage I. Although nine patients were in a high-risk group and six of the patients in the group had been given EMA-CO, the remaining three patients had been given single-agent chemotherapy. The high-risk score group revealed multidrug treatment of EMA-CO, EMA-EP (etoposide, methotrexate, dactinomycin, etoposide, cisplatin), APE (dactinomycin, cisplatin, etoposide), FA (5-fluorouracil, actinomycin-D), FCA (5- fluorouracil, cyclophosphamide, actinomycin-D), FEP (floxuridine, etoposide, cisplatin), and ACM (actinomycin-D, cyclophosphamide, methotrexate) [5-9].

In this study, as shown in Table 1, the incidence of high-risk GTN patients had displayed in 9/56 (16.1%) with lung and brain metastasis. The high-risk score of GTN with brain metastasis showed an incidence rate of GTN patients among 1/56 (1.78%). The ultra-high-risk group was not presented. Among ultra-high-risk scores, ≥ 13 accounted for 29/974, or 3% of GTN patients. Brain metastasis included 17 patients, while 11 patients had died in the ultra-high-risk scores group. For five patients, death was caused by drug-resistant GTN, complications of subarachnoid hemorrhage (n = 3), multi-organ failures (n = 1), bilateral pulmonary embolism (n = 1), and septic shock (n = 1) [9]. However, brain metastasis in GTN ranged between 3% and 21% [10, 11]. The range of age for brain metastasis GTN was 20 to 56 years old, while most brain metastasis GTN patients are aged < 40, affecting younger and premenopausal patients [11]. Death of brain metastasis GTN included 34/109 patients. Salvage therapy has been described as treating high-risk GTN through high-dose chemotherapy with autologous bone marrow stem cell transplant, as well as immunotherapy with pembrolizumab [12, 13]. Some patients had whole-brain radiotherapy, stereotactic radiotherapy, or gamma knife radiotherapy, with or without craniotomy [14]. Hence, the cause of death from brain metastasis is cerebral hernia secondary to intracranial hemorrhage [13-17].

From the review of literature in Table 2 [4, 5, 7-13, 16-19], ultra-high risk is associated with poor survival, whereas death is linked to chemoresistance, severe complications such as multisystem organ failure, hemorrhagic metastasis, infection, or tumor lysis syndrome. Meanwhile, brain metastasis GTN has the best outcome with multimodality therapy including craniotomy, whole brain radiotherapy, and multiagent chemotherapy [14-19]. Nevertheless, the present study did not focus on ultra-high-risk GTN, with one active brain metastasis including multimodality treatment of craniotomy, whole brain radiation, and multiple-agent chemotherapies that improved

Table 2. A Literature Review of the Ultra-High-Risk Score ≥ 13 and Brain Metastasis Choriocarcinoma

Author (year of published)	Country	Year of treatment	Ultra-high-risk score ≥ 13 (n)	Brain metastasis (n)	Treatment	Status n, (%)
Yang et al, 2005 [18]	China	1985 - 2004	Not classified	13	Craniotomy and EMA-CO	Death in brain metastasis 3/13
Whitaker et al, 2015 [10]	UK	2011	1	1	EMA-CO	Alive
Xiao et al, 2015 [11]	China	1990 - 2013	63	109	EMA-CO, FAEV, 5-FU	Death in brain metastasis 34/109
Savage et al, 2015 [12]	UK	1991 - 2013	22	27	EMA-CO, EMA-EP	Death in brain metastasis 4/27
Bolze et al, 2016 [9]	France	1999 - 2014	29/974	17	EMA-CO	FIGO score ≥ 13 14/29 (48%)
						Total death 18/941
						Total death in FIGO score ≥ 13 (11/29)
Yujia et al, 2017 [19]	China	2002 - 2015	143	58	FAEV, EMA-CO, EMA-EP, TE/TP, intrathecal methotrexate	Death 46/143
Makhathini et al, 2019 [4]	South Africa	2013 - 2017	9/63	Not classified	Not classified	Death 3/63 (4.8)
Gavanier et al, 2019 [7]	France	1999 - 2016	17	21	EMA-CO, EMA-EP, APE	Death in brain metastasis 6/21 (28.57)
Zhang et al, 2019 [17]	USA	2014 - 2018	Not classified	3	Not classified	Not classified
Maesta et al, 2020 [5]	Brazil	1990 - 2014	36/147	Not classified	EMA-CO	Death 19/147 (12.9)
						Death in FIGO score ≥ 12 13/36 (36.1%)
Dombrovsky et al, 2020 [16]	USA	2020	1	1	Craniotomy and EMA-CO	Alive
Wang et al, 2021 [8]	China	1999 - 2019	6	14	EMA-CO, EMA-EP, FA, ACM, FCA, FEP	Death in stage IV 7/26 (26.92%)
Li et al, 2022 [13]	China	1990 - 2018	21/35	146	35 craniotomies	Death in brain metastasis with craniotomy 6/35
Present study (2023)	Thailand	2012 - 2022	None	1	Craniotomy, whole brain radiotherapy and EMA-CO	Alive

EMA-CO: etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine; EMA-EP: etoposide, methotrexate, dactinomycin, etoposide, cisplatin; APE: dactinomycin, cisplatin, etoposide; FA: 5-fluorouracil, actinomycin-D, FCA: 5-fluorouracil, cyclophosphamide, actinomycin-D; FCA: floxuridine, etoposide, cisplatin; ACM: actinomycin-D, cyclophosphamide, methotrexate; FAEV: floxuridine, dactinomycin, etoposide, vincristine; 5-FU: fluorouracil; TE/TP: paclitaxel, etoposide/paclitaxel, cisplatin; FIGO: International Federation of Gynecology and Obstetrics.

the survival outcome for 10 years of experience. Hence, ultra-high-risk GTN is classified as having a FIGO score ≥ 13, and modern works of literature have described it as FIGO stage IV or FIGO score ≥ 13. For the risk of death, uncontrolled hemorrhage and metastasis are significant per a FIGO score ≥ 13 with a mortality rate of 38.4%. Although the 5-year mortality rate of high-risk GTN is 12%, a FIGO score < 13 in a high-risk group has a mortality rate of 4.9% [9]. However, the incidence of high-risk group GTN with brain metastasis was 1/56 (1.78%) in this study. Also, the high-risk group of scores between 7 - 12 displayed in 9/56 (16.1%) patients.

A literature review of ultra-high-risk score of ≥ 13 between 2005 to 2022 was shown in Table 2 [4, 5, 7-13, 16-19], while the present study showed no ultra-high-risk group. The surgery of craniotomy was shown in three kinds of literature [13, 16, 18]. Whole brain irradiation was not a treatment option in the literature as in the present study.

Conclusions

Alive 19-year-old patient of high-risk GTN FIGO stage IV

with brain metastasis, who had presented with a seizure, was an unusual and exceedingly rare occurrence of choriocarcinoma. Therefore, treatment improves prognosis, which can be achieved through perioperative multidisciplinary cooperation with intracerebral hemorrhage craniotomy, standard postoperative chemotherapy, and whole-brain irradiation.

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Financial Disclosure

None to declare.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Informed consents from all patients for publication were obtained.

Author Contributions

Dr. Auttaya Ratanakaew contributed to the study design, methodology, and data collection. Dr. Phornsawan Wasinghon conducted the literature search and manuscript writing.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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