Brain metastases from gestational trophoblastic neoplasia: review of pertinent literature

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Summary

Brain metastasis from gestational trophoblastic neoplasia (GTN) is rare with about 222 cases documented in the literature and an incidence of about 11% in living GTN patients. Brain metastasis from GTN was part of a disseminated disease in 90% of patients, single metastases in the brain – 80% and located in the cerebrum – 90%. Brain metastasis was the only manifestation of metastatic GTN in 11.3% of patients, appeared synchronously with metastatic GTN in other sites of the body – 30.6% and was diagnosed from 0.3 to 60 months after diagnosis of metastatic GTN in other sites (most often in the lung) – 58.1%. Overall, 83.9% of patients with brain metastases from GTN had also lung metastases from GTN. Brain metastases from GTN showed a greater tendency to be hemorrhagic compared to brain metastases from other primaries. In patients with brain metastases from GTN, the best outcome was achieved with multimodal therapy including craniotomy, whole brain radiotherapy, and EP-EMA or EMA-CO chemotherapy. Nonetheless, brain metastasis from GTN is a grave disease with a median survival time from diagnosis of brain metastasis of about 12 months.

Key words: Brain; Choriocarcinoma; GTD; GTN; Metastases.

Introduction

Gestational trophoblastic neoplasia (GTN) represents diseases that form the malignant end of the gestational trophoblastic disease (GTD) spectrum, i.e., invasive mole, choriocarcinoma, and placental-site trophoblastic tumor. GTN is divided into non-metastatic GTN (disease confined to uterus, FIGO Stage I) and metastatic GTN (disease extends outside uterus but is limited to genital structures, FIGO Stage II; disease extends to lungs with or without genital tract involvement, FIGO Stage III; disease involves other metastatic sites, FIGO Stage IV) [1, 2]. Thus, in presence of brain metastases, the GTN is automatically allocated FIGO Stage IV. According to the modified WHO prognostic scoring system for GTN as adapted by FIGO in 2000, GTN is divided into low-risk GTN (sum of scores < 7) and high-risk GTN (sum of scores ≥ 7) [3]. Patients with non-metastatic (Stage I) and low-risk metastatic (Stages II and III – score < 7) GTN are treated with single-agent chemotherapy (methotrexate or actinomycin D) with resulting survival rates approaching 100%. Patients with high-risk metastatic (Stage IV – any score, and Stages II-III – score ≥ 7) GTN should be treated with multi-agent chemotherapy (EMA-CO, combination of etoposide, methtrexate, actinomycin D, cyclophosphamide, and vincristine; or EP-EMA, combination of etoposide, cisplatin, methotrexate and actinomycin D) with or without adjuvant radiotherapy or surgery to achieve cure rates of 80% - 90% [2]. In presence of brain metastases, GTN of any WHO/FIGO score is automatically allocated high-risk metastatic GTN. Since the vast majority of invasive moles are non-metastatic (confined to the uterus) and placental site trophoblastic tumor is an extremely rare condition, the term metastatic GTN has become synonymous to choriocarcinoma. Therefore, in this article, the terms metastatic GTN and choriocarcinoma are used interchangeably.

GTN is preceded by hydatidiform mole in 50% of cases, abortion: 25%, full-term pregnancy: 23%, and ectopic pregnancy: 2%. [1,2,4]. There is considerable variation in the incidence of molar pregnancy in different geographic regions and ethnic groups, with the highest rates in the Far East (Japan and the Philippines; two to three per 1,000 pregnancies) and the lowest rates in western countries (0.6 – 1.1 per 1,000 pregnancies). The estimated incidence of choriocarcinoma in North America and Europe is one per 40,000 (0.0025%) pregnancies and one per 40 (2.5%) hydatidiform moles, whereas in Southeast Asia and Japan metastatic GTN rates are higher at 9.2 and 3.3 per 40,000 pregnancies, respectively [1, 5, 6]. In recent years, however, the widespread use of ultrasound in early pregnancy has led to earlier recognition of molar pregnancy and, thus, the ominous consequences of molar pregnancy can be avoided or significantly reduced if, after evacuation of the molar pregnancy, women are registered for follow-up with assay of beta-human chorionic gonadotropin (β-hCG) and promptly treated with chemotherapy if needed. It seems that the incidence rates of both hydatidiform mole and choriocarcinoma have declined over the past 30 years in all populations [1, 4, 7].

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The brain, along with the bone, liver, and lung, is one of the most common sites of metastases. About 170,000 patients are newly diagnosed with brain metastases each year in the USA, a figure which is ten-fold higher than that of patients newly diagnosed with primary malignancy of the brain [8-10]. Brain metastases most commonly arise from lung carcinoma (~ 25% – 50% of lung carcinoma patients develop brain metastases), breast carcinoma (~ 15% – 30% of breast carcinoma patients develop brain metastases) and malignant melanoma (~ 30% – 70% of malignant melanoma patients develop brain metastases), and occur at a reduced frequency in patients with renal and colorectal carcinoma and other cancer types [8,10-12]. Female genital tract cancers, however, are considered "neurophobic" since brain metastases from female genital tract malignancies, apart from metastatic GTN, are rare with only about one percent of ovarian carcinoma, endometrial carcinoma, and cervical carcinoma patients developing brain metastases in the course of their disease [13-15]. Notwithstanding, brain metastasis occur in ~ 10% - 20% of metastatic GTN patients and represents the major cause of death from metastatic GTN [16, 17]. Choriocarcinoma has a tendency to metastasize rapidly by blood-borne dissemination; the most common site of distant metastasis of choriocarcinoma is the lung followed by the brain, liver, gastrointestinal tract, spleen, and kidney [18]. Brain metastases from choriocarcinoma are frequently associated with lung metastases from choriocarcinoma and it seems that in a substantial amount of patients, brain metastasis is secondary to the lung metastasis. This provides an evidence that the hamatogenous route of dissemination of blood-borne malignant trophoblastic cells from the uterus to the brain is through the pelvic veins, inferior vena cava, right atrium, right ventricle, pulmonary artery, lungs, pulmonary veins, left atrium, left ventricle, aorta, carotid arteries, into the brain arterial circulation, and then to the brain parenchyma.

Until more than three decades ago, brain metastases from GTN had rarely been documented in the literature. Vaughan and Howard [19] in 1962 documented a case of intracranial hemorrhage due to metastatic choriocarcinoma. Stilp *et al.* [20] in 1972 reported three women with brain metastases from choriocarcinoma who had been successfully treated. Weed and Hammond [21] in 1980 documented 14 patients with brain metastases from choriocarcinoma and showed that in some circumstances brain metastases can be eradicated. Since then, 36 papers (single case reports and series of patients) on brain metastasis from GTN in living patients have been published in the literature, totaling 222 patients [16, 17, 22-55]. This review summarizes these papers and focuses on the following topics: incidence of GTN as source of brain metastases in patients with brain metastases, incidence of brain metastases in patients with GTN, age of patients with brain metastases from GTN, type of antecedent pregnancy, interval from antecedent pregnancy to diagnosis of metastatic GTN, interval from diagnosis of metastatic GTN to diagnosis of brain metastases, symptoms and signs of brain metastases from GTN, type, amount and site of brain metastases from GTN, treatment of brain metastases from GTN, and survival after diagnosis of brain metastases from GTN.

Incidence of GTN as source of brain metastases in patients with brain metastases

Tom [56] in 1946 reviewed 33 women with brain metastases and found that the breast was the source of brain metastases in 13 (39.4%), gastrointestinal tract: seven (21.2%), lung: three (9.1%), uterine cervix: two (6.1%), malignant melanoma: one (3%), uterus: one (3%), ovary: one (3%), thyroid: one (3%), and undetermined: four (12.1%); in none of the cases, GTN was source of brain metastases. Chason *et al.* [57] in 1963 found brain metastases in 200 (18.3%) of 1,096 autopsies of cancer patients and observed that choriocarcinoma was source of brain metastases in only one (0.5%) of 200 cases with brain metastases. Hunter and Rewcastle [58] in 1968 reviewed 393 autopsies of patients with brain metastases and showed that lung carcinoma was by far the commonest source of brain metastases (34.1%) followed by breast carcinoma (18.6%) and malignant melanoma (6.1%); they could not demonstrate even one case of brain metastases from GTN. Zimm *et al.* [59] in 1981 reviewed 191 patients with brain metastases and did not observed cases of brain metastases from GTN. LeChevalier *et al.* [60] in 1985 reviewed 31 women with brain metastases from various primary tumors and did not find cases of brain metastases from GTN. Nussbaum *et al.* [61] in 1996 reviewed 729 patients with brain metastases and did not specify whether there were cases of brain metastases from GTN. Lagerwaard *et al.* [62] in 1999 surveyed 1,292 patients with brain metastases and observed that lung carcinoma was source of brain metastases in 721 (55.8%), breast: 213 (16.5%), kidney: 48 (3.7%), other sources (not specified): 208 (16.1%), and unknown: 102 (7.9%). The authors [62] did not specify whether there were cases of brain metastases from GTN. Apparently, since metastatic GTN is a rare disease entity, its presentation in the general population of patients with brain metastases is extremely rare.

Incidence of brain metastases in patients with GTN

Kobayashi *et al.* [63] in 1982 surveyed 87 patients with histologically-verified choriocarcinoma treated in their institution during 1965 - 1977 and found that 24 (27.6%) developed brain metastases. Thirty-three (38%) of the 87 patients died of choriocarcinoma; all 33 patients underwent autopsy and brain metastasis was confirmed in 22 (66.7%) of the autopsies. Notably, the lung and brain were the most common sites of metastatic choriocarcinoma followed by the liver, kidney, spleen, pelvis, bowel, and urinary bladder [63]. Ishizuka *et al.* [17] in 1983 surveyed 168 patients with choriocarcinoma treated at their institution over a 24-year period (1957 – 1980) and found that brain metastases

Table 1. — *Incidence of brain metastases in patients with GTN.*

Authors	Study period	No. of women with GTN	No. of women with BM	Percentage
Kobayashi *et al.* 1982 [63].	1965 – 1977	87 (33/87 patients died of disease and had autopsy)	24 (BM was found in 22/33 autopsies)	27.6 (at autopsy: 66.7)
Ishizuka *et al.* 1983 [17]	1957 – 1980	168	36	21.4
Athanassiou *et al.* 1983 [64]	1957 – 1981	782	69	8.8
Evans *et al.* 1995 [34]	1966 – 1992	454	42	9.3
Total		1,491	171	11.4

BM: brain metastases.

developed in 36 (21.4%) patients. A comparative study of the differences in the rate of developing brain metastases from GTN before and after the introduction of chemotherapy with actinomycin-D (Act D) in 1965 revealed a remarkable decrease in the development of brain metastases. Before 1964, the incidence of brain metastases in choriocarcinoma patients was 37.5% (9/24 patients), and after 1965 the incidence dropped to 18.8% (27/144 patients) ($p < 0.05$) [17]. Athanassiou *et al.* [64] in 1983 surveyed 782 patients who had chemotherapy for GTN at their institution during 1957 – 1981 and revealed that 69 (8.8%) had brain metastases; 33/69 (48%) presented with brain metastases prior to chemotherapy, and 36/69 (52%) developed brain metastases while on chemotherapy or relapsed in the brain after an initial complete or partial remission. The periods 1957 – 1973 and 1974 – 1980 were compared. During 1957 – 1973, 42/367 (11.4%) patients with GTN had brain metastases; 20 (5.4%) presented with brain metastases prior to chemotherapy, and 22 (6%) developed brain metastases while on chemotherapy or relapsed in the brain after an initial complete or partial remission. During 1974 – 1980, 26/402 (6.4%) patients with GTN had brain metastases; 13 (3.2%) presented with brain metastases prior to chemotherapy and 13 (3.2%) developed brain metastases while on chemotherapy or relapsed in the brain after an initial complete or partial remission [64]. Kikuchi *et al.* [30] in 1990 stated that the frequency of cerebral metastases in choriocarcinoma patients varied from 7% to 22%, with an average prevalence at diagnosis of 20%. Evans *et al.* [34] in 1995 reviewed 454 patients with metastatic GTN treated at their institution during 1966 – 1992 and identified 42 (9.3%) patients with brain metastases; 16 patients presented with brain metastases before primary therapy and 27 patients received significant therapy prior to presentation with brain metastases. In summary, 171 (11.4%) of 1,491 women with metastatic GTN collated from large series in the literature had brain metastases from GTN (Table 1) [17, 34, 63, 64].

Age of patients with brain metastases from GTN

Age at diagnosis of brain metastases from GTN was available in 174/222 (78.3%) patients with brain metastases from GTN collated from literature and ranged from 17 to 54 years (median, 34 years) (Table 2).

Type of antecedent pregnancy

Type of antecedent pregnancy was available in 170/222 (76.5%) patients and was hydatidiform mole in 72 (42.3%), term pregnancy in 56 (32.9%), miscarriage in 31 (18.2%), stillbirth in seven (4.1%), artificial abortion in two (1.2%), invasive mole in one (0.6%), and tubal pregnancy in one (0.6%) (Table 2). Thus, hydatidiform mole was the most common type of antecedent pregnancy.

Interval from antecedent pregnancy to diagnosis of metastatic GTN

The interval from antecedent pregnancy to diagnosis of metastatic GTN was available in 61/222 (27.4%) patients and ranged from 0 to 240 months (median, 11 months) (Table 2). In 14/61 (23%) patients, metastatic GTN was diagnosed < four months from index pregnancy (in six of the 14 patients, metastatic GTN, and the index pregnancy were diagnosed synchronously). In 12/61 (19.7%) patients, metastatic GTN was diagnosed four to <seven months from index pregnancy. In 9/61 (14.7%) patients, metastatic GTN was diagnosed seven to <13 months from index pregnancy. In 26/61 (42.6%) metastatic GTN was diagnosed ≥ 13 months from index pregnancy. Thus, metastatic GTN was most commonly diagnosed after more than one year from antecedent pregnancy.

Interval from diagnosis of metastatic GTN to diagnosis of brain metastases

The interval from diagnosis of metastatic GTN to diagnosis of brain metastases was available in 124/222 (55.8%) patients and ranged from 0 to 60 months (median, one month) (Table 2). In 14/124 (11.3%) patients, brain metastases from GTN was first and only manifestation of metastatic GTN. In 38/124 (30.6%) patients, brain metastases appeared synchronously with metastatic GTN in other sites of the body. The other sites were: lung – 20, lung and pelvis – four, lung and liver – two, lung, liver and bowel – two, lung and bowel – one, lung and neck – one, lung and kidney – one, lung and vertebra – one, lung, liver, spleen, and kidney – one, lung, spleen, kidney and skin – one, bowel – one, liver and bowel – one, liver and pelvis – one, mediastinal and mesenterial lymph nodes – one. In 72/124 (58.1%) patients, brain metastasis was diagnosed from 0.3 to 60 months after diagnosis of metastatic GTN in other

Table 2. — *Summary of reports on brain metastases from GTN in living patients published in the literature (n = 222 patients).*

Author (year) [ref.]	Age (yrs)	Type of AP	Time from AP to GTN (mon)	Surgery of uterine tumor	Time from GTN to BM (months)	Other sites of metastases	Treatment of BM	Survival after BM (mon)
Barnes 1982 [22]	17	SB	0	No	0	Lung	Craniotomy, Act D → MAC, WBRT	D 90
Ishizuka 1983 [17] 27 pts.	NR	16 mole 1 term 5 misc. 1 TP 3 term 1 SB	1 – 240 (15)	20 hyst. 7 no	0 – 47 (8)	27 Lung	17 Act D 5 Act D, craniotomy 3 craniotomy, Act D 2 Act D, shunt	26 D 0.1 – 50 (1.6) 1 AW 54
Liu 1983 [23] 34 pts.	30 – 50 (33.7)	NR	NR	Some had hyst.	0.3-1	Lung, Vagina	6-MP, MTX, Act D, 5-FU	7 AW 12-120 27 D <1-5
van den Doel 1985 [24]	42	Term	NR	Hyst. 2 yrs before	0	Mediastinal and mesenterial lymph nodes	Craniotomy x 2 to evacuate hematoma	D 1
Momma 1986 [25]	29	Mole	20	NR	0	Bowel, liver	Craniotomy for clot evacuation and OA resection, shunt	D 1
Ilancheran 1988 [26]	26 – 30	1 mole 1 misc.	5 – 21	2 no	0	1 Lung 1 No	2 Craniotomy, MTX + Act D	2 AW 39 – 108
Koulos 1988 [27]	42	Term	156	Hyst.	14	Lung, mediastinum	MAC, BEP, Craniotomy, SRS, EMA-CO	AW 12+
Mates 1988 [28]	17 – 26	1 mole 1 term	4 – 5	2 no	0	1 No 1 lung, liver, b	1 Craniotomy to evacuate hematoma - 1 MTX, Act D	2 D 0.1 – 0.5
Rustin 1989 [29] 25 pts. treated with EMA-CO	24 – 50 (32)	9 mole 8 term 6 misc. 2 SB	NR	NR	NR	23 lung 2 no	25 EMA-CO. Part of pts. had also craniotomy and/or WBRT	15 pts. had a CR to EMA-CO lasting 4 – 74 (33) months
Kikuchi 1990 [30]	36 – 37	2 mole	36 – 45	2 NR	0	1 lung, 1 bowel	2 Craniotomy, MAC, WBRT	1 AW 60, 1 AD 9
Jones 1990 [31] 19 pts.	19 – 54 (32)	9 mole 5 term 2 misc. 1 SB 1 inv. M 1 NR	NR	6 hyst. 1 hyst-o 4 D&C 1 SA 7 NR	0 – 60 (11)	8 lung, liver 4 lung 3 lung, liver, b. 1 lung, neck 1 lung, mediast. 1 lung, liver, sp. 1 No	16 MAC, WBRT 1 Act D, WBRT 2 MAC, WBRT, Cran.	14 D 0.1 – 24 (5.5) 5 AW 48 – 180 (96)
Wilkinson 1991 [32]	36	Term	12	NR	NR	Liver, pelvis, heart	Craniotomy, C	D 1
Giannakopoulos 1992 [33]	30	Term	24	No	0	Lung, kidney	Craniotomy to evacuate hematoma	D 0.5
Evans 1995 [34] 42 pts.	NR	16 mole 15 term 8 Misc.	NR	NR	NR	NR	NR	NR
Leslie 1996 [35]	26	Term	0	CS	18	Lung	EMA-CO, SRS → EMA-CO, intrathecal MTX	AW 24+
Schechter 1998 [36] 21 pts. treated with WBRT	19 – 54 (35)	10 mole 5 misc. 3 term 1 SB 1 NR 1 none	NA	8 D&C 4 hist. 1 his-o 2 SA 4 No 2 NR	21 NR	21 NR	All patients: WBRT Most patients: MTX and Act D-based chemotherapy. Some patients: EMA-CO.	13 D 0.1 – 44 (8) 7 AW 15 – 170 (77) 1 AD 11
Nozue 2000 [37]	25	Term	5	No	0	Lung	EMA-CO	AW 10+
Suresh 2001 [38] 10 pts.	17-35	NR	NR	NR	NR	10 no	Craniotomy to evacuate hemorrhage, 6 pts. referred to chemotherapy	6 AD NA 4 D 1
Mamelak 2002 [39]	27	Term	0	CS	0	No	Delivery at 30W and then craniotomy, EMA-CO, WBRT	AW 12+
Balagopal 2003 [40]	24	Mole	96	NR	0	Bowel, lung	EMA-CO → BEP	Lost

Picone 2003 [41]	20	Term	0	CS	0	Lung, vertebra (D5)	Craniotomy, EMA	AD 4
Ghaemmaghami 2004 [42] 9 pts.	17 – 53 (30)	5 Mole 2 Misc. 1 Term 1 NR	NR	5 Hyst. 4 NR	NR	2 Lung 2 Lung, liver 2 Lung, adrenal 1 Lung, kidney 1 Lung, vagina 1 No	8 EMA-EP, WBRT 1 EMA-CO, WBRT	5 AW 4 D Median, 24 (9 – 50)
Hiramatsu 2005 [43]	31	Term	1	NR	0	Lung	EMA-CO	AW 192+
Saad 2006 [44]	21	SB	2	No	0	Lung, pelvis	NR	NR
Soper 2007 [45] 4 pts.	18-38	4 Term	0.5 – 48 (5.5)	1 Hyst. 3 No	0	3 Lung, pelvis 1 Lung	3 Craniotomy, EMA-EP 1 SRS, EMA-CO	4 AW 12 – 24 (16.5)
Sierra-Bergua 2008 [46]	33	Term	8	Hyst.	2	Lung	EMA-EP → craniotomy → BEP	AW 16+
Chang 2008 [47]	35	TOP	24	NR	0	Lung	SRS → Craniotomy, EMA-CO	D 1
Rocque 2008 [48]	34	Mole	23	D&C	0	Lung, liver, spleen, kidney	Craniotomy for blood evacuation. WBRT, EMA-EP/CO	D 4
Verzair 2008 [49]	37	Term	2	Hist.	0	Lung, spleen, kidney, skin	Craniotomy, EMA-CO	AW 72+
Behtash 2009 [50]	27	Misc.	12	NR	0	Lung	Craniotomy, EMA-EP, WBRT	AW 44+
Grisaru 2009 [51]	36	Misc.	4	No	0	Lung, liver, spleen, kidney, pancreas	No	D 0.2
Dadlani 2010 [52]	25	Term	12	NR	0	Liver, pelvis, spleen	Craniotomy, WBRT, EMA-CO	AW 12+
Singhal 2010 [53]	23	TOP 6W	6	NR	0	No	Craniotomy to evacuate hemorrhage, EMA-CO	AW 2+
Brudie 2011 [54]	28	Term	0	No	0	Lung, liver	EMA-CO during pregnancy. Delivered at 32W a normal baby.	NR
Shrestha 2011 [55]	22	No	0	No	0	NR	Craniotomy to evacuate hematoma and resection of OA	D 0.1
Zairi 2011 [16]	21 – 28	2 Term	6	2 No	0	Lung	Cran. EMA-CO	D 0.1 - 0.5

AP: antecedent pregnancy, AW: alive and well, b.: bowel, BM: brain metastases, CR: complete response, CS: cesarean section, D: dead, Cran.: craniotomy, Hyst: hysterectomy, Hys-o: hysterotomy, Inv. M: invasive mole, MP: mercaptopurine, mediast.: mediastinum, MTX: methotrexate, Misc.: miscarriage, mon: months, NR: not recorded, OA: oncotic aneurysm, pts.: patients, SA: spontaneous abortion, sp.: spleen, SRS: stereotactic radiosurgery, SB: stillbirth, TOP: termination of pregnancy, TP: tubal pregnancy, yrs: years, WBRT: whole brain radiotherapy, Act D: actinomycin-D (dactionmycin), MAC: methotrexate, actinomycin-D and chlorambucil, BEP: bleomycin, etoposide and cisplatin, EMA-CO: etoposide, methotrexate and actinomycin-D alternating with cyclophosphamide and oncovin (vincristine), EMA-EP: etoposide, methotrexate and actinomycin-D alternating with etoposide and cisplatin.

sites, most often in the lung. Overall, 104/124 (83.9%) patients with brain metastases from GTN had also lung metastases from GTN.

Type, amount and site of brain metastases from GTN

Type of brain metastases of GTN with respect to whether the metastasis is confined to the brain only (isolated brain metastases) or is part of a disseminated disease affecting also other parts of the body was available in 157/222 (70.7%) patients (Table 2). Brain metastasis was an isolated disease confined to the brain in 16/157 (10.2%) patients whereas brain metastasis was part of a disseminated disease in 141/157 (89.8%) patients. Amount of brain metastases with respect to whether the metastasis is single (solitary) brain metastases or multiple brain metastases was available in 46/222 (20.7%) patients. Brain metastasis was single brain metastases (one metastases) in 37/46 (80.4%) patients whereas brain metastasis was multiple brain metastases (two or more metastases) in 9/46 (19.6%) patients. Site of metastasis in the brain with respect to whether the metastasis is supratentorial (cerebrum) or infratentorial (cerebellum) or both was available in 78/222 (35.1%) patients. Brain metastasis was located in the cerebrum in 69/78 (88.5%) patients, cerebellum in 5/78 (6.4%) patients, and both cerebrum and cerebellum in 4/78 (5.1%) patients. Thus, brain metastasis from GTN is part of a disseminated disease in ~ 90% of patients, single metastases in the brain in ~ 80% of patients and supratentorial in ~ 90% of patients.

Symptoms and signs of brain metastases from GTN

Symptoms and signs of brain metastases from GTN are not different from symptoms and signs of other space occupying lesions of the brain. Common presenting symptoms and signs of brain metastases from GTN include headache, confusion, dizziness, decreased mental status, consciousness disturbance, general weakness, extremity weakness, gait disturbance, neurological motor deficit, hemiparesis, hemiplegia, ataxia, visual disturbance, incontinence, nausea, vomiting, speech impairment (aphasis), parasthesias, syncope, seizure, and raised intracranial pressure manifested by papilledema. Nevertheless, brain metastases from GTN are characterized by their greater tendency to be hemorrhagic and associated with brain oncotic aneurism and intracranial hemorrhage. In a series of 34 pa-

tients with brain metastases from GTN reported by Liu *et al.* [23], 18 patients presented with headache, ten: hemiparesis, seven: vomiting, six: dizziness, five: blurred vision, three: nausea, two: aphasia, two: depression, two: insomnia, and two: seizure (the number of patients sums up to more than 34 since some patients had more than one symptom). In 19 patients with brain metastases of GTN reported by Jones *et al.* [31], headache, seizure, and dizziness were the most common symptoms. In ten patients with brain metastases from GTN reported by Suresh *et al.* [38], sudden onset of headache, vomiting, and convulsion were the most frequent initial symptoms (seven patients) followed by hemiparesis and sensory disturbances (three patients). In the majority of patients (8/10), the brain lesions seen at cranial CT scan were interpreted as hemorrhagic masses [38]. Zairi *et al.* [16] in 2011 reported two patients in whom intracranial hemorrhage due to ruptured oncotic aneurysm was the first manifestation of metastatic GTN. It has been concluded that metastatic GTN must be considered in the differential diagnosis of any intracranial hemorrhage in women of childbearing age.

Treatment of brain metastases from GTN

Data with respect to treatment modality of brain metastases of GTN was available in 175/222 (78.8%) patients collated from literature (Table 2). Of the 175 patients, 140 (80%) had chemotherapy, 56 (32%) had WBRT, 42 (24%) had craniotomy, four (2.3%) had SRS, two (1.1%) had a shunt, and one (0.6%) had no treatment (number of patients adds up to more than 175 since some patients received more than one treatment modality). The most common unimodal treatment was chemotherapy and the most common multimodal treatment was craniotomy in combination with other treatments such as chemotherapy, WBRT, and SRS. Noteworthy, of the 42 craniotomies performed in patients with brain metastases from GTN, 30 (71.4%) craniotomies were performed for resection of brain metastases and 12 (28.6%) were performed for evacuation of intracranial hematoma and resection of brain oncotic aneurism.

Because of the rarity of metastatic GTN, the accrual of patients with brain metastases from GTN occurred over prolonged periods of time during which treatment approaches and modalities changed. In presence of brain metastases the GTN is allocated Stage IV and if untreated may be rapidly fatal. Over the years, the multi-agent chemotherapy regimen of choice for patients with high-risk metastatic GTN (including brain metastases) changed. In the 1970s and 1980s, the combination of methotrexate, actinomycin D, and cyclophosphamide or chlorambucil (MAC) was the preferred first-line chemotherapy, yielding cure rates of 63-71% [2]. In the 1980s, etoposide (VP-16) was discovered to be a very effective agent for the treatment of metastatic GTN, and the addition of etoposide to multi-agent chemotherapy in the regimen of etoposide, high-dose methotrexate with folinic acid, actinomycin D, cyclophosphamide, and vincristine (EMA-CO) resulted in improved remission and survival rates of 80 - 90% [2]. Of the 140 patients who had chemo-therapy for brain metastases from GTN collated from literature (Table 2), the vast majority of patients treated before 1990 had actinomycin D- and methotrexate-based chemotherapy such as MAC, whereas almost all patients treated after 1990 had etoposide-based multi-agent combination chemotherapy, mainly EMA-CO or EMA-EP. At least one patient had also intrathecal chemotherapy with methotrexate [35].

Survival after diagnosis of brain metastases from GTN

Data with respect to patient status (alive without disease or alive with disease or dead) at the end of follow-up was available for 171/222 (77.3%) patients with brain metastases from GTN documented in the literature (Table 2). Of these 171 patients, 57 (33.3%) were alive without disease at follow-up of two to 192 months, nine (5.2%) were alive with disease at follow-up of four to 11 months, and 105 (61.4%) died of disease from 0.1 to 90 months (median, one month) after diagnosis of brain metastases. Overall, the survival time until the end of follow-up or death in these 171 patients ranged from 0.1 to 192 months (median, 12 months).

The survival after diagnosis of brain metastases from GTN according to mode of therapy of brain metastases was assessed in details in series of more than three patients. Of 27 patients with brain metastases from GTN reported in 1983 by Ishizuka *et al.* [17], 17 (62.9%) had chemotherapy with single-agent actimomycin D (dactinomycin) alone (all died of disease from 0.1 to 46 months [median, 0.9 month] after diagnosis of brain metastases), five (18.5%) had chemotherapy with single-agent actimomycin D followed by craniotomy (all died of disease from 1.2 to 50 months [median, four months] after diagnosis of brain metastases), three (11.1%) had craniotomy followed by chemotherapy with single-agent actimomycin D (two died of disease eight and 18 months, respectively, after diagnosis of brain metastases and one was alive without disease at follow-up of 54 months) and two (7.4%) had chemotherapy with single-agent actimomycin D followed by shunt (both died of disease 0.8 and 21 months, respectively, after diagnosis of brain metastases). Overall, 26 patients died of disease from 0.1 to 50 months (median, 1.6 months) after diagnosis of brain metastases and one patient was alive without disease four months after diagnosis of brain metastases [17]. Liu *et al.* [23] in 1983 reported 34 patients who had chemotherapy (6-MP, MTX, Act D, 5-FU, some had also Chinese herbs) for brain metastases from GTN; seven (20.6%) patients were alive and well at follow-up of 12 to 120 months and 27 (79.4%) patients died of disease from less than one to five months (median, < one month) after diagnosis of brain metastases. Rustin *et al.* [29] in 1989 reported 25 patients who had EMA-CO multi-drug chemotherapy (part of patients had also craniotomy and/or WBRT) for brain

Table 3. — *Survival after diagnosis of brain metastases from GTN according to mode of therapy of brain metastases in 171 patients collated from literature.*

Mode of therapy	Survival range (months)	Median (months)
Single-agent chemotherapy: actinomycin D or methotrexate (either alone or combined with other treatment modality/ies)	0.1 – 170	2
Multidrug chemotherapy: MAC (either alone or combined with other treatment modality/ies)	0.1 – 180	8.5
Multidrug chemotherapy: EP-EMA or EMA-CO (either alone or combined with other treatment modality/ies)	0.1 – 192	26.5
Bimodal therapy: EP-EMA or EMA-CO chemotherapy and WBRT	4 – 50	24
Bimodal therapy: EP-EMA or EMA-CO chemotherapy and craniotomy	1 – 72	12
Triple modal therapy: craniotomy, chemotherapy and WBRT	4 – 90	34
Craniotomy (either alone or combined with other treatment modality/ies)	0.1 – 108	12
WBRT (either alone or combined with other treatment modality/ies)	0.1 – 180	24
SRS (either alone or combined with other treatment modality/ies)	1 – 24	13.5
Shunt (either alone or combined with other treatment modality/ies)	0.8 – 21	1
Craniotomy alone to evacuate an intracranial hematoma	0.1 – 1	0.3
No treatment	0.2	0.2
All modes of therapy	0.1 – 192	12

WBRT: whole brain radiotherapy, SRS: stereotactic radiosurgery.

metastases from GTN; 15 patients had a complete response to EMA-CO lasting from 33 to 74 (median, 33) months. Of note, 18 of the 25 patients presented with brain metastases before EMA-CO whereas seven developed brain metastases on or after EMA-CO [29]. Jones *et al.* [31] in 1990 reported 18 patients who had MAC and one patient who had actinomycin-D chemotherapy followed by WBRT (two patients had also craniotomy) for brain metastases from GTN; 14 patients died of disease from 0.1 to 24 (median, 5.5) months after diagnosis of brain metastases and five patients were alive without disease at follow-up of 48 to 180 (median, 96) months. Overall, median survival time until end of follow-up or death was seven months (range, 0.1 to 180 months) [31]. Schechter *et al.* [36] in 1998 reported 21 patients with brain metastases from GTN who had WBRT (most patients had also MTX and Act D-based chemotherapy); 13 patients died of disease from 0.1 to 44 (median, eight) months after diagnosis of brain metastases, seven patients were alive without disease at follow-up of 15 to 170 (median, 77) months, and one patient was alive with disease at follow-up of 11 months. Suresh *et al.* [38] in 2001 reported ten patients with brain metastases from GTN who had craniotomy to evacuate brain hemorrhage (six patients were also referred to chemotherapy); six patients were alive with disease at follow-up of unknown duration and four patients died of disease within one month after diagnosis of brain metastases. Ghaemmaghami *et al.* [42] in 2004 reported nine patients with brain metastases from GTN who had EMA-EP (eight patients) or EMA-CO (one patient) multi-agent chemotherapy followed by WBRT; five patients were alive without disease and four patients died of disease at follow up of nine to 50 (median, 24) months. Soper *et al.* [45] in 2007 documented four patients with brain metastases from GTN; three had craniotomy followed by EMA-EP multi-agent chemotherapy and were alive without disease at follow-up of 12, 18, and 24 months (median, 18), respectively, after diagnosis of brain metastases and one patient had brain stereotactic radiosurgery (SRS) followed by EMA-CO and was alive without disease at follow-up of 15 months.

Survival according to mode of therapy of brain metastases in all patients collated from literature (case reports and series of patients) in whom data with respect to mode of therapy and survival was available is displayed in Table 3. The evolution of chemotherapy for high-risk metastatic GTN over the years from single-agent chemotherapy (such as methotrexate or actinomycin-D) through multidrug chemotherapy composed of MAC and eventually multidrug chemotherapy composed of EP-EMA or EMA-CO has improved the outcome of patients with high-risk metastatic GTN including patients with brain metastases from GTN. Thus, it seems that in patients in whom it is feasible, the best results may be achieved with multimodal therapy including craniotomy, WBRT, and EP-EMA or EMA-CO chemotherapy.

Conclusion

Brain metastasis from GTN is rare with about 222 cases documented in the literature and an estimated incidence of about 11% in living GTN patients. Age at diagnosis of brain metastases from GTN ranged from 17 to 54 years (median, 34 years). Antecedent pregnancy before GTN was hydatidiform mole in 42.3% of patients, term pregnancy: 32.9%, miscarriage:18.2%, stillbirth: 4.1%, termination of pregnancy: 1.2%, invasive mole: 0.6% and tubal pregnancy: 0.6%. Time from antecedent pregnancy to GTN ranged from 0 to 240 months (median, 11 months). Time from

GTN to diagnosis of brain metastases ranged from 0 to 60 months (median, one month). Brain metastasis from GTN was part of a disseminated disease in ~ 90% of patients, single metastases in the brain in ~ 80% of patients, and located in the cerebrum in ~ 90% of patients. Brain metastasis was first and only manifestation of metastatic GTN in 11.3% of the patients, appeared synchronously with metastatic GTN in other sites of the body in 30.6%, and was diagnosed from 0.3 to 60 months after diagnosis of metastatic GTN in other sites, most often in the lung, in 58.1%. Overall, 83.9% of patients with brain metastases from GTN had also lung metastases from GTN. Symptoms and signs of brain metastases from GTN are not different from symptoms and signs of other space occupying lesions of the brain. Nevertheless, brain metastases from GTN are characterized by their greater tendency to be hemorrhagic and associated with brain oncotic aneurism and intracranial hemorrhage. Chemotherapy for high-risk metastatic GTN has evolved over the years from single-agent chemotherapy to multidrug chemotherapy composed of EP-EMA or EMA-CO. It seems that in patients with brain metastases from GTN, the best outcome may be achieved with multimodal therapy including craniotomy, WBRT, and EP-EMA or EMA-CO chemotherapy. Nonetheless, brain metastasis from GTN is a grave disease with a median survival time overall from diagnosis of brain metastasis of only about 12 months. Current knowledge of brain metastases from GTN is based on the experience of authors who reported series of patients or singular cases. Because of the rarity of brain metastases from GTN, patient accrual occurred over prolonged periods during which treatment approaches and modalities changed. Consequently, very few individuals or even referral centers can build up an adequate experience of handing this disease and, thus, the understanding of the variable biologic behavior and treatment alternatives of brain metastases from GTN is still limited. Hence, the reporting of further cases of brain metastases from GTN should be encouraged since analysis of information from even small series or singular cases may form an important source of knowledge for future research and treatment recommendations.

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