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TREATMENT OF METASTATIC GESTATIONAL TROPHOBLASTIC NEOPLASIA

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In the late 1950s and early 1960s, Hertz and colleagues at the US National Cancer Institute (NCI) first demonstrated the efficacy of chemotherapy in the treatment of metastatic gestational trophoblastic neoplasia (GTN) [1,2]. They obtained complete remissions in 47% of patients with methotrexate alone [1] and in 74% of patients treated with both methotrexate and actinomycin D sequentially [2]. These investigators also recognized that successful outcome of therapy was dependent to a large extent on duration of disease, height of the pretreatment human chorionic gonadotropin (hCG) level, presence or absence of brain or liver metastases, and expertise in the use of the chemotherapy drugs. Over 95% of patients who were diagnosed early and treated vigorously were cured, whereas patients in whom there was a delay in diagnosis and consequently had more extensive disease achieved only a 36% remission rate.

This observation led to the recognition of certain prognostic factors which placed patients with trophoblastic tumors at higher risk of treatment failure: (1) longer than four months from the antecedent pregnancy event to diagnosis; (2) pretreatment hCG level >100 000 IU/24 h urine or >40 000 IU/L serum; (3) metastases to sites other than the lung and vagina; (4) an antecedent term gestation; and (5) previous failed therapy. Most major US trophoblastic disease centers used a clinical classification system based on these prognostic factors,

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originally described by the NCI investigators, to determine treatment and report results. In this system, patients were divided into three disease groups: non-metastatic; low-risk metastatic; and high-risk metastatic. High-risk referred to patients whose disease was not likely to be cured by single-agent chemotherapy and who were at the highest risk of treatment failure.

In 1983, the World Health Organization (WHO) adopted a prognostic scoring system, initially proposed by Bagshawe and subsequently modified, based on the patients' age, parity and type of antecedent pregnancy, interval between antecedent pregnancy and trophoblastic tumor event, hCG level, number and site of metastases, largest tumor mass and previous chemotherapy. Factors affecting prognosis are assigned numerical values that, when added together, are used to divide patients into low-risk (<7) and high-risk (≥7) groups [3].

An anatomic staging system was adopted by the International Federation of Gynecology and Obstetrics (FIGO) Cancer Committee in 1982 and was changed to include the modified WHO score in 2002 [4]. In this system, FIGO stage is designated by a Roman numeral followed by the modified WHO score designated by an Arabic numeral, separated by a colon (Table 1).

Table 1 FIGO Staging and Scoring System for GTN

Stage I	confined to the uterus
Stage II	extends outside the uterus but is limited to the genital structures (adnexa, vagin
Stage III	extends to the lungs with or without genital tract involvement
Stage IV	metastatic to any other site

Risk Factor

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	0	1	2	
Age	≤ 39	>39		
Antecedent pregnancy	Mole	Abortion	Term	
Pregnancy event to treatment interval (mo)	<4	4-6	7-12	
Pretreatment hCG (mIU/mL)	$<10^3$	10^3-10^4	10^4-10^5	
Largest tumor mass, including uterus (cm)	< 3	3-4	≥ 5	
Site of metastases		Spleen, Kidney	GI trct	F
No. of metastases		1-4	4-8	
Previously failed chemotherapy			Single Drug	

The total score for a patient is obtained by adding the individual scores for each factor: low-risk ≤ 7; high-risk ≥ 7.

Patients with low-risk metastatic GTN (stages II and III, score <7) can be treated with initial single-agent chemotherapy, while patients with high-risk metastatic GTN (stages II-III, score ≥ 7 and stage IV) should be treated more aggressively with initial multiagent chemotherapy with or without adjuvant radiotherapy or surgery. The benefit of this approach was first noted at the John I. Brewer Trophoblastic Disease Center in 1968. Patients with high-risk disease who were initially treated with the triple chemotherapy regimen of methotrexate, actinomycin D and cyclophosphamide or chlorambucil (MAC) had a survival rate of 65%, whereas the survival rate for similar patients who were treated initially with a single agent followed by MAC as secondary therapy was 39% [5]. In 1973, Hammond *et al.* [6] reported the results of therapy in 91 patients with metastatic GTN. Seventy-one 'good-prognosis' patients were treated initially with single-agent chemotherapy with a 98.6% survival. Of 17 'poor prognosis' patients, seven received initial single-agent chemotherapy followed by MAC combination chemotherapy if resistance developed, and 10 were treated initially with MAC. Only one of seven patients (14%) treated with single-agent chemotherapy followed by MAC

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survived as compared to seven of 10 patients (70%) treated initially with MAC.

Others subsequently confirmed the value of initial combination chemotherapy in treating patients with high-risk metastatic GTN [7—10]. The added toxicity of such combination chemotherapy, however, does not appear to warrant its use in patients with less extensive metastatic disease, in which survival can be anticipated to approach 100% with the use of initial single-agent chemotherapy. It is imperative, therefore, that patients with metastatic trophoblastic tumors be chosen for treatment with single-agent or multiagent chemotherapy based on careful attention to selection criteria in order to ensure the best outcome with the least morbidity.

17.1 LOW-RISK METASTATIC DISEASE

Patients categorized as having low-risk metastatic GTN (FIGO stages II and III, score < 7) can usually be treated successfully with single-agent chemotherapy with methotrexate or actinomycin D, according to one of the protocols described in Table 2.

Table 2   Chemotherapy for Low-Risk Metastatic Gestational Trophoblastic Neoplasia

Methotrexate 0.4 mg/kg (max 25 mg) IV or IM. q.d. x 5d; repeat every 14 d (9-day window)

Methotrexate 1 mg/kg IM. days 1, 3, 5, 7; folinic acid 15 mg/po. days 2, 4, 6, 8; repeat every 14 d (9-day window)

Actinomycin D 10—12 μg/kg IV. q.d. x 5d; repeat every 14 d (9-day window)

The weekly methotrexate or biweekly single-dose actinomycin D protocols currently in use for non-metastatic postmolar GTN should not be employed for treatment of metastatic disease. Methotrexate should be avoided if there is an abnormality in hepatic or renal function, or if effusions or large theca lutein cysts are present. At the Brewer Trophoblastic Disease Center, we prefer to begin treatment with a five-day methotrexate regimen unless contraindicated and to administer the drugs sequentially; that is, when resistance to the first drug occurs, the second drug is begun. Patients who develop resistance to sequential single-agent chemotherapy are then treated with combination chemotherapy, as for high-risk disease.

Several studies have demonstrated the high curability of low-risk metastatic GTN when appropriate therapy is administered. Ross and co-workers were the first investigators to identify the highly favorable prognosis in this group of patients, curing 20 of 21 patients (95%) with relatively non-toxic sequential methotrexate and actinomycin D chemotherapy [2]. Subsequent reports from Brewer *et al.* [5], Hammond *et al.* [6,12], Goldstein and coworkers [11,13,15], Bagshawe[7], Jones and Lewis[9,14] and Lurain *et al.*[10] documented virtually l00% cures of low-risk metastatic disease using initial single-agent chemotherapy. Three studies have analyzed treatment of this group of patients in detail (Table 3).

Table 3 Treatment of Low-Risk Metastatic Gestational Trophoblastic Neoplasia with Single-Agent Chemotherapy

Reference	No. of Patients	Primary Remission %	Multiagent Chemotherapy %	Su: Res:	Survival %

DuBeshter et al. [16]	48	48	15	12	100
Soper et al. [17]	52	60	4	2	100
Roberts & Lurain [18]	92	67	1	0	100

Modified from Roberts and Lurain [18]

DuBeshter *et al.* [16] at the New England Trophoblastic Disease Center treated 48 patients with low-risk metastatic gestational trophoblastic neoplasia with single-agent methotrexate or actinomycin-D between 1965 and 1990. All patients achieved sustained remission, although 51% required a second single-agent regimen, 14% needed multiagent chemotherapy, and 12% underwent resection of resistant tumor foci. Multiagent chemotherapy was more often required following the use of methotrexate—folinic acid protocols (30%) than single-agent methotrexate or actinomycin D (4%).

Soper *et al.*[17] at the Southeastern Regional Trophoblastic Disease Center retrospectively analyzed 52 patients with low-risk metastatic GTN treated with five-day cycles of intramuscular methotrexate repeated every 12—14 days. Primary remission was achieved in 60%. Therapy was changed because of drug resistance in 19% and toxicity in 21%. Only two patients (4%) required multiagent therapy, one of whom also underwent hysterectomy. Pre-therapy hCG >10, 000 IU/L was associated with development of drug resistance. Sustained remission was achieved in all patients.

At the Brewer Center, we treated 92 low-risk metastatic disease patients between 1962 and 1992 [18]. Initial treatment consisted of methotrexate (61), actinomycin D (4), alternating methotrexate and actinomycin D (5), and hysterectomy with single-agent chemotherapy (22). All patients were cured; 72 (78.3%) required only one drug with

or without hysterectomy, 19 (20.4%) received two drugs sequentially, and only one (1.1%) needed multiagent chemotherapy. Toxicity was relatively mild and easily remedied, necessitating a change in chemotherapeutic agents in just 10.7% of patients. Patients in whom initial therapy failed tended to be older, had higher pretreatment hCG levels and WHO scores, and had larger vaginal metastases than those successfully treated.

In 2012, we updated our results on treatment of low-risk GTN at the Brewer Trophoblastic Disease Center from 1979 to 2009. Of 258 FIGO-defined low-risk patients treated with first-line methotrexate chemotherapy, 59 (16%) had metastatic disease. The patients with stage II-III disease had an increased rate resistance to initial single-agent methotrexate (31%) when compared to patients with stage I disease (17%) (p=.018), however, all 59 low-risk metastatic disease patients were cured and only 15% required multiagent chemotherapy [19].

In summary, single-agent chemotherapy with methotrexate or actinomycin D, given according to one of the protocols described in Table 3, is the preferred treatment for patients with low-risk metastatic GTN. Single-agent chemotherapy is safe, highly effective, and avoids the greater morbidity associated with multiagent chemotherapy. With appropriate initial classification and selection of patients as well as proper administration of treatment, cure should approach 100%.

It is apparent, however, that 30-50% of patients in this category will develop resistance to the first chemotherapeutic agent and require alternate treatment. It is, therefore, very important to carefully

monitor patients undergoing treatment for evidence of drug resistance (plateau or rise in hCG level and/or development of new metastases) so that a change to a second agent can be made at the earliest possible time. Approximately 5-15% of patients treated for low-risk metastatic disease with sequential single-agent chemotherapy will require multi-agent chemotherapy with or without surgery to achieve complete remission.

Surgery may be necessary to eradicate persistent disease in the uterus, if all evidence of metastatic disease has disappeared and the hCG remains elevated despite repeated courses of chemotherapy, or rarely to excise isolated pulmonary metastases [12,17,19]. Hysterectomy may also be incorporated into the initial management of the patient with low-risk metastatic disease resulting in a higher likelihood of single-agent chemotherapy success, fewer courses of chemotherapy, and a shorter duration of treatment [12].

17.2 HIGH-RISK METASTATIC DISEASE

Patients categorized as having high-risk metastatic gestational trophoblastic neoplasia (stages II-III, score $\geq$ 7 and stage IV) should be treated with initial multiagent chemotherapy with or without adjuvant radiotherapy or surgery. Overtime, the multiagent chemotherapy regimen of choice for high-risk disease has changed [20]. Until the mid-1980s, the primary multi-drug regimen used as initial therapy in these patients was MAC: methotrexate, actinomycin D, and cyclophosphamide or chlorambucil. Reported cure rates ranged

from 63% to 71% [12,21-23]. In the mid-1970s, Bagshawe and colleagues at Charing Cross Hospital in London introduced the seven-drug CHAMOCA protocol, employing cyclophosphamide, hydroxyurea, actinomycin D, methotrexate with folinic acid, vincristine and doxorubicin for the treatment of high-risk patients, and reported a primary remission rate of 82% [24]. However, in a randomized clinical trial comparing MAC and CHAMOCA for primary treatment of high-risk patients, the Gynecologic Oncology Group (GOG) found that the cure rate was higher in patients who were treated initially with the MAC regimen (95%) as compared with the CHAMOCA regimen (70%) and that the MAC regimen was also less toxic [25].

After discovery in the late 1970s that etoposide was a very effective chemotherapeutic agent for treatment of GTN, Newlands et al. from London formulated the EMA-CO regimen employing etoposide, high-dose methotrexate with folinic acid, actinomycin D, cyclophosphamide and vincristine (Table 4). They originally reported an 80% complete clinical response rate and 82% survival with minimal toxicity in 76 high-risk patients who had received no prior chemotherapy [26].

Table 4 EMA-CO Chemotherapy for High-Risk GTN

Day	Drug	Dose
1	Etoposide	100 mg/m² IV over 30 min
	Actinomycin D	0.5mg IV push
	Methotrexate	100 mg/m² IV push
		200 mg/m² IV in 1000 ml

		D5W over 12h
2	Etoposide	100 mg/m² IV over 30 mm
	Actinomycin D	0.5mg IV push
	Folinic acid	15mg IM or PO every 12 h for 4 doses
		starting 24 h after start of methotrexate
8	Cyclophosphamide	600 mg/m² IV infusion
	Vincristine	1.0 mg/m² IV push

EMA-CO = etoposide, high-dose methotrexate with folinic acid, actinomycin D,
cyclophosphamide and vincristine.
Repeat cycle on days 15, 16 and 22 (every 2 weeks).

Since then, complete response rates and long-term survival rates of

over 80% have been reported by several groups (Table 5). Indeed, a

retrospective comparison of MAC, CHAMOCA, and EMA-CO from

Korea demonstrated remission rates of 67.5%, 76.2%, and 90.6%,

respectively, validating EMA-CO as the most appropriate

chemotherapy protocol for the treatment of high-risk GTN [27].

Table 5 Treatment of High-Risk Metastatic Gestational Trophoblastic
Neoplasia with EMA-CO

	Primary Therapy				Complete	
	No. of	Complete Response	Survival	No	Response	Sur
Reference	Patients	%	%	Pati	%	
Newlands et al. [26]	72	80[a]	82	7	82	8
Bolis et al. [28]	17	94	88	1	71	6
Schink et al. [29]	12	83	100		-	
Soper et al. [30]	6	67	67	1	81	6
Quinn et al. [31]	35	--	89		--	
Bower et al. [32][b]	151	78	85	1:	79	9
Kim et al. [33]	96	--	91	6	--	7
Soto-Wright et al. [34] [c]	7	71	100	2	95	1
Matsui et al. [35] [c]	27	78	89	1	67	8
Escobar et al. [36]	25	--	94	2	--	9
Turan et al. [37]	23	82	91	1	90	9
Lu et al. [38]	45	78	93	(	78	
Cagayan [39]	56	72	86		-	

Modified from Lurain JR (2002) J. Reprod. Med. 47:451-457.
   a. Ten patients who died before response to EMA-CO could be assessed were
excluded.
   b. Includes patients reported by Newlands et al. [26].
   c. EMA only.

Early reports on the use of EMA-CO for treatment of high-risk

GTN confirmed the Charing Cross experience of high response rates

and survival. Bolis et al. [28] from Italy reported an initial complete

response rate of 94% and survival in 88% of 17 patients with high-risk disease treated primarily with EMA-CO. Only one patient failed to achieve an initial complete response, and three patients (19%) relapsed from remission. Schink et al [29] from the Brewer Center reported our initial results of a prospective study evaluating the efficacy and toxicity of EMA-CO for primary treatment of patients with high-risk metastatic GTN in 1992. Ten (93%) of the first 12 patients we treated had complete responses to EMA-CO. There was no life-threatening toxicity and neutropenia necessitating a one-week delay in treatment occurred in only 12% of treatment cycles. Soper and colleagues [30] treated 22 high-risk patients with EMA-CO. Four (67%) of six patients receiving primary therapy and 13 (81%) of 16 patients receiving secondary therapy had complete responses. Six (35%) of the 17 complete responders developed recurrences within six months of therapy. Overall, 15 patients (68%) remained without evidence of disease after completing therapy. Quinn et al. [31] from Australia treated 35 patients with metastatic trophoblastic disease with EMA-CO. Most of the patients had high-risk features and all had WHO scores>4. The survival rate was 89%. All four deaths occurred in patients who had hepatic and/or central nervous system metastases, one of whom had a placental site tumor.

Bower et al. [32] updated the Charing Cross-London experience using EMA-CO to treat 272 women with high-risk disease in 1997. There were 11 (4%) early deaths, 214 (78%) complete remissions to EMA-CO, and an additional 33 (12%) complete responses to subsequent cisplatin-based chemotherapy and surgery, yielding an

overall survival rate of 88%. Kim et al. [33] from Korea treated 165 high-risk patients with the EMA-CO regimen. Of 96 patients who received EMA-CO as first-line treatment, 87 (91%) had complete remissions, whereas the complete remission rate was only 74% in the 69 patients who received EMA-CO as second-or third-line treatment. The overall survival rate was 84%. Factors that predicted poor prognosis were: (1) tumor age greater than 12 months, (2) metastases to more than two organ systems, and (3) incomplete previous treatment including unplanned operation and inadequate chemotherapy. Similarly, Turan et al. [37] from Turkey, Lu et al. [38] from China, and Cagayan [39] from the Philippines reported complete response rates of 82%, 78% and 72% and survival rates of 91%, 93% and 86%, respectively, when the EMA-CO chemotherapy regimen was used as primary therapy for the treatment of high-risk GTN.

Two groups reported on the use of an EMA protocol without CO for the treatment of high-risk disease, yielding similar results. Soto-Wright, et al [34] from the New England Trophoblastic Disease Center were able to achieve remissions in 5 (71%) of 7 patients treated primarily with EMA and in 21 (95%) of 22 patients treated secondarily with EMA, eventually placing all 29 patients into remission. Matsui, et al [35] from Japan reported obtaining complete remissions using EMA in 21 (78%) of 27 patients who were treated primarily and in 8 (67%) of 12 patients who had received prior chemotherapy; overall survival was 87%.

In 2003, we updated our experience with EMA-CO for treatment of high-risk GTN at the Brewer Trophoblastic Disease Center from

1986 to 2001[36]. Of the 45 patients treated with EMA-CO (25 as primary therapy and 20 as secondary therapy), 32 (71%) had a complete response, 9 (20%) developed resistance but were subsequently placed into remission with platinum-based chemotherapy, and 4 (9%) died of widespread metastatic disease. An additional five patients were treated primarily with EMA-CO for high-risk metastatic GTN through 2005. All were cured, resulting in an overall survival of 93% (28/30) when EMA-CO was used as primary therapy from 1986 – 2005 [40].

In 2010, we reported on a series of 40 patients with metastatic high-risk GTN strictly defined by FIGO criteria (stage II-IV, risk factor score of $\geq$ 7)who were treated at the Brewer Center with EMA-CO between 1986 and 2009, including 26 who were treated primarily and 14 who were treated secondarily. The overall survival was 90% (36/40): 92% (24/26) for primary treatment and 86% (12/14) for secondary treatment. Durable complete response to initial EMA-CO chemotherapy was achieved in only 21 patients (53%), while 15 additional patients (37%) were cured with subsequent platinum-based chemotherapy with or without surgery. Complete response to initial therapy and survival were both significantly influenced by FIGO stage and risk factor score. All patients who died had stage IV disease and risk factor scores $\geq$ 12 [41].

The high response rates and good long-term survival, as well as the minimal acute and cumulative toxicity, associated with the EMA-CO protocol make it, or some variation of it, the current initial treatment of choice for patients with high-risk metastatic gestational

trophoblastic neoplasia. Colony-stimulating factors should be used when necessary to avoid treatment delays, since the success of the EMA-CO regimen seems to depend on treatment given at short intervals without interruption. Therefore, if any neutropenia-associated delay is encountered, we recommend that granulocyte colony stimulating factor (G-CSF), 300 mcg subcutaneously, be administered on days 9-14 of each subsequent treatment cycle. Chemotherapy should be continued until three consecutive weekly normal hCG values are reached and two to four courses of EMA-CO have been given after the first normal hCG level.

In 2013, the Charing Cross-London group reported on 140 high-risk patients treated with EMA-CO between 1995 and 2010, yielding an overall survival of 94.3%. Induction chemotherapy with low-dose weekly etoposide and cistplatin for 1-2 cycles before EMA-CO was given to 23% of high-risk patients who had extensive disease in the chest, liver or brain, FIGO scores >12, and/or hCG levels >1 million in an attempt to reduce early deaths. The overall cure rate in these highest-risk patients was 88%, and there was only 1 early death (0.7%) in this group of 140 patients compared to an early death rate of 7.2% in 151 patients treated with EMA-CO prior to 1995 [42].

Primary treatment of high-risk patients using cisplatin/etoposide combinations has also been reported [43-45], yielding remission rates of 67%-93%. However, when cistplatin is used as a component of primary therapy, significant acute and cumulative toxicity often occurs before a complete response is accomplished and may compromise the ability to deliver adequate salvage therapy. In one study, 83% of

patients experienced grade 3-4 neutropenia, 40% of patients required treatment changes related to ototoxicity, and 67% of patients had to have dose reductions or modifications [44].

Approximately one-third of patients with high-risk GTN will have an incomplete response to first-line chemotherapy or will relapse from remission and require secondary chemotherapy [46-48]. The EMA-EP regimen (Table 6), substituting etoposide and cisplatin for cyclophosphamide and vincristine in the EMA-CO regimen seems to be the most appropriate therapy for patients who have responded to EMA-CO but have plateauing low hCG levels or who have developed re-elevation of hCG levels after having had a complete response to EMA-CO [49-51].

Table 6 EMA-EP Regimen for Incomplete Response to or Remission Relapse after EMA-CO for High-Risk GTN

Day	Drug	Dose
1	Etoposide	100 mg/m² IV over 30 min
	Actinomycin D	0.5mg IV push
	Methotrexate	100 mg/m² IV push then
		200 mg/m² IV infusion in 1000 mL D5W
2	Etoposide	100 mg/m² IV over 30 mm
	Actinomycin D	0.5mg IV push
	Folinic acid	15mg IM or PO every 12 h for 4 doses
		starting 24 h after start of methotrexate
8	Etoposide	100 mg/m² IV over 30 minutes
	Cisplatin	75 mg/m² IV infusion

Repeat cycle on days 15, 16 and 22 (every 2 weeks).
Administer filgrastim 300μg SQ days 9-14 of each treatment cycle.

Patients who have clearly developed resistance to methotrexate-containing treatment protocols should be treated with drug combinations employing a platinum agent and etoposide with bleomycin, ifosfamide, or paclitaxel. The BEP (bleomycin, etoposide, cisplatin), VIP (etoposide, ifosfamide, cisplatin) and ICE (ifosfamide, carboplatin, etoposide), and TP/TE (paclitaxel-cisplatin/paclitaxel-

etoposide) protocols (Tables 7-10) have all produced cures in patients

who have failed EMA regimens [52-56].

Table 7 BEP Regimen for Refractory Metastatic High-Risk GTN

Day	Drug	Dose
1	Bleomycin	30 U IV infusion over 24 h
	Etoposide	100 mg/m² IV push over 30 min
	Cisplatin	20 mg/m² IV infusion
2-4	Etoposide	100 mg/m² IV over 30 mm
	Cisplatin	20 mg/m² IV infusion
8	Bleomycin	30 U IV push
15	Bleomycin	30 U IV push

Repeat cycle every 3 weeks.
Monitor for bleomycin toxicity with pulmonary function tests; maximum bleomycin dose 270 U.
Administer pegfilgrastim 6 mg SQ day 8 or filgrastim 300 µg SQ days 6-14.

Table 8 ICE Regimen for Refractory Metastatic High-Risk GTN

Day	Drug	Dose
1	Ifosfamide	1.2 g/m² IV over 30 min
	Mesna	120 mg/m² IV bolus just prior to ifosfami
		1.2 g/m² IV 12-h infusion after ifosfamide
	Carboplatin	AUC 4 IV
	Etoposide	75 mg/m² IV over 30 min
2-3	Ifosfamide	1.2 g/m² IV over 30 min
	Mesna	1.2 g/m² IV 12-h infusion after ifosfamide
	Etoposide	75 mg/rn² IV over 30 min

Repeat cycle every 3 weeks.
Administer pegfilgrastim 6 mg SQ day 4 or filgrastim 300 µg SQ days 6-14.

Table 9 VIP Regimen for Refractory Metastatic High-Risk GTN

Day	Drug	Dose
1-4	Ifosfamide	1.2 g/m² IV over 30 min
	Mesna	120 mg/m² IV bolus just prior to ifosfami
		1.2 g/m² IV 12-h infusion daily after each
	Etoposide	75 mg/m² IV over 30 min
	Cisplatin	20 mg/m² IV infusion

Repeat cycle every 3 weeks.
Administer pegfilgrastim 6 mg SQ day 5 or filgrastim 300 µg SQ days 6-14.

Table 10 TP/TE Regimen for Refractory Metastatic High-Risk GTN

Day	Drug	Dose
1	Paclitaxel	135 mg/m² IV
	Cisplatin	75 mg/m² IV
15	Paclitaxel	135 mg/m² IV
	Etoposide	150 mg/m² IV

Repeat cycle every 4 weeks.
Administer pegfilgrastim 6 mg SQ day 2 and 16 or filgrastim 300 µg SQ days 6-14 and days 20-28.

At the Brewer Trophoblastic Disease Center, we initially reported in 2005 on 26 patients with persistent/relapsed high-risk GTN who received secondary platinum-based salvage chemotherapy: 19 (73%) had a complete response and 16 (61.5%) survived [57]. Nine (90%) of 10 patients who failed primary treatment with EMA-CO had a complete clinical response to secondary chemotherapy with EMA-EP (3) or BEP (6), and six (60%) were placed into lasting remission. Ten (63%) of 16 patients who failed primary treatment with methotrexate/actinomycin D-based chemotherapy without etoposide had complete clinical responses to BEP (8), VIP (1) or ICE (1), and 10 (63%) were cured. In 2012, we again noted the importance of salvage chemotherapy in the management of women with high-risk GTN who had developed resistance to EMA-CO at the Brewer Center [58]. The overall complete response rate to etoposide/platinum-based salvage chemotherapy regimens was 63% (58% EMA-EP, 69% for BEP, 50% for VIP, 67% for ICE, and 67% for TP/TE), and the survival rate was 82%. Factors found to have a significant adverse effect on survival were hCG level >100 IU/L at the start of salvage therapy, number of metastatic sites >2, and FIGO stage IV disease.

Wang et al from Charing Cross reported on the alternating biweekly regimen of paclitaxel with cistplatin or etoposide (TP/TE) to treat patients with EMA-CO or EMA-EP resistant GTN. The complete response rate to the chemotherapy protocol was only 19%, however, 44% of patients were ultimately cured [59].

17.3 BRAIN METASTASES

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Brain metastases occur in approximately 10% of patients with metastatic high-risk GTN. Although metastatic disease to the central nervous system is regarded as a very poor prognostic indicator, cure ratesr of 38%-80% have been reported, depending on patient symptoms as well as number, size and location of the brain lesions [60-66]. Most centers employ whole brain irradiation (3000 cGy in 200 cGy fractions) given simultaneously with the initiation of systemic chemotherapy. During radiotherapy, the methotrexate infusion dose in the EMA-CO protocol is increased to $1gm/m^2$ and folinic acid is given every 12 hours for 3 days starting 32 hours after the infusion begins. An alternative to whole brain irradiation is the use of intrathecal as well was high-dose intravenous methotrexate with or without brain surgery or stereotactic irradiation.

Yordan et al.[60] reported that death due to brain involvement occurred in 11 (44%) of 25 patients (44%) treated with chemotherapy alone, but in none of 18 patients treated with brain irradiation and chemotherapy. Evans et al. [45] at the Southeastern Regional Trophoblastic Disease Center reported on the treatment of 42 patients with brain metastases using brain irradation and chemotherapy. Of 16 patients who presented initially with evidence of brain lesions and no prior therapy, 12 (75%) were successfully treated. Only 5 (22%) of the 23 patients who had received prior therapy (5/13) or developed brain lesions while undergoing systemic chemotherapy (0/10) survived.

At the Brewer Center, we treated 26 patients with chemotherapy and whole brain irradiation for GTN metastatic to the brain between 1962 and 1994. The overall five-year actuarial survival rate was 51%:

100% (6/6) for patients with asymptomatic or minimally symptomatic brain disease at presentation, 39% (5/14) for patients with symptomatic brain metastases at presentation, and 17% (1/6) for patients who developed brain metastases during chemotherapy [62]. In 2012, we updated our results to include 11 additional patients treated for brain metastases from 1995-2009. Overall survival was 64% (7/11), including 50% (3/6) for patients who developed brain metastases during treatment [63].

As an alternative to whole brain irradiation, the Charing Cross Hospital group has recommended intrathecal along with high-dose intravenous methotrexate in the EMA-CO protocol. In 1989, they reported an 86% remission rate and 72% overall survival in patients with brain lesions using this intensive chemotherapy regimen [64]. A subsequent report from the same institution, noted a complete response rate of 100% with chemotherapy combined with surgical excision or radiosurgery compared to 62% with chemotherapy alone [65]. Bakri and associates at the New England Trophoblastic Disease Center reported achieving sustained remissions in 4 of 8 patients (50%) with brain metastases who were treated with cisplatin, etoposide, and actinomycin D chemotherapy combined with intrathecal methotrexate without brain irradiation [66].

17.4 LIVER METASTASES

Liver metastases occur in less than 10% of patients with metastatic GTN with reported survival rates ranging from 10% to 48% [67-73]. Most patients with liver metastases have extensive disease at multiple

sites when they present for treatment and this is the primary reason for treatment failure. Jones and colleagues [69] from Memorial Sloan-Kettering reported that all 10 patients who presented with concurrent brain and liver metastases died, whereas 3 (43%) of 7 patients with liver metastases but no brain lesions survived. Bakri et al. [70] were able to achieve remission in 5 (62.5%) of 8 patients with liver metastases treated with cisplatin, etoposide and actinomycin D as compared to their past experience of no survivors using MAC chemotherapy. At the Brewer Center, we reported an overall survival rate of 41% in 17 patients with hepatic metastases. Survival increased from 17% to 55% after the introduction of EMA-CO chemotherapy in 1986. The only factor that significantly predicted decreased survival was the presence or absence of concomitant intra-abdominal or brain metastases (11% vs 75%) [73].

17.5 ADJUVANT SURGICAL PROCEDURES

Adjuvant surgical procedures, especially hysterectomy and thoracotomy, often play an important role in removing chemotherapy-resistant disease or treating complications in selected patients with persistent or recurrent metastatic gestational trophoblastic neoplasia [12,74,75]. At the Brewer Center, 24 (48%) of 50 high-risk patients who received EMA-CO chemotherapy from 1986 to 2005 underwent 28 surgical procedures, including hysterectomy (17), pulmonary resection (5), salpingectomy (1), wedge resection of the uterus (1) and small bowel resection (1), as well as procedures strictly for control of hemorrhage (3). Twenty-one (87.5%) of these 24 patients who had

adjuvant surgical procedures as part of their treatment for high-risk GTN were cured [76].

Hysterectomy may be considered as part of primary therapy in selected patients with metastatic GTN who have small extrauterine tumor burdens and do no desire to maintain fertility, but the most frequent indications for hysterectomy are to remove chemotherapy-resistant disease in the uterus and to control excessive uterine bleeding. Lurain et al from the Brewer Center reported that 12 (86%) of 14 patients who had hysterectomy for resistant choriocarcinoma survived [76]. Mutch et al reported curing 10 (71%) of 14 patients who underwent hysterectomy as part of treatment for recurrent GTN [79]. The Sheffield-UK Trophoblastic Disease Center noted that 18 (82%) of 22 patients who underwent hysterectomy for chemotherapy-resistant uterine disease survived [78]. The Charing Cross-UK group reviewed the role of hysterectomy in 25 patients who developed resistance to initial chemotherapy or relapsed. The only 3 patients who died all had high-risk metastatic disease [79]. Although hysterectomy clearly has a place in the management of high-risk GTN, it is not often indicated in the primary management of patients with widely metastatic disease unless there is a large uterine tumor causing troublesome bleeding. It is also uncommon to see refractory disease only in the uterus with the use of contemporary multiagent chemotherapy.

Resection of pulmonary metastases via thoracotomy or thoracoscopy in carefully selected patients with drug-resistant GTN (solitary pulmonary nodule, no evidence of other metastatic or uterine

disease, hCG level <1000 IU/L) may also be curative. Tomoda et al. [80] were able to cure 14 (93%) of 15 patients who satisfied these criteria with pulmonary resection as compared to none of the patients who had one or more unfavourable factors. Xu, et al [81] reported 50% survival with resection of pulmonary metastatic choriocarcinoma in 43 drug-resistant patients. They noted improved survival in patients who had a solitary lung lesion without metastases to other organs as well as a good response to chemotherapy. Mutch et al. [77] reported that 4 of 9 patients (44%) who underwent thoracotomy with pulmonary wedge resection of resistant choriocarcinoma survived. Fleming et al [82] from the New England Trophoblastic Disease Center reported that thoracotomy was successful in eradicating drug-resistant pulmonary disease in 10 (91%) of 11 high-risk patients. Of the patients who survived, only one had disease outside the lung (brain metastasis) at the time of thoracotomy and all had solitary lung nodules as well as hCG levels below 1,500 IU/L. Of 15 patients who underwent pulmonary resection for drug-resistant high-risk metastatic GTN, at the Brewer Center from 1986-2014, 11 (73%) were cured. Prompt hCG regression within one to two weeks of surgical resection predicts a favourable outcome [80-82].

Surgery may also play a role in therapy for high-risk disease as a means of controlling tumor hemorrhage, relieving bowel or urinary obstruction, treating infection, or dealing with other life-threatening complications [74-76]. Selective angiographic embolization of the uterine arteries may also be employed to control uterine or pelvic tumor bleeding in lieu of surgical intervention [83].

17.6 SUMMARY

In summary, intensive multi-modality therapy with appropriate combination chemotherapy (EMA-CO or some variation of it), and adjuvant radiotherapy and surgery when indicated, will result in cure rates of 80—90% in patients with high-risk metastatic gestational trophoblastic neoplasia. It is clear, however, that approximately one-third of high-risk patients will fail first-line therapy or relapse following remission. Most of these patients will have a clinicopathologic diagnosis of choriocarcinoma, multiple metastases to sites other than the lung and vagina, and inadequate or failed previous chemotherapy, resulting in high ($\geq$12) FIGO scores [84]. Salvage chemotherapy with platinum agents, etoposide, and bleomycin, ifosfamide or paclitaxel, often combined with surgical resection of sites of persistent tumor, usually in the uterus or lungs, will result in cure of most of these high-risk patients [58]. High-dose chemotherapy with autologous bone marrow transplantation or peripheral stem cell support may play a role in the management of very selected high-risk patients [86].

REFERENCES

1.   Hertz R, Lewis J Jr, and Lipsett MD (1961). Five years experience with chemotherapy of metastatic choriocarcinoma and related tumors in women. *Am. J. Obstet. Gynecol.* 82: 631—640.

2.   Ross, GT, Goldstein, DP, Hertz, R. *et al.* (1965) Sequential use of methotrexate and actinomvcin D in the treatment of metastatic choriocarcinoma and related trophoblastic diseases in women. *Am. J. Obstet. Gynecol.* 93: 223—229.

3.   World Health Organization Scientific Group on Gestational Trophoblastic Diseases (1983) Gestational Trophoblastic Diseases *WHO Tech. Rep. Ser* 692.

4.   Ngan HYS, Bender H, Benedet JL, et al. (2003) Gestational trophoblastic neoplasia. FIGO staging and classification. *Int. J. Obstet. Gynecol.* 83:175-177.

5.   Brewer JL, Eckman TR, Dolkart RE, *et al.* (1971) Gestational trophoblastic disease: a comparative study of the results of therapy in patients with invasive mole and with choriocarcinoma. *Am. J. Obstet. Gynecol.* 109: 335—340.

6.   Hammond CB, Borchert LG, Tyrey L, *et al.* (1973) Treatment of metastatic trophoblastic disease: good and poor prognosis. *Am. J. Obstet. Gynecol.* 115: 451—457.

7.   Bagshawe KD. (1976) Risk and prognostic factors in

trophoblastic neoplasia. *Cancer* 38: 1373-1385.

8. Surwit EA and Hammond CB. (1980) Treatment of metastatic trophoblastic disease with poor prognosis. *Obstet. Gynecol.* 55: 565-570.

9. Jones WB and Lewis JL Jr. (1974) Treatment of gestational trophoblastic disease. *Am. J. Obstet. Gynecol.* 120: 14—20.

10. Lurain JR, Brewer JL, Torok EE, *et al.* (1982) Gestational trophoblastic disease: treatment results at the Brewer Trophoblastic Disease Center. *Obstet. Gynecol.* 60: 354-360.

11. Goldstein DP. (1972) The chemotherapy of gestational trophoblastic disease: principles of clinical management. *JAMA* 220: 209—513.

12. Hammond CB, Weed JC Jr and Currie JL. (1980) The role of operation in the current therapy of gestational trophoblastic disease. *Am. J. Obstet. Gynecol,* 136: 844—856.

13. Goldstein DP and Berkowitz RS. (1982) Nonmetastatic and low-risk metastatic gestational trophoblastic neoplasms. *Semin. Oncol.* 9: 191—197.

14. Jones WB. (1981) Management of low-risk metastatic gestational trophoblastic disease. *J. Reprod. Med.* 26: 213-217.

15. Berkowitz RS, Goldstein DP and Bernstein MR. (1986) Ten years' experience with methotrexate and folinic acid as primary therapy for gestational trophoblastic disease. *Gynecol. Oncol.* 23: 111—118.

16. DuBeshter B, Berkowitz RS, Goldstein DP, *et al.* (1991) Management of low-risk metastatic gestational trophoblastic

tumors. *J. Reprod. Med.* 36: 36—39.

17. Soper JT, Clarke-Pearson DL, Berchuck A, et al. (1994) Five-day methotrexate for women with metastatic gestational trophoblastic disease. *Gynecol. Oncol.* 54: 76—79.

18. Roberts JP and Lurain JR. (1996) Treatment of low-risk metastatic gestational trophoblastic tumors with single-agent chemotherapy. *Am. J. Obstet. Gynecol.* 174: 1917—1924.

19. Chapman-Davis E, Hoekstra AV, Rademaker AW, et al. (2012) Treatment of nonmetastatic and metastatic low-risk gestational trophoblastic neoplasia: factors associated with resistance to single-agent methotrexate chemotherapy. *Gynecol Oncol.* 125: 572—575.

20. Lurain JR. (2002) Advances in the management of high-risk gestational trophoblastic tumors. *J. Reprod. Med.* 47:451-459.

21. Berkowitz RS, Goldstein DP and Bernstein MR. (1984) Modified triple chemotherapy in the management of high-risk metastatic gestational trophoblastic tumors. *Gynecol. Oncol.* 19: 173—181.

22. Gordon AN, Gershenson DM, Copeland LJ, et al. (1985) High-risk metastatic gestational trophoblastic disease. *Obstet. Gynecol.* 65: 550—556.

23. Lurain JR and Brewer JI. (1985) Treatment of high-risk gestational trophoblastic disease with methotrexate, actinomycin D and cyclophosphamide chemotherapy. *Obstet. Gynecol.* 65: 830-834.

24. Begent RHJ and Bagshawe KD. (1982) The management of

high-risk choriocarcinoma. *Semin. Oncol.* 9: 198—203.

25. Curry SL, Blessing JA, DiSaia PJ, et al. (1989) A prospective randomized comparison of methotrexate, actinomycin D and chlorambucil (MAC) versus modified Bagshawe regimen in 'poor-prognosis' gestational trophoblastic disease. *Obstet. Gynecol.* 73: 357—62.

26. Newlands ES, Bagshawe KD, Begent RHJ, et al. (1991) Results with EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen in high risk gestational trophoblastic tumors, 1979—1989. *Br. J. Obstet. Gynecol.* 98: 550—557.

27. Kim SJ, Bae SN, Kim JH, et al. (1998) Effects of multiagent chemotherapy and independent risk factors in the treatment of high-risk GTT – 25 years experiences of KRI-TRD. *Int J Gynecol Obstet.* 60: S 85—96.

28. Bolis G, Bonazzi C, Landoni F, et al. (1988) EMA/CO regimen in high-risk gestational trophoblastic tumor. *Gynecol. Oncol.* 31: 439—444.

29. Schink JC, Singh DK, Rademaker AW, et al. (1992) Etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine for the treatment of metastatic, high-risk gestational trophoblastic disease. *Obstet. Gynecol.* 80: 817—820.

30. Soper JT, Evans AC, Clarke-Pearson DL, et al. (1994) Alternating weekly chemotherapy with etoposide methotrexate-dactinomycin/ cyclophosphamide—vincristine for high-risk gestational trophoblastic disease. *Obstet. Gynecol.* 83: 113-117.

31. Quinn M, Murray J, Friedlander M, et al. (1994) EMACO in high-risk gestational trophoblastic disease; the Australian experience. *Aust. NZ J. Obstet Gynecol.* 34: 90-92.

32. Bower M, Newlands ES, Holden L, et al. (1997) EMA/CO for high-risk gestational trophoblastic tumors; results from a cohort of 272 patients. *J. Clin. Oncol.* 15:2636-2643.

33. Kim SJ, Bae SN, Kim JH, et al. (1998) Risk factors for the prediction of treatment failure in gestational trophoblastic tumors treated with EMA/CO regimen. *Gynecol. Oncol.* 71: 247-253.

34. Soto-Wright V, Goldstein DP, Bernstein MR, et al. (1997) The management of gestatioanl trophoblastic tumors with etoposide, methotrexate, and actinomycin D. *Gynecol. Oncol.* 64:156-159.

35. Matsui H, Suzuka K, Iitsuka Y, et al. (2000) Combination chemotherapy with methotrexate, etoposide, and actinomycin D for high-risk gestational trophoblastic tumors. *Gynecol. Oncol.* 78: 28-31.

36. Escobar PF, Lurain JR, Singh DK, et al. (2003) Treatment of high-risk gestational trophoblastic neoplasia with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine chemotherapy. *Gynecol. Oncol.* 91:552-557.

37. Turan T, Karacay O, Tulunay G, et al. (2006) Results with EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) chemotherapy in gestational trophoblastic neoplasia. *Int J Gynecol Cancer.* 16:1432-1438.

38. Lu WG, Ye F, Shen YM, et al. (2008) EMA-CO chemotherapy

for high-risk gestational trophoblastic neoplasia: clinical analysis of 54 patients. *Int J Gynecol Cancer.* 18:357-362.

39. Cagayan MSFA. (2012) High-risk gestational trophoblastic neoplasia: primary treatment with EMA-CO (etoposide, methotrexate, actinomycin D, cydophosphamide and vincristine) chemotherapy. *J Reprod Med.* 57:231-236.

40. Lurain JR, Singh DK, Schink JC. (2006) Primary treatment of metastatic high-risk gestational trophoblastic neoplasia with EMA-CO chemotherapy. *J. Reprod. Med.* 51:767-772.

41. Lurain JR, Singh DK, Schink JC. (2010) Management of metastatic high-risk gestational trophoblastic neoplasia FIGO stages II-IV: risk factor score $\geq$ 7. *J. Reprod. Med.* 55:199-207.

42. Alifrangis C, Agarwal R, Short D, et al. (2013) EMA/CO for high-risk gestational trophoblastic neoplasia: good outcomes with induction low-dose etoposide-cisplatin and genetic analysis. *J Clin Oncol.* 31:280-286.

43. Cyriac S, Rajendranth R, Sridevi V, Sagar TG. (2011) Etoposide cisplatin-etoposide, methotrexate, actinomycin D as primary treatment for management of very-high-risk gestational trophoblastic neoplasia. *Int J Gynecol Obstet.* 115:37-39.

44. Han SN, Amant F, Leunen K, et al. (2012) EP-EMA regimen (etoposide and cisplatin with etoposide, methotrexate, and dactinomycin) in a series of 18 women with gestational trophoblastic neoplasia. *Int J Gynecol Cancer.* 22:875-880.

45. Evan C, Pautier P, Duvillard P, et al. (2014) Actinomycin D, cisplatin, and etoposide regimen is associated with almost

universal cure in patients with high-risk gestational trophoblastic neoplasia.. *Eur J Cancer.* 50:2082-2089.

46. Yang J, Xiang Y, Wan X, et al. (2006) Recurrent gestational trophoblastic tumor: management and risk factors for recurrence. *Gynecol Oncol.* 103:587-590.

47. Ngan HY, Tam KF, Lam KW, et al. (2006) Relapsed gestational trophoblastic neoplasia: a 20-year experience.. *J. Reprod. Med.* 51:829-834.

48. Powles Y, Savage PM, Stebbing J, et al. (2007) A comparison of patients with relapsed and chemo-refractory gestational trophoblastic neoplasia. *Br J Cancer.* 96:732-737.

49. Newlands, ES, Mulholland PJ, Holden L, et al. (2000) Etoposide and cisplatin/etoposide, methotrexate and actinomycin D (EMA) chemotherapy for patients with high-risk gestational trophoblastic tumors refractory to EMA/cyclophosphamide and vincristine and patients presenting with metastatic placental site trophoblastic tumors. *J. Clin. Oncol.* 18: 854-859.

50. Sarwar N, Newlands ES, Seckl MJ. (2004) Gestational trophoblastic neoplasia: the management of relapsing patients and other recent advances. *Curr. Oncol. Rep.* 6:476-482.

51. Mao Y, Wan X, Lv W, Xie X. (2007) Relapsed or refractory gestational trophoblastic neoplasia treated with etoposide and cisplatin/etoposide, methotrexate, actinomycin D (EP/EMA) regimen. *Int J Gynecol Obstet.* 98:44-47.

52. Willemse PHB, Aalders JG, Bouma J, et al. (1988) Chemotherapy-resistant gestational trophoblastic neoplasia

treated successfully with cisplatin, etoposide, and bleomycin. *Obstet. Gynecol.* 71: 438-40.

53. Theodore C, Azab M, Droz J-P, et al. (1989) Treatment of high-risk gestational trophoblastic disease with chemotherapy combinations containing cisplatin and etoposide. *Cancer* 64: 1824-1828.

54. Azab M, Droz J-P, Theodore C, et al. (1989) Cisplatin, vinblastine, and bleomycin combination in the treatment of resistant high-risk gestational trophoblastic tumors. *Cancer* 64:1829—1832.

55. Sutton GP, Soper JT, Blessing JA, et al. (1992) Ifosfamide alone and in combination in the treatment of refractory malignant gestational trophoblastic disease. *Am. J. Obstet. Gynecol.* 167: 489—495.

56. Piamsomboon S, Kudelka AP, Termrungruanglert W, et al. (1997) Remission of refractory gestational trophoblastic disease in the brain with ifosfamide, carboplatin, and etoposide (ICE): first report and literature review. *Eur J. Gynecol. Oncol.* 18: 453-456.

57. Lurain JR, Nejad B. (2005) Secondary chemotherapy for high-risk gestational trophoblastic neoplasia. *Gynecol. Oncol.* 97:618-623.

58. Lurain JR, Schink JC. (2012) Importance of salvage therapy in the management of high-risk gestational trophoblastic neoplasia. *J. Reprod. Med.* 57:219-224.

59. Wang J, Short D, Sebire NJ, et al. (2008) Salvage chemotherapy

of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE). *Ann Oncol.* 19:1578-1583.

60. Yordan EL, Schlaerth J, Gaddis 0, Morrow CP. (1987) Radiation therapy in the management of gestational choriocarcinoma metastatic to the central nervous system. *Obstet. Gynecol.,* 69, 627—30.

61. Evans AC Jr, Soper JT, Clarke-Pearson DL, et al. (1995) Gestational trophoblastic disease metastatic to the central nervous system. *Gynecol. Oncol.* 59: 226-230.

62. Small W Jr, Lurain JR, Shetty RM, et al. (1996) Gestational trophoblastic disease metastatic to the brain. *Radiology* 200: 277-280.

63. Neubauer NL, Latif N, Kalakota K, et al. (2012) Brain metastasis in gestational trophoblastic neoplasia: an update. *J. Reprod. Med.* 57:288-292.

64. Rustin GJ, Newlands ES, Begent RH, et al. (1989) Weekly alternating etoposide, methotrexate and actinomycin D/vincristine and cyclophosphamide chemotherapy for the treatment of CNS metastases of choriocarcinoma. *J. Clin. Oncol.* 7: 900—904.

65. Newlands ES, Holden L, Seckl M, et al. (2002) Management of brain metastases in patients with high-risk gestational trophoblastic tumors. *J. Reprod. Med.* 47:465-471.

66. Bakri Y, Berkowitz RS, Goldstein DP, et al. (1994) Brain metastases of gestational trophoblastic tumor. *J. Reprod. Med.* 39:

179-184.

67. Wong LC, Choo YC, Ma HK. (1986) Hepatic metastases in gestational trophoblastic disease. *Obstet, Gynecol.* 67:107-111.

68. Wang YE, Song HZ. (1988) Liver metastases of choriocarcinoma. *Chin Med J.* 101:637-642.

69. Jones WB, Cardinale C, Lewis JL Jr. (1997) Management of high-risk gestational trophoblastic disease. The Memorial Hospital experience. *Int. J. Gynecol. Cancer .*7: 27-33.

70. Bakri YN, Subhi J, Amer M, et al. (1993) Liver metastases of gestational trophoblastic tumor. *Gynecol. Oncol.* 48: 110-113.

71. Crawford RA, Newlauds E, Rustin GJ, et al. (1997) Gestational trophoblastic disease with liver metastases. The Charing Cross experience. *Br J Obstet Gynecol.* 104:105-109.

72. Ahamed E, Short D, North B, et al. (2012) Survival of women with gestational trophoblastic neoplasia and liver metastases. Is it improving?. *J. Reprod. Med.* 57:262-269.

73. Barber EL, Schink JC, Lurain JR. (2014) Hepatic metastases in gestational trophoblastic neoplasia: patient charactersitics, prognositic factors, and outcomes. *J. Reprod. Med.* 59:199-203.

74. Soper JT. (1994) Surgical therapy for gestational trophoblastic disease. *J. Reprod. Med.* 39: 168—174.

75. Lurain JR. (2010) The role of surgery in the management of high-risk gestational trophoblastic neoplasia. Cytoreductive Surgery in Gynecologic Oncology: A Multidisciplinary Approach, Ed. Y. Yildirim, *Transworld Research Network,* Kerala, India.

76. Lurain JR, Singh DK, Schink JC. (2006) The role of surgery in the management of high-risk gestational trophoblastic neoplasia. *J. Reprod. Med.* 51:773-776.

77. Mutch DG, Soper JT, Babcock CJ, et al. (1990) Recurrent gestational trophoblastic disease. *Cancer 66*: 978-982.

78. Alazzam M, Hancock BW, Tidy J. (2008) Role of hysterectomy in managing persistent gestational trophoblastic disease. *J Reprod Med.* 53:519-524.

79. Doumplis D, Al-Khatib K, Sieunarine K, et al. (2007) A review of the management by hysterectomy of 25 cases of gestational trophoblastic tumors from March 1993 to January 2006. *Por J Obstet Gynecol* 114:1168-1171.

80. Tomoda Y, Arii Y, Kaseki S, et al. (1980) Surgical indications for resection of pulmonary metastases of choriocarcinoma. *Cancer* 46: 2723-2730.

81. Xu L-T, Sun C-F, Wang Y-E, et al. (1985) Resection of pulmonary metastatic choriocarcinoma in 43 drug-resistant patients. *Ann. Torca. Surg.* 39:257-259.

82. Fleming EL, Garrett L, Growdon WB, et al. (2008) The changing role of thoracotomy in gestational trophoblastic neoplasia at the New England Trophoblastic Disease Center. *J Reprod Med.* 53:493-498.

83. Lim AK, Agarwal R, Seckl MJ, et al. (2002) Embolization of bleeding residual uterine vascular malformations in patients with treated gestational trophoblastic tumors. *Radiology* 222:640-644.

84. Lurain JR, Casanova LA, Miller DS, et al. (1991) Prognostic

factors in gestational trophoblastic tumors: a proposed new scoring system based on multivariate analysis. *Am.J. Obstet. Gynecol.* 164: 611—616.

86.   El-Helw LM, Seckl MJ, Haynes R, et al.. (2005) High-dose chemotherapy and peripheral blood stem cell support in refractory gestational trophoblastic neoplasia. *Br J Cancer.* 93:620-621.