

Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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Incidence and epidemiology

Gestational trophoblastic disease (GTD) comprises a spectrum of disorders from the pre-malignant conditions of complete (CHM) and partial (PHM) hydatidiform moles through to the malignant invasive mole, choriocarcinoma (CC) and very rare placental site trophoblastic tumour/epithelioid trophoblastic tumour (PSTT/ETT). The malignant forms of the disease are also collectively known as gestational trophoblastic tumours or neoplasia (GTN). In the UK, all GTD cases are nationally registered, with central pathology review. The incidence is estimated at 1–3: 1000 pregnancies for CHM and 3: 1000 pregnancies for PHM, respectively, with other western countries reporting similar data [1]. GTD appears to be more frequent in Asia than in North America or Europe. This may be because of discrepancies between hospital- and population-based data, availability of central pathological review or may reflect dietary and genetic influences. An increased risk of molar pregnancy is seen in the very young (<16 years), but is most associated with advanced maternal age (>45 years) [1]. Following a molar pregnancy, the risk of a further CHM or PHM increases to ~1%. After two molar gestations, the risk of a third mole is 15%–20% and is not decreased by changing partners.

The frequency of CC and PSTT is less clear, since these can arise after any type of pregnancy. CC develops after around 1:50 000 deliveries, while recent data suggest that PSTT represents 0.2% of UK GTD cases [2]. GTN risk may also relate to hormonal factors since women with menarche after 12 years of age, light menstrual flow and prior use of oral contraceptives are at increased risk. Additionally, the subsequent risk of malignancy following a hydatidiform mole (HM) has been linked in some but not all series to oral contraceptives, if started while the human chorionic gonadotrophin (hCG) is still elevated [1]. This hormone is essential for the diagnosis, management and subsequent surveillance of GTD and details regarding hCG and its measurement are provided in [Box 1](#).

Box 1. hCG measurement

HCG comprises an alpha subunit common to all glycoprotein hormones including luteinising hormone (LH) and thyroid-stimulating hormone (TSH) and a specific beta subunit. Consequently, assays to detect hCG use antibodies directed against the beta subunit. In pregnancy, this subunit is usually intact and becomes hyperglycosylated particularly during the first trimester. In contrast, cancer-related beta hCG can exist in several different forms/fragments including nicked free beta, c-terminal peptide, hyperglycosylated and so it is essential that the hCG assay used to detect hCG in cancer patients can measure all forms of beta hCG equally well. There are currently many commercial hCG assays available that are very good for assessing hCG in pregnancy, but their ability to work well in cancer is less clear. Several reports indicate that some assays either fail to detect all the hCG isoforms/fragments or significantly under or over-read certain isoforms. This can lead to false-negative results and there are also several assays that appear to have particular problems with false-positive results. Clinicians need to be aware of these potential problems and when hCG results do not fit the clinical picture, they should measure the hCG on a different assay. When a false positive is suspected, assessment of the urine hCG can also be helpful as cross-reactive molecules in the blood that cause false positives rarely get into the urine. Consequently, a positive urine hCG excludes a false-positive serum result. Further details on hCG assays and monitoring in GTN are available in ref. [1].

diagnosis, genetics/molecular biology and pathology

diagnosis

CHMs and PHMs most commonly present with vaginal bleeding in the first trimester of pregnancy. Previously reported features such as anaemia, uterine enlargement, pre-eclampsia, hyperemesis, hyperthyroidism and respiratory distress are now

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rare [3], reflecting the introduction of routine ultrasonography in early pregnancy. Characteristic sonographic findings for CHM in the second trimester, of a heterogeneous mass ('snowstorm'), without foetal development and with theca-lutein ovarian cysts, are not seen in the first trimester, and ultrasonography is not diagnostically reliable [4]. Indeed, false positive and negative rates are high with ultrasound, especially for PHM, and histological examination is essential to achieve a correct diagnosis [4]. All products of conception from non-viable pregnancies must undergo histological examination regardless of ultrasound findings [5].

The safest method of evacuation is suction dilation and curettage (D&C) under ultrasound control to ensure adequate emptying of uterine contents and to avoid uterine perforation [1]. A proportion of women who miscarry or who undergo medical terminations will have unsuspected molar pregnancies. As histological examination is not routinely requested, the diagnosis of GTN can be delayed resulting in significantly greater morbidity [6]. Histological examination of every termination is impractical, and perhaps a simple measurement of the urine or serum hCG level 3–4 weeks post-treatment to ensure return to normal is indicated [6]. All women with a diagnosis of molar pregnancy require careful hCG monitoring to look for the recurrence of disease, suggesting malignant change indicated by a plateaued or rising hCG on three and two consecutive samples, respectively (see [Box 1](#) for details about hCG testing) [1]. Re-biopsy to confirm malignant change is not advised because of the risk of triggering life-threatening haemorrhage.

The other malignant forms of GTD, CC and PSTT/ETT can be much more tricky to diagnose as the disease can develop months or many years after a prior pregnancy with protean presentations possible. Although change in menstruation is frequent, it does not always occur. It is therefore essential to measure the hCG in any woman of childbearing age who has unexplained metastatic disease. Biopsy of lesions without the ability to control bleeding is highly risky in this very vascular disease and is not essential before commencing chemotherapy. However, where complete excision is possible this can provide useful histological confirmation of the diagnosis and material for genetic analysis (see below).

genetics/molecular biology

CHMs are usually diploid and androgenetic in origin, ~80% resulting from duplication of the haploid genome of a single sperm while 20% arise by dispermic fertilisation of an ovum (Figure 1A and B). In either case maternal chromosomes are lost before, or shortly after, fertilisation. However, while nuclear DNA is entirely paternal in CHM, mitochondrial DNA remains maternal in origin [1].

Recent evidence indicates that some patients with recurrent CHM have diploid biparental CHM (BiCHM) rather than the typical androgenetic CHM (AnCHM) (Figure 1C). In these cases, the molar phenotype is due to an autosomal recessive condition, familial recurrent HM (FRHM) that predisposes women to recurrent pregnancy loss, most usually CHM. Mutations in two genes have now been associated with this condition: *NLRP7* and, more rarely, *KHDC3L*. While women

with recurrent AnCHM are likely to have normal live births in subsequent pregnancies and benefit from conventional *in vitro* fertilisation, women with FRHM are unlikely to achieve a normal pregnancy except through ovum donation from an unaffected individual [7].

PHMs are almost always triploid, usually as a result of fertilisation of an apparently normal ovum by two sperm or occasionally a diploid sperm (Figure 1D). The existence of diploid PHM is unlikely, most reported cases representing misdiagnosed complete moles, hydropic abortions or twin pregnancies.

While most molar pregnancies are diploid CHM or triploid PHM, numerical and structural abnormalities have been reported in both CHM and PHM. In addition, CHM, and occasionally PHM, can be associated with a twin pregnancy with a coexistent normal twin [8]. The continuance of such twin pregnancies results in healthy babies in ~40% of cases, without an obvious increase in the risk of malignant change [8].

Since post-molar GTN is treated on a clinical, rather than pathological, diagnosis tumour tissue is rarely available for genetic analysis. However, where tissue is available from GTN, the genotype will reflect that of the causative pregnancy, having both maternal and paternal chromosomes if the tumour originated in a term pregnancy, hydropic abortion or PHM but only paternal genes if the causative pregnancy was a CHM. Since the interval from the causative pregnancy to the time of GTN diagnosis carries prognostic information, genotyping can be helpful particularly in patients with multiple pregnancies [1]. Genetics can also be important in the differential diagnosis between gestational and non-gestational tumours, such as lung and gastric cancers, that can occasionally present as CC, but will have a genotype reflecting that of the patient [9]. These non-gestational CC often initially respond to GTN-based therapies, but their outcome is invariably poor, reflecting the originating tissue [1].

pathology

All forms of GTD are derived from components of the normal human placenta; HM plus CC, and PSTT/ETT, representing abnormal counterparts of the villous and extravillous (interstitial) trophoblast, respectively. Most CHM and PHM have distinctive morphological characteristics, but it is recommended that cases of suspected GTD be reported by specialist histopathologists. CHMs show a characteristic villous architecture, associated with abnormal trophoblast hyperplasia, stromal hypercellularity, stromal karyorrhectic debris and collapsed villous blood vessels (Figure 2A). In contrast, PHMs show patchy villous hydropic change with scattered abnormally shaped irregular villi with trophoblastic pseudoinclusions and patchy trophoblast hyperplasia (Figure 2B) [10]. The morphological distinction between non-molar miscarriage, especially when associated with chromosomal abnormality, and PHM can sometimes be difficult, and ancillary techniques may be required including immunostaining with p57^{KIP2} (negative in CHM), ploidy analysis by *in situ* hybridisation or flow cytometry or molecular genotyping. Genotyping can also be useful in the identification of BiCHM, associated with FRHM, since most are pathologically indistinguishable from typical

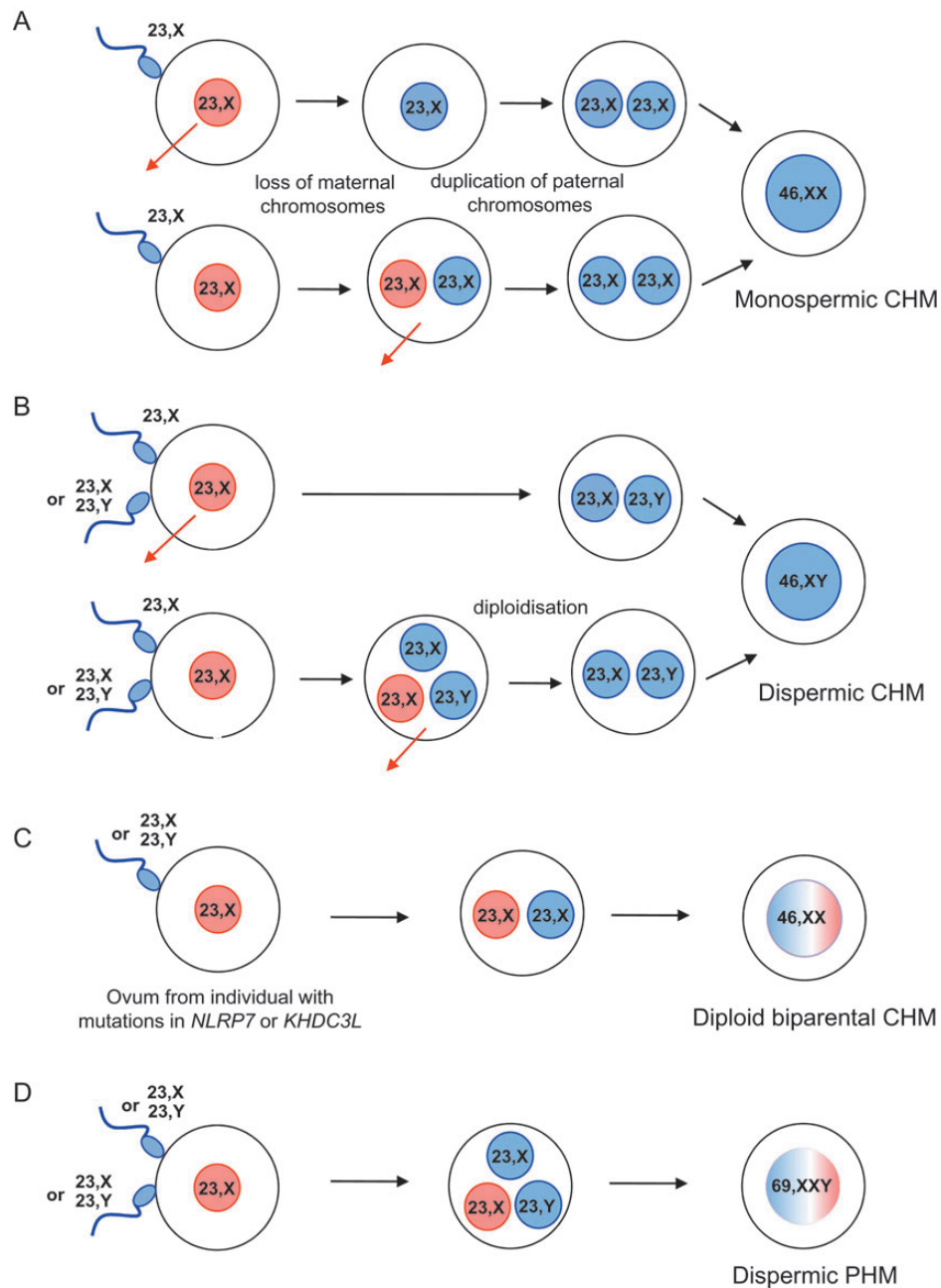


Figure 1. Genetic origins of molar pregnancies. (A) Monospermic CHMs arise as a result of pre- or post-fertilisation loss of the maternal nuclear genome and duplication of the paternal genome. These androgenetic diploids are 46,XX, 46,YY conceptuses being presumed non-viable. (B) Dispermic CHMs arise as a result of two sperm fertilising an ovum from which the maternal nuclear genome is lost. These androgenetic diploid conceptuses may be 46,XX or 46,XY. (C) Biparental CHMs occur in females who are homozygous, or a compound heterozygote, for mutations in *NLRP7* or *KHDC3L*. These biparental conceptuses are phenotypically CHM and may be 46,XX or 46,XY. (D) Dispermic PHMs arise as a result of fertilisation of a single ovum by two sperm. These diandric triploid conceptions may be 69,XXX, 69,XXY or 69,XYY.

AnCHM [11]. Unfortunately, there are no histological or immunohistochemical features that reliably predict which patients will subsequently develop persistent GTD (pGTD)/GTN, and hence all HMs require hCG surveillance.

CC (Figure 2C) are malignant hCG-producing epithelial tumours with differentiation towards a villous trophoblast phenotype, usually demonstrating central necrosis and characteristic biphasic architecture recapitulating cytotrophoblast-like cells and multinucleate, pleomorphic

syncytiotrophoblast-like areas. Intraplacental CC are rare but probably represent the source of metastatic CC, which occur following apparently uncomplicated term pregnancies. PSTT (Figure 2D) is the malignant equivalent of extravillous interstitial implantation site-like trophoblast and forms uterine lesions with less haemorrhage and necrosis, and lower hCG levels, than CC. The histological features show locally infiltrating nests and sheets of monomorphic, interstitial-type trophoblast, with moderate pleomorphism and mitotic activity,

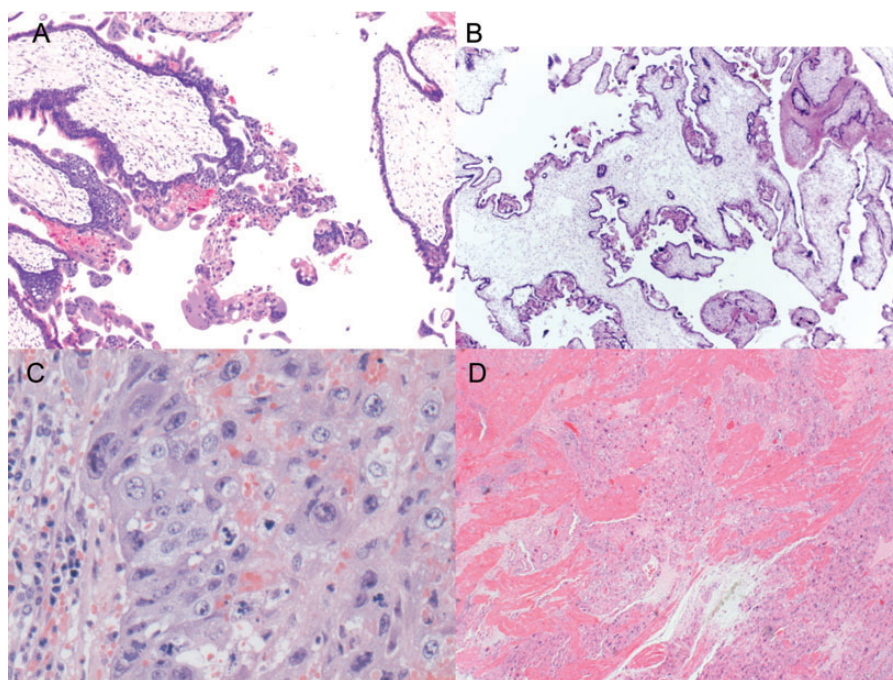


Figure 2. Photomicrographs demonstrating the various histopathological forms of GTD. (A) Complete hydatidiform mole, (B) partial hydatidiform mole, (C) choriocarcinoma and (D) placental site trophoblastic tumour. All are characterised by abnormal forms of trophoblast proliferation, associated with dysmorphic chorionic villi in CHM and PHM, but no villi and abnormal trophoblast invasion in CC and PSTT. (Original magnifications $\times 40$, $\times 20$, $\times 200$ and $\times 100$, respectively.)

and expression of human placental lactogen (hPL) and other extravillous trophoblast markers. A specific variant of PSST with distinctive hyalinisation and a slightly different immunohistochemical profile has been reported, ETT which is clinically thought to behave like PSTT [12].

staging and risk assessment

indications for treatment

Following suction curettage of a PHM, patients should have anti-Rhesus D prophylaxis. After any HM, the onset of malignant change, referred to as pGTD or post-mole GTN, is nearly always indicated by a plateaued or rising hCG (Table 1). In the UK, this occurs after 15% and 0.5%–1% of CHM and PHM, respectively [1]. In other countries, these rates may be higher, possibly reflecting differences in hCG assays, hCG criteria for the diagnosis of GTN, lack of whole population demographics or, less likely, a genuine difference in disease biology. The precise hCG surveillance protocol varies by country, but principles are similar. In the UK, serum and urine hCG is measured two weekly until normal and then monthly in urine [1]. The durations of monitoring once the hCG is normal also vary between countries, reflecting uncertainty around the importance of a very low risk of disease recurrence once the hCG is normal. Women completing the UK scheme have an estimated 1:2000 chance of missed disease [13], but the risk is already very low with the first normal hCG value even for CHM. The UK indications for commencing chemotherapy are listed in Table 1 and are broadly similar to those of the International Federation of Gynecology and Obstetrics (FIGO) [14]. The

Table 1. UK indications for chemotherapy following the diagnosis of GTD

Indications for chemotherapy
Plateaued or rising hCG after evacuation ^a
Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage
Histological evidence of choriocarcinoma
Evidence of metastases in the brain, liver or gastrointestinal tract, or radiological opacities of >2 cm on chest X-ray
Serum hCG of $\geq 20\,000$ IU/l >4 weeks after evacuation, because of the risk of uterine perforation
Raised hCG 6 months after evacuation even if still falling (now omitted [15])

^aPlateaued or rising is defined as four or more equivalent values of hCG over at least 3 weeks (days 1, 7, 14 and 21) and two consecutive rises in hCG of 10% or greater over at least 2 weeks (days 1, 7 and 14), respectively.

commonest is a plateaued or rising hCG, but others include a tissue diagnosis of CC and spread to other organs. However, our UK experience indicates that the disease is also unlikely to spontaneously remit if the hCG is $>20\,000$ IU/l 1 month after HM evacuation (also associated with an increased risk of uterine perforation) or there are lung or vaginal metastasis of >2 cm (smaller lesions may spontaneously regress) [1]. In addition, in the UK, chemotherapy is started to help stop heavy bleeding that requires transfusion even if the hCG is falling. Interestingly, recent data have overturned the previous UK and FIGO guidance that women who continue to have a falling hCG 6 months after uterine evacuation automatically need chemotherapy. Indeed, the hCG spontaneously normalised in

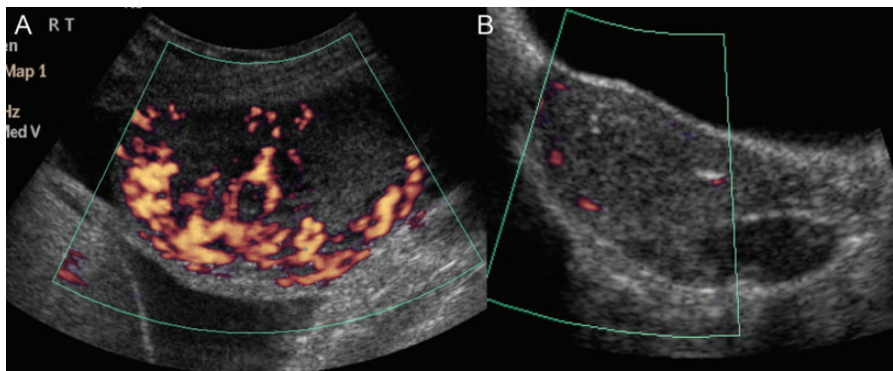


Figure 3. Pelvic Doppler ultrasonography of persisting GTN following a HM. (A) Pre-chemotherapy. (B) Post-chemotherapy. (Reprinted from ref. [1], Copyright 2010, with permission from Elsevier.)

Imaging investigations in GTN

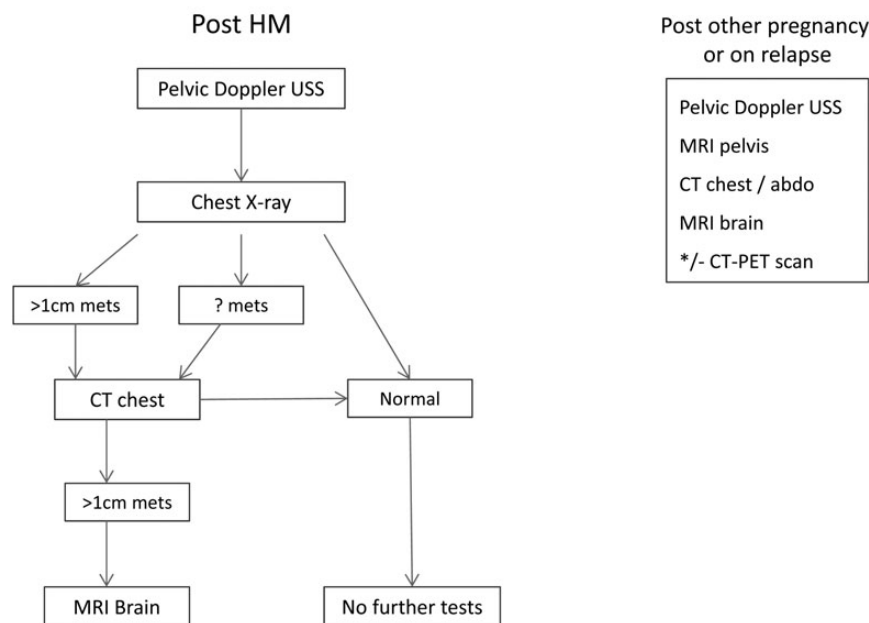


Figure 4. Algorithm of imaging investigations for patients with GTN following a HM on hCG surveillance (left-hand panel) or after any other type of pregnancy (right-hand panel). USS, ultrasound scan; CT, computerised tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; –ve, negative; +ve, positive; mets, metastases.

all such individuals left on surveillance [15]. Thus, this indication for chemotherapy has now been removed from UK guidelines.

staging investigations and treatment stratification after a molar pregnancy

Most patients developing GTN post-HM are detected early via hCG monitoring and so extensive investigation is rarely required. Information to determine therapy can be obtained from the clinical history, examination, measurement of serum hCG and a Doppler pelvic ultrasound to confirm the absence of a pregnancy, to measure the uterine size/volume, spread of disease within the pelvis and its vascularity (Figure 3). The latter assessed by the Doppler pulsatility index is an independent prognostic factor for resistance to single-agent methotrexate

(MTX) therapy [16] and is now being evaluated in a prospective trial. Pulmonary metastases are most common, so a chest radiograph is essential [17]. Computed tomography (CT) of the chest is not required if the chest X-ray (CXR) findings are normal, since discovery of micrometastases, which may be seen in ~40% of patients, does not influence outcome [18]. However, if lesions are noted on CXR, magnetic resonance imaging (MRI) of the brain and CT body are indicated (Figure 4) to exclude more widespread disease involving, for example, the brain or liver, which would significantly alter management.

FIGO reports data on GTN using prognostic scoring and anatomic staging systems (Table 2) [19]. Since 2002, all physicians treating GTN should use this system to enable the comparison of data. The prognostic score predicts the potential for developing resistance to single-drug chemotherapy with MTX or actinomycin D (ActD). A score of 0–6 and ≥ 7 indicates

Table 2. FIGO 2000 scoring system for GTN

Prognostic factor	Score			
	0	1	2	4
Age (years)	<40	≥40	–	–
Antecedent pregnancy (AP)	Mole	Abortion	Term	–
Interval (end of AP to chemotherapy in months)	<4	4–6	7–12	>12
hCG (IU/l)	<10 ³	10 ³ –10 ⁴	10 ⁴ –10 ⁵	>10 ⁵
Number of metastases	0	1–4	5–8	>8
Site of metastases	Lung	Spleen and kidney	GI tract	Brain and liver
Largest tumour mass	–	3–5 cm	>5 cm	–
Prior chemotherapy	–	–	Single drug	≥2 drugs

The total score for a patient is obtained by adding the individual scores for each prognostic factor. Low risk, 0–6; high risk, ≥7. PSTT should not be scored and instead requires staging. Stage I, disease confined to the uterus; stage II, disease extending into the pelvis; stage III, disease spread to lungs and/or vagina; stage IV, all other metastatic sites including liver, kidney, spleen and brain. (Reprinted [19] Copyright 2002, with permission from Elsevier for the International Federation of Gynecology and Obstetrics.)

a low and high risk of resistance, respectively. The latter has almost no chance of being cured with single-drug therapy and requires multi-agent treatment. The anatomical staging does not help with determining therapy, but provides additional information to help clinicians who compare results between centres. The variables that are assessed in the prognostic score include: (i) tumour volume (hCG level, size of metastases and number of metastases), (ii) site of involvement, (iii) prior chemotherapy resistance and (iv) duration of disease from antecedent pregnancy (Table 2) [19].

staging investigations for CC and PSTT/ETT

Women who present with an elevated hCG and suspected GTN (CC or PSTT/ETT) following a prior pregnancy require much more extensive staging investigations, which include a contrast enhanced CT of the chest and abdomen, MRI of the brain and pelvis, a Doppler ultrasound of the pelvis and may benefit from a lumbar puncture to assess the cerebrospinal fluid to serum hCG ratio. The latter if more than 1:60 suggests occult central nervous system disease [1]. In addition, where there is doubt over the clinical diagnosis, tissue should be obtained and genetic analysis undertaken to confirm the gestational origin of the tumour through the presence of paternal genes. For CC, the FIGO scoring/staging system is the same as described above. However, PSTT/ETT has a discrete biological behaviour with less hCG production, slower growth, late metastasis and slightly less chemosensitivity. Consequently, the scoring system is not valid for PSTT/ETT, but FIGO staging is used to help adapt treatment intensity (see below). Some investigators have recently started using positron emission tomography (PET)/CT imaging, but experience is still quite limited. It appears that this imaging modality is more helpful in relapsed disease to identify sites for resection and, as with other cancers, is prone to both false-positive and false-negative results [1].

management of low-risk disease

About 95% of patients with HM who develop GTN are low risk (score 0–6). In women with stage I disease apparently confined to the uterine cavity, the role of second D&C in reducing the

need for chemotherapy remains controversial. UK results indicate that this procedure is only valuable if the hCG is <5000 IU/l with disease in the cavity rather than myometrium. Indeed, the low efficacy of a second D&C, small risks of introducing infection, causing haemorrhage and uterine perforation should be balanced against the almost 100% cure rate and relative safety of chemotherapy (reviewed in [1]). Sometimes patients with stage I GTN who have completed their families request hysterectomy, which, although possible, may not completely obviate the need for chemotherapy.

Consequently, for nearly all low-risk GTN patients, single-agent chemotherapy with either MTX or ActD is the preferred treatment. A variety of regimens have been developed, which in non-randomised, mostly retrospective, studies demonstrate a 50%–90% chance of inducing remission [20]. This variability reflects differences in dose, frequency and route of administration as well as criteria used to select patients for therapy [17]. Some investigators have argued that more intense therapies given daily over 5–8 days every 2 weeks are superior to treatments given once every 2 weeks [21]. Others have suggested that ActD is more likely to induce remission than MTX. The few randomised studies to address some of these issues [22] have been underpowered and compared regimens that are not frequently used internationally [20]. Consequently, a new larger international randomised trial has recently commenced comparing the more commonly used MTX regimens in Europe/many parts of the world (Table 3) and some centres elsewhere [MTX 0.4 mg/kg (maximum 25 mg) IV d1–5 every 2 weeks] [23] with ActD 1.25 mg/m² IV every 2 weeks. Importantly, patients failing first-line therapy, usually because of resistance, can be easily salvaged with second and occasionally third-line chemotherapy so that the overall survival (OS) is ~100% [23–25]. As survival is so high, it seems sensible to start with the least toxic therapy first to minimise the exposure of patients to more harmful treatments.

The MTX with folinic acid rescue (MTX/FA) regimen developed at Charing Cross Hospital (Table 3) is effective, well-tolerated and unlike ActD, does not induce hair loss, so MTX/FA has been widely adopted [24]. After a short stay in hospital to monitor for bleeding complications, most of the patients can

be treated at home, with their general practitioner, or in their nearest hospital depending on local health service arrangements. About 2% of women suffer mouth ulcers, sore eyes or rarely pleuritic or peritoneal pains from serositis [24]. During chemotherapy, the hCG should ideally be measured at least once per week, so that at least two samples with a plateau or rise are available to enable an early decision regarding the onset of resistance indicating a need for a change in therapy. In those developing resistance to MTX/FA, a switch to ActD or combination agent chemotherapy depending on whether the hCG was <300 or >300 IU/l, respectively, will cure nearly all remaining women [25]. Chemotherapy should be continued until the hCG is normal and then for a further 6 weeks (Figure 5). The latter helps to eliminate any residual tumour cells and to minimise the chances of relapse [26]. Indeed, non-randomised data suggest that reducing the consolidation therapy by just one cycle doubles the risk of relapse [26]. In view of these data, the Dutch have recently moved from giving two to now using three consolidation cycles. Only 30% of patients scoring 5–6 can expect to be cured with low-risk therapy [1]. Consequently, it would be helpful to refine the FIGO scoring system, so that the 70% of women in this group who develop MTX/FA resistance could be identified initially for more intensive therapy. It is possible that the vascularity seen on

Doppler ultrasound may help [16]. Moreover, recent data indicate that women in this category with an hCG of >400 000 IU/l are unlikely to be cured by MTX/FA and so multi-agent treatment should be given from the outset [27]. Other promising strategies to identify patients with drug resistance at an early time-point during initial therapy have employed normograms and hCG kinetic analyses [28, 29].

management of high-risk GTN

Patients scoring of ≥ 7 (Table 2) are at high risk of developing drug resistance and so are very unlikely to be cured with single-agent chemotherapy. Consequently, several different multi-agent therapies have been developed including: MTX, FA and ActD (MFA); MTX, ActD, cyclophosphamide, doxorubicin, melphalan, hydroxyurea and vincristine (CHAMOCA); MTX, ActD and cyclophosphamide (MAC); etoposide, MTX and ActD (EMA) and others [30]. At Charing Cross Hospital, after many years of progressive experience, a regimen was developed consisting of EMA alternating weekly with cyclophosphamide and vincristine (CO; see Table 4). This has been widely adopted worldwide [30], because it is effective with predictable and easily managed short-term toxicity. Indeed, a retrospective comparison from the Korean GTD centre's experience of MFA, MAC, CHAMOCA with EMA-CO demonstrated a remission rate of 63.3% (31 of 49), 67.5% (27 of 40), 76.2% (32 of 45) and 90.6% (87 of 96), respectively [31]. The EMA/CO regimen requires one overnight stay every 2 weeks and causes reversible alopecia. It is myelosuppressive but granulocyte colony stimulating factor (G-CSF) support helps to maintain neutrophil count, treatment intensity and avoid neutropenic febrile episodes [1].

Five-year OS of patients treated with this schedule has been reported to vary between 75% and 90% [31–33]. In the 272 cases at Charing Cross Hospital treated between 1980 and 1994,

Table 3. Methotrexate and folinic acid chemotherapy regimen for low-risk patients

Methotrexate (MTX)	50 mg by intramuscular injection repeated every 48 h for a total of four doses
Calcium folinate (folinic acid)	15 mg orally 30 h after each injection of MTX

Courses repeated every 2 weeks, i.e. days 1, 15, 29, etc.

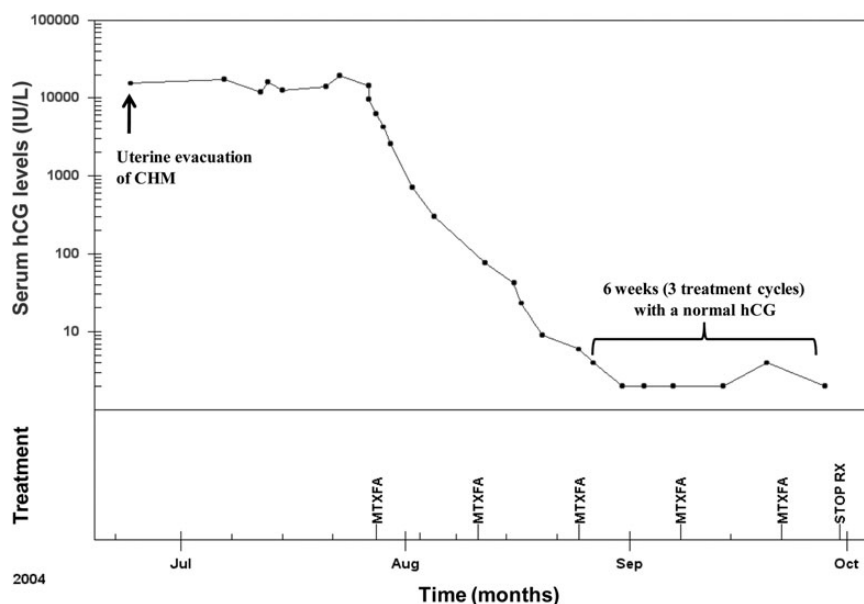


Figure 5. HCG tumour marker treatment graph demonstrating a patient responding to low-risk chemotherapy. Following uterine evacuation of a CHM, the hCG remained plateaued indicating persisting GTD/GTN, so the patient was commenced on methotrexate and folinic acid (MTX/FA). Therapy was continued for 6 weeks after the hCG was normal (<5 IU/l) as indicated. (Reprinted from ref. [1], Copyright 2010, with permission from Elsevier.)

Table 4. EMA/CO chemotherapy regimen for high-risk patients

EMA	
Day 1	
Etoposide	100 mg/m ² by i.v. infusion over 30 min
Actinomycin D	0.5 mg i.v. bolus
Methotrexate	300 mg/m ² by i.v. infusion over 12 h
Day 2	
Etoposide	100 mg/m ² by i.v. infusion over 30 min
Actinomycin D	0.5 mg i.v. bolus
Folinic acid rescue (starting 24 h after commencing the methotrexate infusion)	15 mg i.v. or orally every 12 h for four doses
CO	
Day 8	
Vincristine	1 mg/m ² i.v. bolus (maximum 2 mg)
Cyclophosphamide	600 mg/m ² i.v. infusion over 30 min

EMA alternates with CO every week. To avoid extended intervals between courses caused by myelosuppression, it may occasionally be necessary to reduce the EMA by omitting the day 2 doses of etoposide and actinomycin D. i.v., intravenous. (Reprinted from ref. [1], Copyright 2010, with permission from Elsevier.)

OS was 86.2% [95% confidence interval (CI) 81.9% to 90.5%] [32]. While these results were good, the presence of liver or brain metastases correlated with only 27% or 70% long-term survival, respectively, and was just 10% with both liver and brain metastases (reviewed in [1]). Most of the patients with adverse outcomes did not have a prior HM, were not registered for hCG follow-up and consequently presented with extensive disease. This was associated with death from haemorrhage or metabolic complications of overwhelming disease within 4 weeks of admission and/or before adequate chemotherapy could be given. If such patients are excluded, survival of patients with brain metastasis is similar to other patients [34]. The situation with liver metastasis may be similar; of 37 patients with liver metastasis treated between 1977 and 2005 at Charing Cross Hospital, OS had increased to ~50% at 5 years but if early deaths were excluded, survival was nearly 70% [35]. In addition to disease extent, other factors associated with poor outcome include the type of, and duration from, the antecedent pregnancy and the prior use of chemotherapy (reviewed in [1]).

To reduce early deaths in patients with very advanced disease, we have found that commencing chemotherapy gently with low-dose etoposide 100 mg/m² and cisplatin 20 mg/m² on days 1 and 2 repeated weekly for 1–3 weeks has virtually eliminated this problem. Indeed, low-dose induction etoposide and cisplatin combined with genetic testing to exclude non-gestational CC has helped to improve long-term OS data to over 94% in high-risk patients [36]. Further details on the management and modifications of treatment required for these and other challenging clinical situations such as brain metastasis and pulmonary failure are beyond the scope of the present review, but are contained within the following references [34, 37].

Table 5. TP/TE schedule for relapsed GTN

Regimen	Schedule
Day 1	
Dexamethasone	20 mg oral (12 h pre-paclitaxel)
Dexamethasone	20 mg oral (6 h pre-paclitaxel)
Cimetidine	30 mg in 100 ml NS over 30 min i.v.
Chlorphenamine	10 mg bolus i.v.
Paclitaxel	135 mg/m ² in 250 ml NS over 3 h i.v.
Mannitol	10% in 500 ml over 1 h i.v.
Cisplatin	60 mg/m ² in 1 l NS over 3 h i.v.
Post-hydration	1 l NS + KCl 20 mmol + 1 g MgSO ₄ over 2 h i.v.
Day 15	
Dexamethasone	20 mg oral (12 h pre-paclitaxel)
Dexamethasone	20 mg oral (6 h pre-paclitaxel)
Cimetidine	30 mg in 100 ml NS over 30 min i.v.
Chlorphenamine	10 mg bolus i.v.
Paclitaxel	135 mg/m ² in 250 ml NS over 3 h i.v.
Etoposide	150 mg/m ² in 1 l NS over 1 h i.v.

NS, normal saline; i.v., intravenous. (Reprinted from ref. [1], Copyright 2010, with permission from Elsevier.)

Similar to low-risk disease, therapy is continued for 6 weeks of normal hCG values or 8 weeks if poor prognostic features such as liver or brain metastases are present [1]. Patients are then re-imaged to document the post-treatment appearance for future comparison. Removal of residual masses is unnecessary as it does not reduce the risk of recurrence which is less than ~3% [1].

management of drug-resistant disease

About 20% of high-risk GTN patients will progress on or after primary chemotherapy, but these individuals still have an excellent outcome with ~75%–80% still being salvaged [36]. This is partly because relapse is detected early due to hCG monitoring so disease volume is small. Moreover, hCG monitoring enables the early detection of resistance during therapy, which could potentially be more rapidly detected through the use of normograms and kinetic models [28, 29, 38]. In relapsed patients, fluorine-18 fluorodeoxyglucose-PET (FDG-PET) scanning may help identify the site of active disease to facilitate surgical resection and cure [39]. The $T_{1/2}$ for hCG is ≤ 48 h after surgery if all the disease has been removed [1]. However, if surgery is not possible or the hCG falls inappropriately, several salvage regimens have been either created or adopted from the germ cell tumour setting [40]. At Charing Cross Hospital, we developed a regimen combining etoposide with cisplatin (EP) alternating weekly with EMA that omitted the second day of etoposide and ActD [41]. Survival rates are >80% but toxicity is significant [41], and less toxic salvage therapies are required. Several cases of drug-resistant GTN have been reported to respond and/or be cured by paclitaxel-based single-agent or combination therapy [42–45], gemcitabine and capecitabine [46, 47]. Of these, an alternating two weekly doublet of paclitaxel/cisplatin and paclitaxel/etoposide (TP/TE; Table 5) appears from non-randomised data to be much better tolerated than EP/EMA and is effective in patients with relapsed and/or refractory GTN [45]. In view of

these results, the International Society of the Study of Trophoblastic Diseases (ISSTD) has recently proposed a randomised trial of TE/TP versus EP/EMA to determine the optimal therapy for patients relapsing after non-cisplatin/paclitaxel-based combination therapies such as EMA/CO.

Another approach in patients with refractory disease involves high-dose chemotherapy with peripheral stem-cell transplantation. However, cures are not common [48], so improved patient selection may be required to achieve better outcomes from this approach.

management of PSTT and ETT

PSTT differs from CC, growing more slowly, metastasising later, involving lymph nodes more commonly and producing less hCG [1]. However, like CC, it can arise after any type of pregnancy, including PHM, [49] and usually presents with abnormal vaginal bleeding [2]. PSTT may be suspected if the hCG level is low for the volume of disease present on imaging combined with an elevated free beta form of hCG, but none of these features are diagnostic [50, 51]. Consequently histological confirmation is essential.

A recent large population-based series of PSTT comprised 62 cases over 30 years, representing 0.2% of UK GTD cases, and examined prognostic features [2]. On univariate analysis, stage, hCG, mitotic index and a duration of >4 years from the preceding pregnancy were prognostic, but the FIGO score was unhelpful. Only the duration from the prior pregnancy remained predictive of survival on multivariate analysis with 100% (13 of 13) dying and 98% (48 of 49) surviving for those ≥ 48 and <48 months, respectively. This effect was not explained by differences in disease stage or hCG levels, but may reflect a biological switch in the tumours after this time [2].

The management of PSTT differs from CC. Patients with metastatic disease require combination chemotherapy with, for example, EP/EMA continued for 8 weeks of normal hCG levels [2]. Unlike CC, residual masses are removed surgically, including the uterus, as this can harbour microscopic disease. This may cause difficulties in the management of stage I disease [52]. The safest option is hysterectomy with pelvic lymph node sampling and ovarian conservation unless there is a family history of ovarian cancer or the patient is post-menopausal. In the absence of sufficient data regarding adjuvant therapy, we currently advocate 8 weeks of EP/EMA or TE/TP when there are poor risk factors such as disease presenting beyond 4 years of the antecedent pregnancy. Indeed, in the latter group, a case can be made for including high-dose chemotherapy. However, in younger nulliparous women, there is often a strong desire to preserve fertility particularly when there appears to be a focal abnormality in the uterus. While uterine-sparing surgery is possible [1], multifocal microscopic uterine disease can occur [52], which could compromise survival and careful counselling is required.

Currently, it is thought that ETT behaves very similarly to PSTT but in reality, little data are available to be sure of this. PSTT and ETT are so rare that it is unlikely that their treatment will ever be fully optimised, so that the ISSTD has now launched an international PSTT/ETT database to pool cases [53].

personalised medicine

GTN is one of the rare examples of a group of related cancers where novel molecularly targeted agents have not been employed, as cure has been achieved through the use of conventional chemotherapeutic agents. This is because GTN are exquisitely sensitive to these drugs and the serial measurement of hCG, a highly sensitive biomarker of the disease [1], has enabled early recognition of resistance, so that second- and third-line therapies can be commenced before significant tumour re-growth has occurred. Very rarely, multi-drug-resistant disease develops that is not amenable to surgical resection or any other existing treatment, so it is unclear whether anything can be done in this case. Since GTN is very vascular it is plausible that vascular targeting agents such as bevacizumab might be active. The tumours can also over-express epidermal growth factor receptor, leading to the question whether erlotinib or gefitinib could demonstrate efficacy. Anecdotally, thus far, we have not seen any benefit from these agents in several multi-drug-resistant patients. The potential for an anti-hCG targeted therapy has not been explored and could be of interest in women who have completed their families or have run out of other options.

follow-up and long-term implications

The risk of relapse after chemotherapy is ~3% and most occur in the first year of follow-up. Therefore, careful hCG monitoring is required and pregnancy should ideally be delayed until beyond this period. Any method of contraception can be used including the oral contraceptive pill, as long as there are no other contraindications to their use. In the UK, the hCG is monitored weekly for 6 weeks post-chemotherapy, and then in serum and urine two weekly until 6 months, before switching to just urine assessments, initially monthly, but eventually decreasing to just six monthly (Table 6). We continue this for life as we are currently uncertain when it is safe to stop monitoring and it enables us to collect long-term data concerning late effects of treatment including second cancers.

Table 6. UK follow-up protocol of GTN patients who have been treated with chemotherapy

	Low-/high-risk post-chemotherapy patients, hCG concentration sampling	
	Urine	Blood
Year 1		
Week 1–6 after chemotherapy	Weekly	Weekly
Month 2–6	Two weekly	Two weekly
Month 7–12	Two weekly	–
Year 2	Four weekly	–
Year 3	Eight weekly	–
Year 4	Three monthly	–
Year 5	Four monthly	–
After Year 5	Six monthly	–

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Fortunately, apart from EMA/CO bringing forward the menopause date by 3 years, fertility is not otherwise affected with 83% of women becoming pregnant after either MTX/FA or EMA/CO chemotherapy [1]. Moreover, there is no obvious increase in the incidence of congenital malformations. When a patient does become pregnant, it is important to confirm by ultrasound and other appropriate means that the pregnancy is normal. Follow-up is then discontinued, but the hCG should be rechecked at 6 and 10 weeks after the pregnancy to ensure no recurrence or new disease.

Late sequelae from chemotherapy have been remarkably rare. In 15 279 patient-years of follow-up, there was no significant increase in the incidence of second tumours [54] following MTX therapy. In contrast, 26 patients receiving combination chemotherapy for GTN developed another cancer when the expected rate was only 16.45, a significant difference [54]. Most of this risk appears to occur if combination chemotherapy is continued beyond 6 months. Interestingly, new data in over 30 000 patient-years of follow-up now show that, for EMA/CO, there is no overall increased risk of second cancers with a slight but significant excess of leukaemias but reduction in other cancers including breast cancer risk (data submitted). This emphasises the continued importance of long-term monitoring of our treated patient populations.

summary of recommendations

Recommendations are largely based on non-randomised retrospective cohort studies from single centres and/or national experiences where the level of evidence (LOE) is IV. However, because of the measurable large benefit to patients, the grade of recommendation (GOR) is generally very high at A. LOE and GOR are given in brackets.

- Management of GTN is optimised by the centralisation of care, pathology review and hCG monitoring [IV, A].
- Women with singleton molar pregnancies should, in general, have these terminated by suction D&C [IV, A]. Second D&C for recurrence does not usually prevent the subsequent need for chemotherapy and should only be attempted after discussion with a GTD reference centre [IV, A].
- Anti-D prophylaxis is recommended following suction D&C of PHM [IV, A].
- The FIGO scoring system should be used to determine the risk of GTN becoming resistant to single-agent chemotherapy, but is not of value in PSTT/ETT [IV, A].
- Patients with a FIGO score of 0–6 can be treated with either single-agent MTX with or without FA, or ActD [II–IV, A]. In most European centres, MTX/FA (Table 3) is preferred because it is less toxic than MTX alone or single-agent ActD, and all patients can expect to be cured even if first-line therapy fails [II–IV, A]. A randomised trial comparing the most frequently used MTX/FA and ActD regimens is currently underway.
- Chemotherapy for low-risk disease should be continued for 6 weeks of maintenance treatment after hCG normalisation [IV, A].
- Patients with a FIGO score of ≥ 7 should receive multi-agent chemotherapy and most centres now use EMA/CO (Table 4),

as it is highly effective, simple to administer and relatively non-toxic [IV, A].

- Patients with high-risk disease should have maintenance therapy for 6 weeks extended to 8 weeks with poor prognostic features such as liver with or without brain metastasis [IV, A].
- Early deaths in ultrahigh-risk GTN can be reduced by induction of low-dose etoposide and cisplatin [IV, A]. Such patients may also benefit from substitution of EMA/CO with EP/EMA [IV, A].
- Residual lung or uterine masses following chemotherapy for low-risk or high-risk diseases are not predictive of recurrence and do not require surgical excision [IV, A].
- High-risk failures can be frequently salvaged with further chemotherapy and most centres use either EP/EMA or TE/TP (Table 5) [IV, A]. A randomised trial comparing these regimens is being developed.
- Surgery alone can effectively salvage some patients with isolated foci of chemoresistant disease [IV, A].
- PSTT/ETT is managed according to its stage and risk factors for poor outcome, the most dominant of which is the interval from last known pregnancy. Hysterectomy with pelvic lymph node sampling is recommended for stage I disease presenting within 4 years of the last known pregnancy [IV, A]. Multi-agent chemotherapy with, for example, EP/EMA is recommended for metastatic disease [IV, A]. Patients presenting beyond 4 years may benefit from multi-agent and subsequent high-dose chemotherapy [IV, B].

search strategy and selection criteria

All authors performed a detailed review of published work and contributed to the writing, review and editing of the manuscript. MJS had access to all the data used to write the report and had final responsibility for submission. All authors saw and approved the final version. Our search strategy was formulated to identify any meta-analyses and previous systematic reviews in all aspects of GTD, in addition to all published cohort studies (and where appropriate, comparison groups) and case-control studies. We searched the Cochrane Library, Medline (via PubMed, Internet Grateful Med, OVID and Knowledgefinder), with a combination of keywords including: ‘trophoblastic disease’, ‘GTD’, ‘GTN’, ‘choriocarcinoma’, ‘molar pregnancy’, ‘hydatidiform mole’, ‘placental site trophoblastic tumor’, ‘genetics’, ‘epidemiology’, ‘pathology’, ‘treatment’, ‘chemotherapy’, ‘methotrexate’, ‘actinomycin D’, ‘dactinomycin’, ‘cisplatin’, ‘paclitaxel’, ‘high-dose’, ‘management’, ‘risk factors’, ‘hCG’, ‘imaging’, ‘ultrasound’, ‘PET’, ‘CT’, ‘MRI’, ‘prognosis’, and ‘staging’. The reference lists and bibliographies of all previous publications were scanned to find any publications not already identified by our electronic search strategy.

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 7. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

Table 7. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System^a)

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

^aDykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

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conflict of interest

The authors have declared no potential conflicts of interest.

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