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Original Research

Practical clinical guidelines of the EOTTD for treatment and referral of gestational trophoblastic disease

Christianne Lok [a,*,1], Nienke van Trommel [a,1], Leon Massuger [b], François Golfier [c,1], Michael Seckl [d,**,1] on behalf ofthe Clinical Working Party of the EOTTD[2]

[a] *Department of Gynecologic Oncology, Centre for Gynecologic Oncology Amsterdam, Location Antoni van Leeuwenhoek - The Netherlands Cancer Institute, Amsterdam, the Netherlands*
[b] *Department of Gynecologic Oncology, Radboud University Medical Hospital, Nijmegen, the Netherlands*
[c] *Department of Gynecologic and Oncologic Surgery and Obstetrics, French Trophoblastic Disease Centre, Lyon University Hospitals, Lyon Sud Hospital, France*
[d] *Charing Cross Gestational Trophoblastic Disease Centre, Charing Cross Hospital, Imperial College London, London, UK*

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Abstract ***Background and aim:*** Gestational trophoblastic disease (GTD) is a heterogeneous group of disorders characterised by abnormal proliferation of trophoblastic tissue. Since GTD and its malignant sequel gestational trophoblastic neoplasia (GTN) are rare diseases, little evidence is available from randomised controlled trials on optimal treatment and follow-up. Treatment protocols vary within Europe, and even between different centres within countries. One of the goals of the 'European Organisation for Treatment of Trophoblastic Diseases' (EOTTD) is to harmonise treatment in Europe. To provide a basis for European standardisation of definitions, treatment and follow-up protocols in GTD, we composed a set of guidelines for minimal requirements and optimal management of GTD.

Methods: Members from each EOTTD country attended multiple workshops during annual EOTTD meetings. Clinical guidelines were formulated by consensus and evidence where available. The following guidelines were discussed: diagnostics of GTD and GTN, treatment of low-risk GTN, high-risk GTN, ultra-high-risk GTN, placental site and epithelioid trophoblastic tumours and follow-up.

Results: Between 40 and 65 EOTTD members from 17 European countries and 7 non-European countries attended the clinical workshops held on 6 occasions. Flow diagrams for

* *Corresponding author.*
** *Corresponding author.*
E-mail address: c.lok@nki.nl (C. Lok), m.seckl@imerial.ac.uk (M. Seckl).
[1] Authors contributed equally to the manuscript. [2] The collaboration group clinical working party of the EOTTD are listed in Appendix section.

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patient management were composed to display minimum and best practice for most treatment situations. New agreed definitions of recurrence and chemotherapy resistance were formulated.

Conclusions: Despite the many differences between and within the participating countries, an important step in uniform treatment of GTD and GTN within Europe was made by the Clinical Working Party of the EOTTD. This is an example on how guidelines and harmonisation can be achieved within international networks.

1. Introduction

Gestational trophoblastic disease (GTD) is a heterogeneous group of disorders characterised by abnormal proliferation of trophoblastic tissue. It encompasses the premalignant partial hydatidiform mole (PM) and complete hydatidiform mole (HM) and the malignant invasive mole, choriocarcinoma, placental-site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). The malignant trophoblastic disorders are also collectively known as gestational trophoblastic neoplasia (GTN). A hydatidiform mole is the most common type of GTD. Worldwide incidence rates differ but in Europe, hydatidiform moles have an incidence of 0.5–3.0 per 1000 pregnancies [1–3].

With these low incidences, GTD and certainly GTN fulfil the criteria of a rare disease. In Europe, a disease or disorder is defined as rare when it affects less than 1 in 2000 persons [4].

The care for patients with a rare disease is complicated by fundamentally different challenges compared to the care for patients with more common disorders. The small number of patients often scattered across countries, lack of evidence-based treatment protocols and limited clinical expertise are some of these problems. International cooperation and formation of networks are critical to overcome these problems.

In Europe, the first steps towards formation of networks of international experts in rare diseases have been recently undertaken. The European Rare Adult Cancer Network (EURACAN) was established in 2017 to help professionals in different countries to share knowledge, experience and hold international multidisciplinary tumour boards. However, for trophoblastic diseases, a network of European experts already existed. The European Organisation for Treatment of Trophoblastic diseases (EOTTD) was founded in 2010 and is dedicated to optimise diagnosis, treatment, follow-up and research in GTD by bringing together knowledge of clinicians and researchers from many countries working in the field of GTD in Europe. One of the purposes of the EOTTD was to formulate uniform clinical guidelines for GTD and GTN in Europe.

Since GTD and GTN are rare diseases, little evidence is available from randomised controlled trials on optimal treatment and follow-up. This combined with differences in access to health care and organisation of health care in Europe has contributed to considerable variance in treatment protocols, which also likely influences disease outcomes. In an attempt to harmonise and optimise the care of GTD patients in Europe, the Clinical Working Party of the EOTTD has developed new guidelines with minimal requirements that can be followed everywhere together with best practice advice. These guidelines are principally targeted at well-resourced health economies, although input was also received from less well-funded developing world countries.

2. Methods

The Clinical Working Party was founded in 2010 in Lyon, France. One of the goals of the Working Party was to formulate guidelines applicable for all European countries. In all EOTTD meetings since then, members from each EOTTD country attended multiple workshops (2012: Geneva, Swiss, 2014: Liege, Belgium, 2015: Amsterdam, The Netherlands, 2016: Cork, Ireland, 2017: Amsterdam, The Netherlands, 2018: London, UK) until finalisation of the guidelines in May 2018. A chairperson and note taker were elected for each meeting and all members engaged in active discussion with majority voting used to resolve any areas of disagreement. Where variance in practice existed and no resolution could be achieved, then minimum guidelines were agreed which could encompass this variance. For example, if the frequency of hCG monitoring following chemotherapy varied considerably between centres, with some centres measuring the hCG weekly and others only monthly, we might simply suggest that follow-up with hCG monitoring is necessary and the frequency is according to local GTD centre advice.

Clinical guidelines were formulated by consensus and based on published evidence where available. To facilitate clinical use, flow diagrams were created. In each subsequent meeting, the latest flow diagrams were reviewed and either approved or modified and then approved by the present attendees.

Minimal requirements and optional best practices were formulated.

3. Results

Given the lack of a uniform definition for both chemotherapy resistance and recurrence of GTN following treatment, the Clinical Working Party of the EOTTD made an attempt to address this issue during a clinical guideline workshop in May 2016. Consensus was reached on a definition of recurrence consisting of four statements (Textbox 1) and the definition of MTX resistance consisting of five statements (Textbox 2).

In addition, over the course of several meetings, minimal requirements were described for: 1) diagnostic pathway for hydatidiform mole, 2) diagnostic pathway for hydatidiform mole to GTN, 3) post-molar GTN assessment/staging, 4) post-molar GTN treatment, 5) low-risk GTN treatment, 6) follow-up low-risk GTN, 7) high-risk GTN treatment, 8) ultra-high-risk GTN treatment, 9) follow-up high-risk and ultra-high-risk GTN, 10) diagnosis of PSTT/ETT, 11) treatment of PSTT/ETT, 12) follow-up after PSTT/ETT and 13) persistent low-level elevated hCG.

1) Diagnostic pathway for hydatidiform mole (Fig. 1)
Minimal requirements

When hydatidiform mole is suspected with an (Doppler) ultrasound, hCG and a blood group and screen/save (G&S) must be determined. A suction curettage is advised under ultrasound guidance with the immediate availability of units of blood available because of the potential haemorrhage during surgery. Ultrasound guidance is not proven to result in more complete evacuations or less perforations, but is generally accepted and in line with literature on treatment of GTD [5,6].

Diagnosis should be confirmed by histology with or without ancillary techniques such as genotyping and p57kip2 staining [7].

Best practice

If metastases are suspected, imaging can be performed. If genetic analysis is available, this can be considered if deemed necessary. In cases of Rhesus negative patients, anti-D prophylaxis should be considered [8].

2) Diagnostic pathway for hydatidiform mole to GTN (Fig. 2)
Minimal requirements

Histological confirmation of GTD is mandatory after evacuation. Following a confirmed partial or complete mole, hCG follow-up should be initiated with a frequency of at least once every two weeks. Partial mole does not require prolonged follow-up and can be discontinued after one confirmatory normal hCG value. For complete moles, the chance of recurrence after a normal hCG is higher, so up to 6 months follow-up is advised. Currently, several EU countries including Belgium, France, Ireland, Netherlands, Norway, Sweden, Denmark and UK have

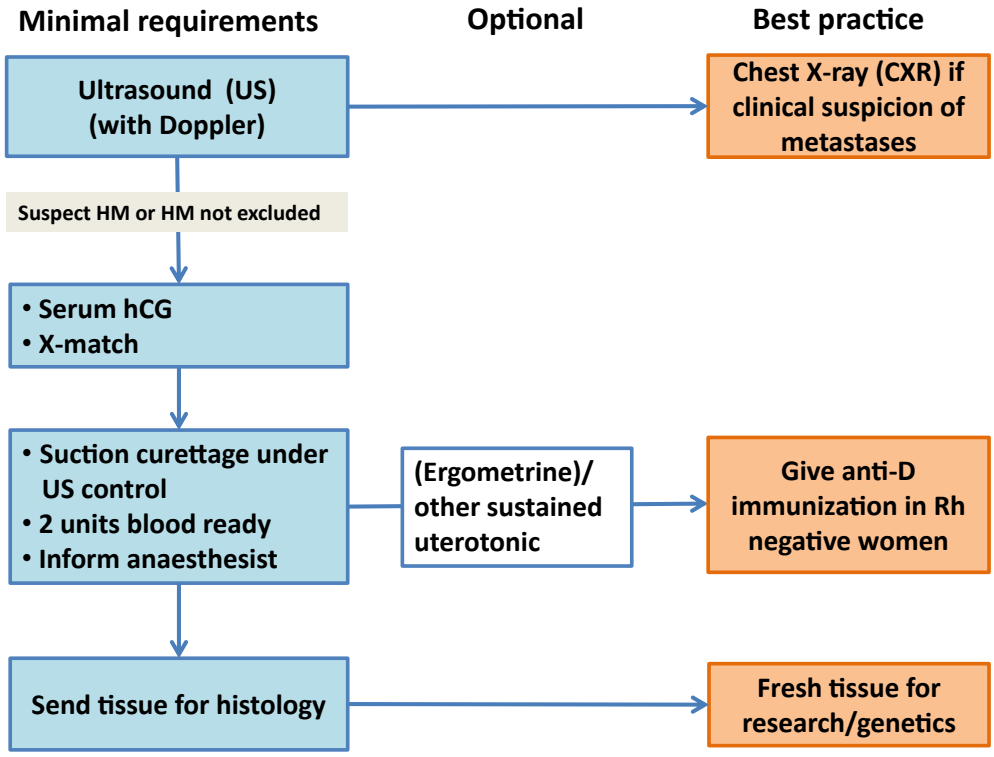

Fig. 1. Diagnostic pathway for hydatidiform mole (HM).

GTD centres that can provide expert advice and all new patients in those countries should be registered with their GTD centre. Other EU countries including Germany, Poland, Portugal, Spain and Italy are currently developing GTD centres. Although, patients may be followed up at a local centre, discussing and registering these cases with the GTD centre and following GTD centre advice is essential to prevent unnecessary complications and deaths. If the hCG plateaus over three weekly values or rises over two weekly values according to the FIGO criteria [9], referral to a GTD centre is advisable. After diagnosing GTN, FIGO scoring and staging are performed [9].

Best practice

It has been shown that expert pathology review changes diagnosis in 26% of cases [10] Therefore, obtaining pathological review by a GTD expert reference pathologist should be considered.

hCG should be monitored on a platform as advised by the GTD centre or hCG should be measured in the GTD centre itself.

In low-risk GTN, a second curettage can be discussed with a patient, which in a prospective trial had curative effect in 40% of patients [11] and in retrospective studies had a curative effect ranging between 9% and 80% [12–15].

3) Post-molar GTN assessment/staging (Fig. 3)
Minimal requirements

After urgent patient review and staging with ultrasonography (US), chest X-ray and CT in case of possible metastases, the FIGO score [9] and stage can be determined [16]. For FIGO 2000 scoring, a chest X-ray is used to count the number of metastases. MRI brain is performed when lung metastases are present.

Best practice

Patients are urgently referred to a GTD centre. Imaging and hCG measurement should be performed prior to start of treatment. Pelvic MRI can be considered. The regular use of PET-CT in staging does not provide any additional information to conventional imaging and is not routinely recommended [17].

4) Post-molar GTN treatment (Fig. 4)
Minimal requirements

There are several options for treatment of GTN. Before the start of treatment, all patients should at least be discussed with a GTD referral centre. In case of low-risk GTN (with a FIGO score between 0 and 6), monotherapy is often successful. In case of high-risk GTN (FIGO score 7–12), patients are treated with multiagent chemotherapy. In case of ultra-high-risk GTN, patients have to be referred to a GTD centre.

Best practice

Initial treatment can be started in a GTD centre in both low- and high-risk GTN. On-going therapy should be supervised by the GTD centre, but can be given locally where possible. In case of ultra-high-risk GTN, treatment should be performed in a GTD centre with

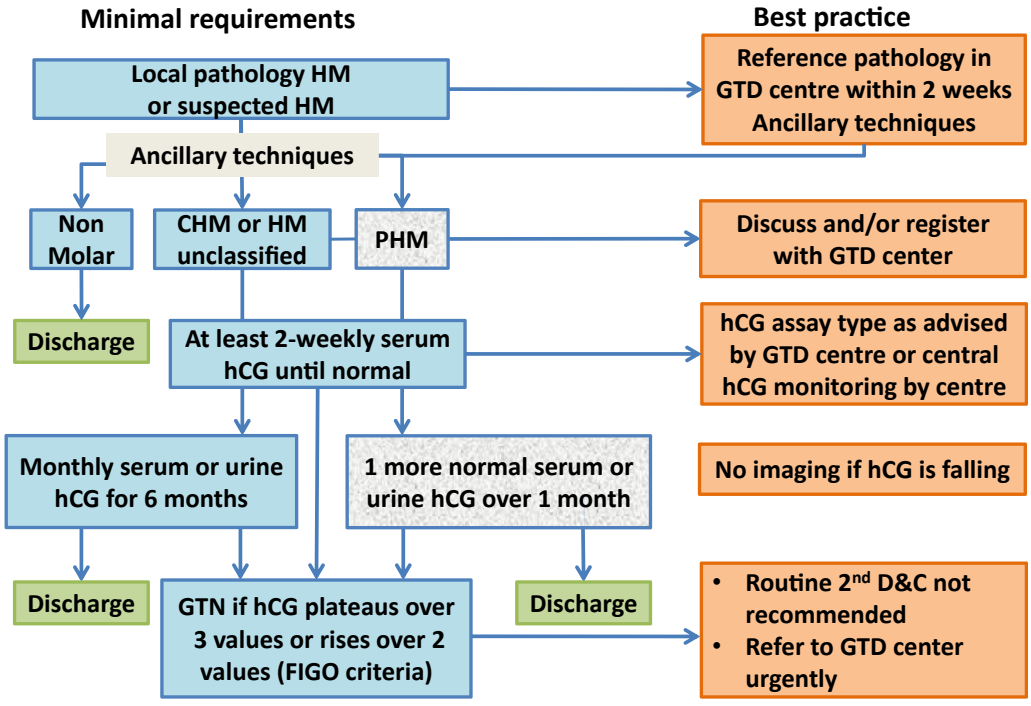

Fig. 2. Diagnostic pathway for HM to GTN.

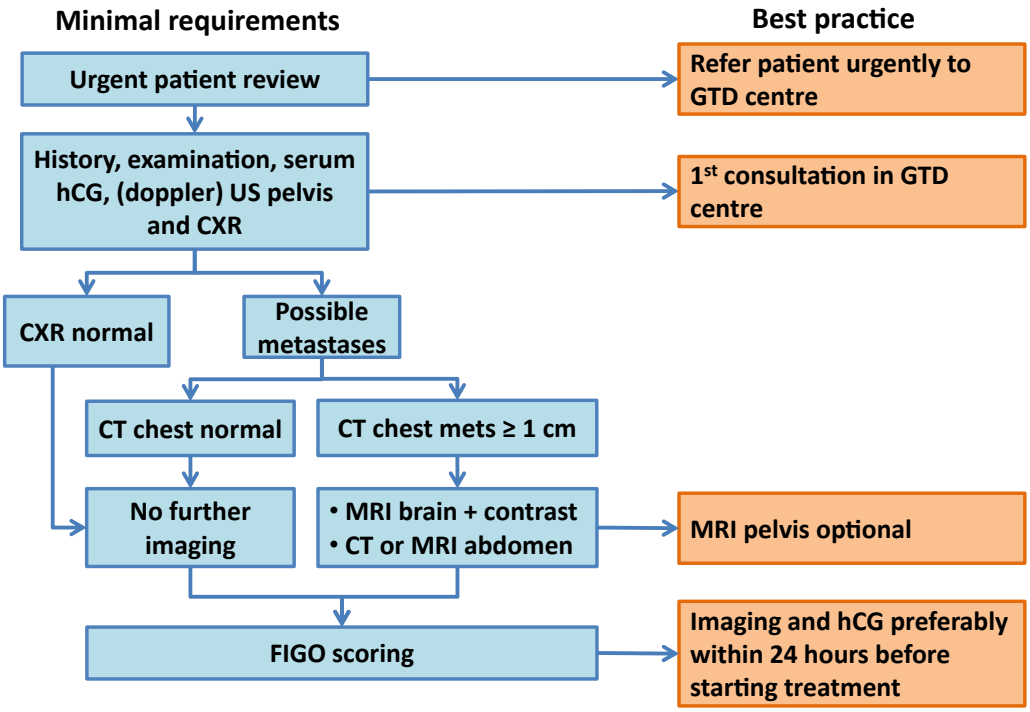

Fig. 3. Post-molar GTN staging.

experience in these rare cases. Low-dose induction chemotherapy can be considered to avoid early deaths from bleeding or metabolic complications.

5) Low-risk GTN treatment (Fig. 5)
Minimal requirements

In Europe, methotrexate (MTX) is most widely used, although up to 23–43% of patients will need to switch chemotherapy because of toxicity and/or resistance (Appendix 1A) [18,19]. During treatment, hCG should be measured at least two weekly. Patients are monitored for the occurrence of MTX resistance following the criteria as formulated in Textbox 1. In case of MTX resistance, patients should either switch to actinomycin D (Appendix 1B) (hCG $\leq$ 1000 IU/L) or EMA/CO (hCG $>$ 1000 IU/L) or other multiagent chemotherapy as advised by the GTD centre. In case of the histological diagnosis of choriocarcinoma and falling hCG, spontaneous regression can be awaited and immediate treatment is not advised.

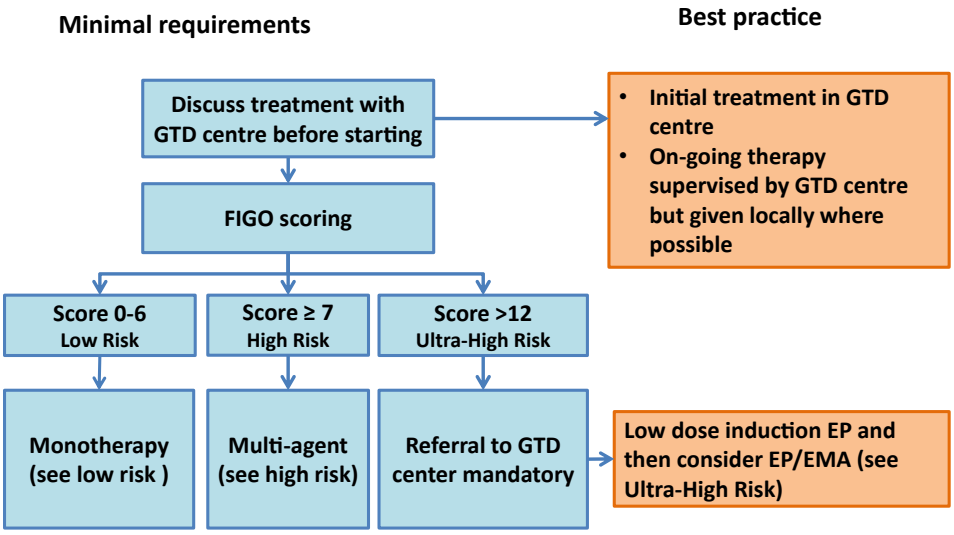

Fig. 4. Post-molar GTN treatment.

Best practice

As an alternative to MTX, patients with low-risk GTN can be, after consultation with the GTD centre, treated with actinomycin D [20–23]. Since in low-risk disease, a hysterectomy has a curative effect in 82% of cases [24], this option should be discussed with women who have fulfilled their child wish.

In case MTX resistance occurs, consider re-imaging and change treatment as advised by the GTD centre.

Textbox 1. Definition of MTX resistance in low-risk disease.

Primary resistance: after initial two courses, if hCG is rising, change treatment. If hCG plateaus (<10% change), continue to third course and if still plateaued, change treatment.
Acquired resistance after initial response: hCG plateau (<10%) over two courses (4 wks) or rise over at least 2 wks
Consider excluding other causes of persistent low raised hCG

6) Follow-up low-risk GTN (Fig. 6)
Minimal requirements

The concentration of normal hCG varies between assays and will be defined by the local laboratory where the hCG assay is performed. Once hCG has normalised, patients are treated for a minimum of four consecutive weeks with consolidation courses according to local GTD centre advice. During follow-up, hCG is measured in a frequency and over a period as defined by the local GTD centre. Recurrence is defined according to Textbox 2. Typically, patients are advised to use contraception during one year after normalisation of hCG but this may differ between GTD centres.

Best practice

After normalisation of hCG, imaging of previously known metastatic sites can be performed as baseline for future follow-up but abnormalities on imaging with a normalised hCG should not be treated since hCG is an excellent marker for active disease. hCG can be checked 6 weeks after each subsequent pregnancy and histological examination of the placenta of subsequent pregnancies can be considered.

7) High-risk GTN treatment (Fig. 7)
Minimal requirements

In case of suspected high-risk GTN following any type of pregnancy, extensive imaging should be performed including a CT chest and abdomen and if necessary, MRI pelvis and brain all with contrast. Patients should be scored according to the FIGO criteria [9]. In case of high-risk GTN with a FIGO score 7–12, patients are treated with EMA/CO (Appendix 1C). After normalisation of hCG, patients receive consolidation courses between 4 and 8 weeks according to GTD centre advice.

Best practice

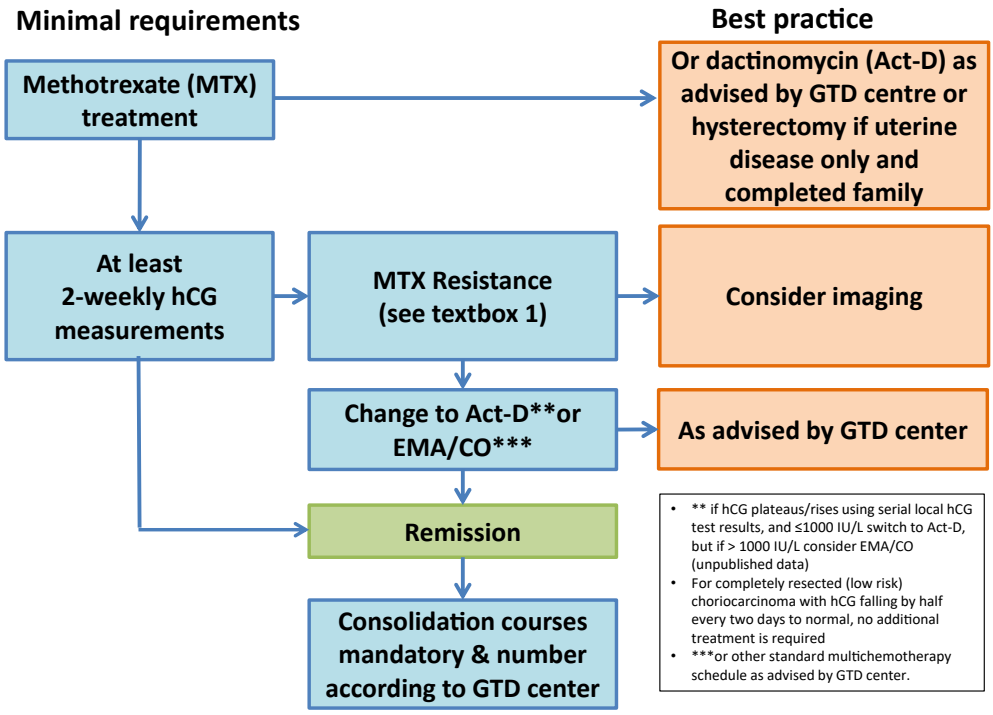

Fig. 5. Low-risk GTN treatment.

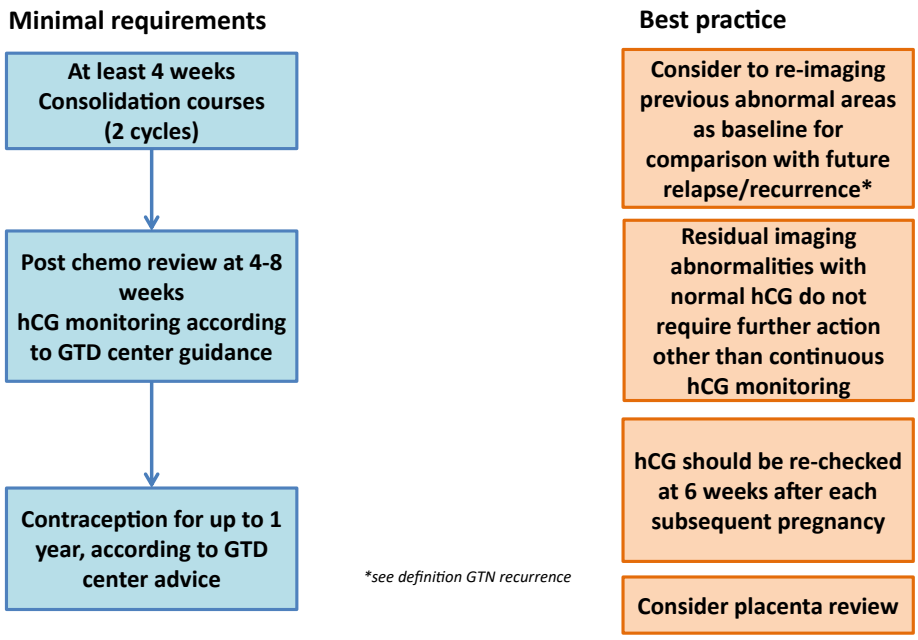

Fig. 6. Follow-up after low-risk GTN.

Patients should be referred to a GTD centre for treatment of high-risk GTN. In case of liver metastases, EP/EMA (Appendix 1D) should be considered (which omits the second day of EMA treatment to prevent myelotoxicity) to reduce the risk of late drug-resistant disease [25]. In case of brain metastases, liver metastases or advanced lung disease or other cause of increased risk of bleeding or metabolic complications, consider avoiding this by starting treatment with low-dose induction EP chemotherapy (Appendix 1E) [26].

8) Ultra-high-risk GTN treatment (Fig. 8)
Minimal requirements

Patients should immediately be referred to a GTD centre. Imaging should be performed if not recently done (contrast CT-chest/abdomen, MRI brain, MRI pelvis). Low-dose EP 1–3 cycles should be considered depending on the clinical condition followed by EP/EMA or EMA/CO. After normalisation, consolidation courses should be given for 8 weeks according to local GTD centre advice.

Textbox 2. Definition of GTN recurrence.

- Rise of hCG after normalisation and cessation of treatment (including consolidation)
- Two sequential rising hCG values (at least one week apart) above the reference level of GTD centre
- Patients should be called in for review (unless confirmed pregnancy)

Best practice

Following low-dose induction EP, in case of brain or meningeal metastatic disease, treat with EMA in which the MTX dose is increased to 1 g/m^2 (EMA-CNS) alternating weekly with CO. Intra-thecal MTX can be considered with CO according to local GTD centre advice. EP alternating weekly with EMA (EP/EMA) is favoured in patients with liver metastases in the absence or presence of brain involvement. With liver and brain involvement, the EMA part of EP/EMA should be given as EMA-CNS and in either case, the EMA in EP/EMA omits the second day of etoposide and actinomycin D. Treatment delays should be avoided by using G-CSF (granulocyte colony stimulating factor) support each week with either EMA/CO or EP/EMA. Details of these regimens are provided in Appendix 1C and 1D.

9) Follow-up high-risk and ultra-high-risk GTN (Fig. 9)
Minimal requirements

After consolidation courses, patients should be reviewed after 4–8 weeks. hCG monitoring is compulsory. Patients should refrain from pregnancy for at least a year.

Best practice

Perform at least weekly hCG measurements for 6 weeks after normalisation, then at least monthly for 12 months and then with reducing frequency. A minimum of 5-year-follow-up is advised and current evidence suggests that relapses beyond 7 years are exceptionally rare [27]. Whole body imaging post treatment can be

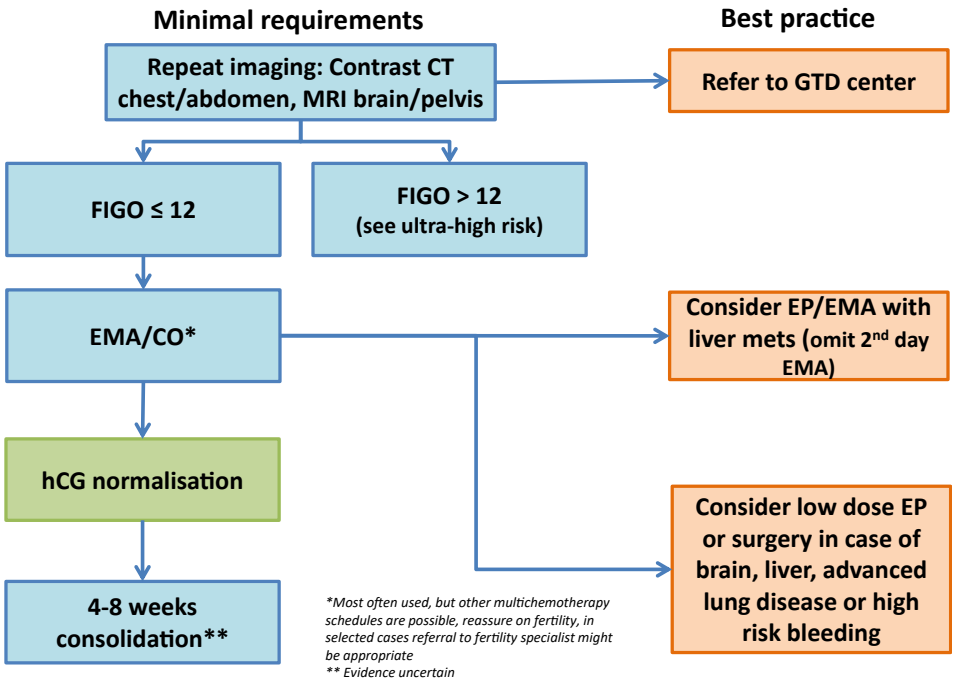

Fig. 7. High-risk GTN treatment.

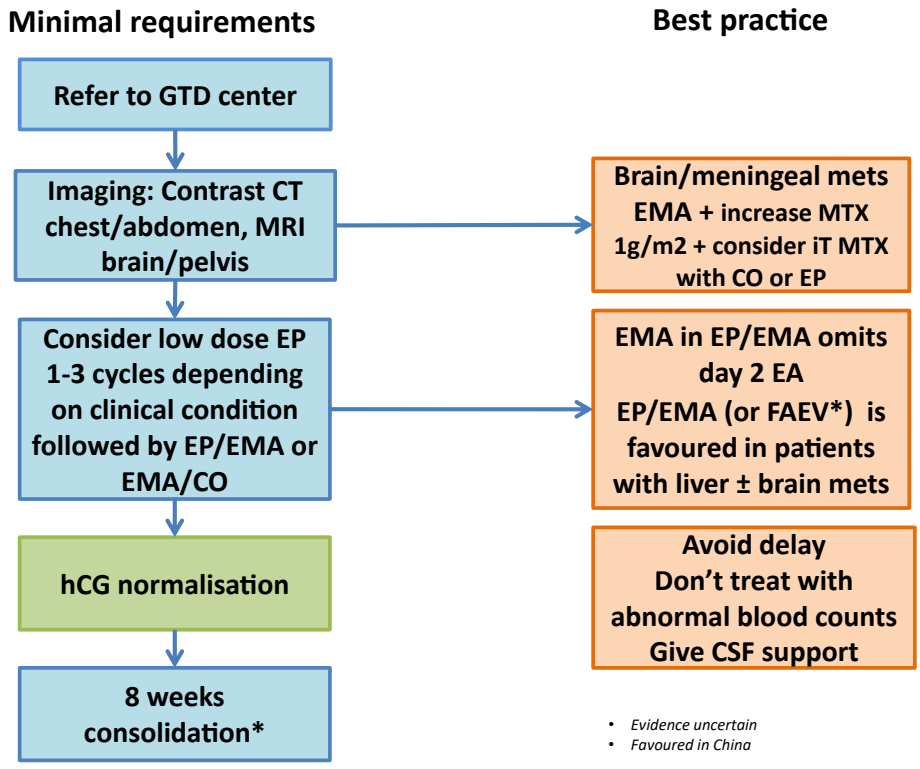

Fig. 8. Ultra-high-risk GTN treatment.

helpful as a baseline of any residual lesions/changes so that new imaging performed in the event of a relapse can be better interpreted to help identify active sites of disease. If lesions are visible post treatment and there is doubt as to the presence of active residual cancer, removal of the largest remaining lesion can be considered to ensure absence of active tumour. In high-risk GTN, 86.4% of recurrences occur in the first year after

normalisation. Women are advised not to conceive for at least 1 year after cessation of therapy. Contraception is strongly advised and any form is acceptable. Earlier conception after 1 year in older women who wish to conceive can be discussed. Excessive UV exposure should be avoided for 1 year to prevent UV-induced skin toxicity after chemotherapy. To gain more knowledge on ultra-high-risk GTN, patients can be registered in the ISSTD database for ultra-high-risk GTN (http://stdc.group.shef.ac.uk/psttuhr/).

10) Diagnosis of PSTT/ETT (Fig. 10)
Minimal requirements

PSTT or ETT should be suspected if the hCG is relatively low for the volume of disease seen at imaging. A histological diagnosis is essential and biopsy or resection of the whole primary or metastatic site should be undertaken. CT and MRI are necessary to stage according to the FIGO 2000 staging system. The scoring system is not applicable in these cases.

Best practice

After diagnosis, the GTD centre should be contacted. The histology has to be confirmed by a reference pathologist. In addition, these patients can be registered with the international database of the ISSTD (http://stdc.group.shef.ac.uk/psttuhr/).

11) Treatment of PSTT/ETT (Fig. 11)
Minimal requirements

Treatment is guided by the interval from the last pregnancy. In stage I and an antecedent pregnancy <48 months, hysterectomy and surveillance are advised. In case of an interval ≥ 48 months, adjuvant platinum containing chemotherapy can be initiated after hysterectomy according to the negative effect of this long interval on recurrence free survival. Even high dose chemotherapy [28,29] or pembrolizumab [30] can be considered.

In stage II and III with an interval from the antecedent pregnancy <48 months, hysterectomy followed by platinum-based combination chemotherapy (e.g. EP/EMA) is suggested. Resection of any visible residual disease post chemotherapy is advised. In case of an interval ≥ 48 months or in stage IV regardless of interval, besides this treatment, also high dose chemotherapy or pembrolizumab can be considered. The order of surgery versus systemic therapy first is uncertain.

Best practice

For optimal treatment, free surgical margins are essential. Therefore, radical hysterectomy and/or extensive radical surgery in a centre of expertise can be necessary. Furthermore, suspicious lymph nodes should be removed for staging or debulking purposes. In early disease, a laparoscopic approach might be feasible but morcellation should be avoided as this destroys histopathological analysis of surgical margins and may seed tumour. Women with stage I disease where the interval is less than 48 months from the causative pregnancy who have a strong desire to retain fertility may be considered

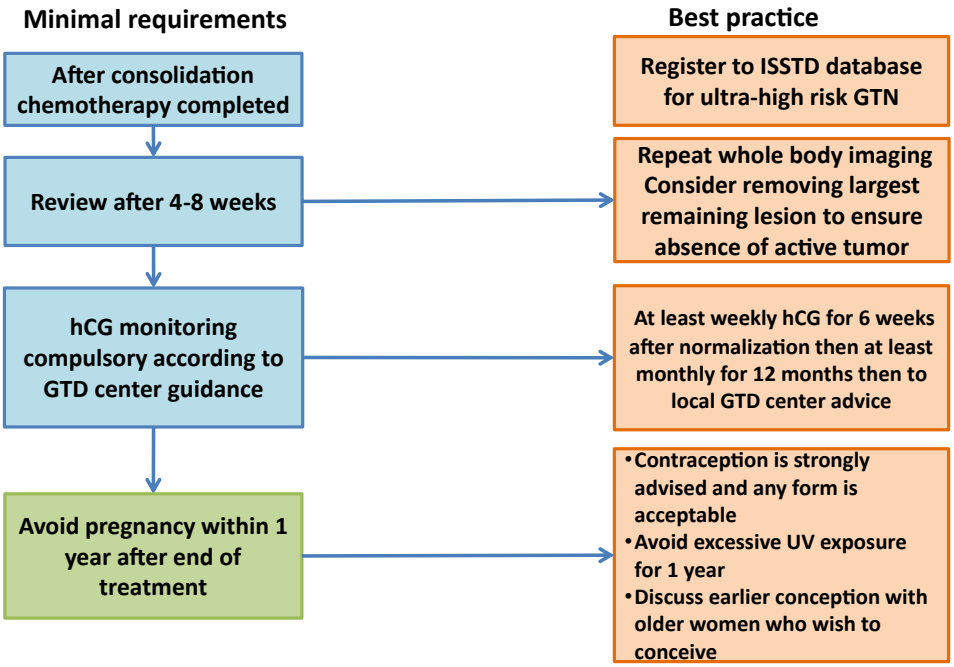

Fig. 9. Follow-up after high-risk and ultra-high-risk GTN.

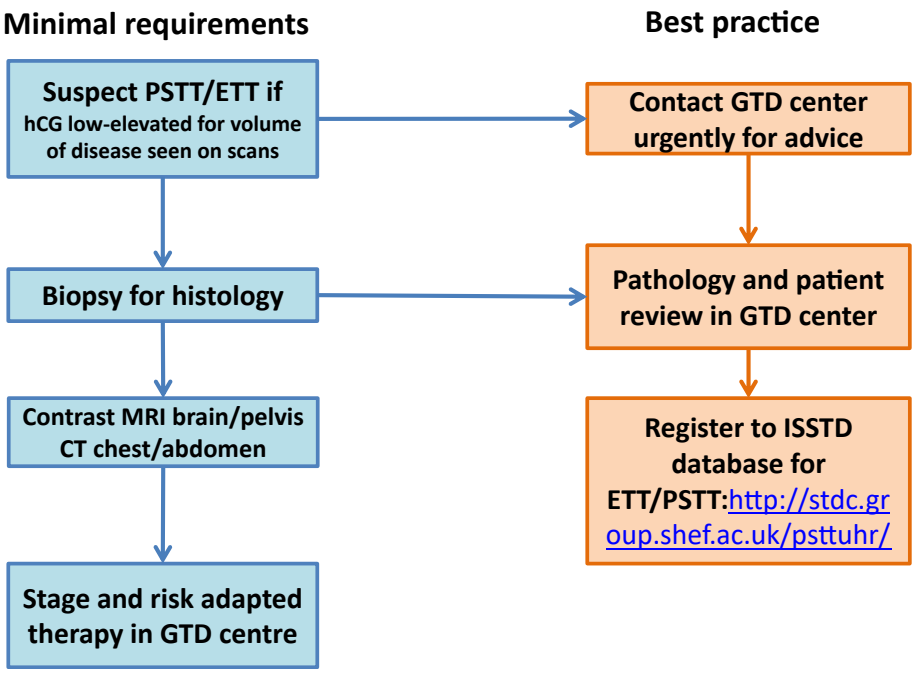

Fig. 10. Diagnosis of PSTT/ETT.

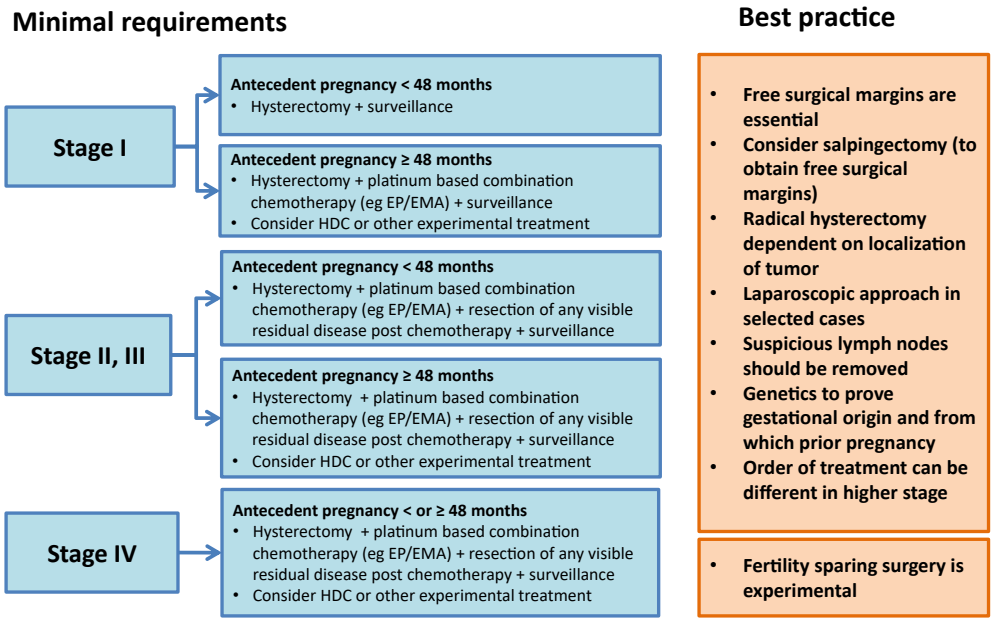

Fig. 11. Treatment of PSTT/ETT.

for experimental approaches. These might include focal resection of uterine tumour and/or chemotherapy. However, careful counselling is required as these cannot be regarded as standard of care and may carry additional risks.

Genetics can be helpful to prove the gestational origin and to determine from which prior pregnancy the PSTT or ETT developed.

12) Follow-up after PSTT/ETT treatment (Fig. 12)

Minimal requirements

In patients who only had a slightly elevated or normal hCG at presentation, this marker alone cannot be relied upon to detect recurrence and so these patients should be considered for imaging follow-up. However, if there was an elevated hCG at presentation, hCG monitoring is useful.

Best practice

Unfortunately, no data on best schedule of follow-up is available. A suggestion is to do at least weekly hCG

for 6 weeks after normalisation followed by 12 months at least monthly after which the frequency can be reduced until at least 10 years of follow-up are completed. Follow-up with imaging should be done according to local GTD centre advice.

13) Persistent low-level elevated hCG (Fig. 13)

Sometimes a persistent low level of hCG is found. This is a challenging clinical finding.

The following differential diagnosis is applicable:

- *Non-gestational tumour (germ cell, epithelial or other carcinoma),*
- *GTD or failing normal pregnancy,*
- *Pituitary hCG released during menopause,*
- *Familial or non-familial raised hCG,*
- *Injected hCG (body building programmes) and*
- *False positive: HAMA's (human anti-mouse antibodies)/ HARA's (human anti-rabbit antibodies).*

The necessary steps to take to solve the problem are:

- Measure hCG in urine and serum to exclude a false positive.
- *Send hCG to reference centre to measure on multiple hCG assays and exclude false positive.*
- *Exclude pregnancy.*
- *Contrast CT (chest/abdo) or MRI (pelvis/brain with pituitary views) to exclude a non-gestational hCG secreting tumour (germ cell, epithelial or other carcinoma).*
- *Hormone profiling for menopause and ovulation.*
- *(serial) Ultrasound of ovaries to show ovulation.*
- *Oral contraception test will lead to suppression of pituitary hCG released in menopause or from a chemo-induced menopause.*

- Differential diagnosis:
  - Non-gestational tumour (germ cell, epithelial or other carcinoma)
  - Pregnancy related GTD or failing normal pregnancy
  - Pituitary hCG/menopause
  - Familial raised hCG
  - False positive: HAMA's / HARA's
- Steps to take to solve the problem: measure hCG in urine and another assay, hCG to reference center, exclude pregnancy, contrast CT chest/abdo MRI pelvis / brain with pituitary views, menopause hormone screen, (serial) ultrasound of ovaries and hormone profiling for ovulation, oral contraception test

Fig. 13. Persistent low-level elevated hCG.

4. Discussion and summary of recommendations

In this article, we described the consensus on guidelines for referral and treatment of GTD and GTN. This was a first step of the EOTTD, to formulate uniform clinical guidelines for GTD and GTN in Europe. The results of a recent questionnaire within EOTTD countries demonstrated that there was limited agreement on definitions and clinical practice of GTD and GTN [31]. The majority of countries used nationwide or local hospital guidelines. This is not surprising as the access to healthcare in Europe differs between countries. By generating minimal requirements for care that should be applicable in all participating countries, we aimed to achieve a standard minimal level of care for all women with trophoblastic disease in Europe. Because many countries participated in the development of these consensus-based guidelines, the chance of implementation may be increased.

The finding that there was no agreement on the definitions of chemotherapy resistance and recurrence was remarkable. Different interpretation of these definitions could lead to distinct time points to start treatment in refractory or relapsed GTN patients and subsequently influence outcome and complicate comparisons between studies.

Although treatment protocols were shown to vary significantly within Europe, and even between different centres within countries, experts agreed on many topics [32].

It is widely accepted that exposure of a medical specialist to a rare health problem is related to knowledge and quality of care. This is why the European Reference Networks were developed so that rare diseases could be focused in specialist expert centres. These centres required multidisciplinary teams, presence of appropriate facilities needed for malignancy specific

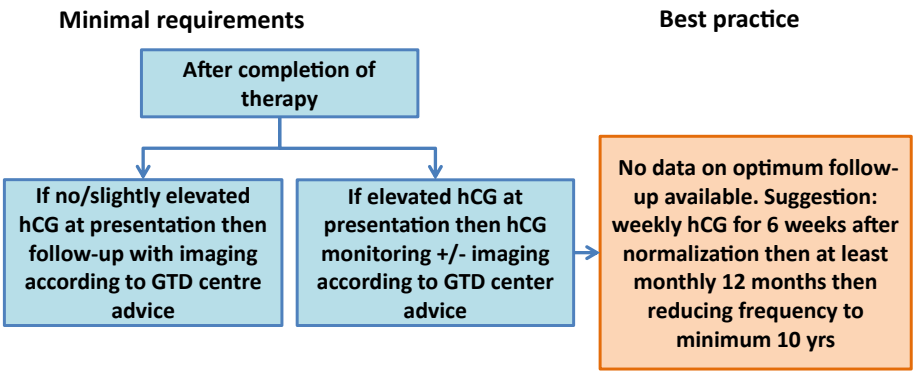

Fig. 12. Follow-up after PSTT/ETT treatment.

optimal care, participation in clinical trials and national registrations to evaluate quality of care. Moreover, to be an expert centre requires a minimum number of patients with a specific malignancy seen each year (for less common malignancies a minimum of 10 per year). Such guidelines and requirements are being developed for GTD as well.

As defined by the WHO and the European Commission, a disease is considered rare if the number of affected people is less than 5 per 10 000. All different trophoblastic diseases fulfil this definition. The care for patients with a rare disease is complicated by fundamentally different challenges compared to patients with more common diseases. The small number of patients, lack of validated diagnostic and treatment options, logistic problems due to scattering of these patients across countries and limited clinical expertise are only some of these challenges. With this fragmented disease knowledge, international networks are critical to develop well-organised research, adequate infrastructures and training of health professionals.

The EOTTD has created a platform to share data and knowledge to answer questions concerning GTD in the future. Further steps are necessary to improve the actual care of this rare patient population in Europe. The EOTTD is building networks of healthcare professionals in Europe, with the goal to provide patients with rare diseases-specialised treatment in expert centres. In line with the European reference network for rare adult solid cancer (EURACAN), EOTTD has succeeded in developing and sharing 'best practice' guidelines to prevent suboptimal treatment and to improve prognosis of GTD patients.

The main limitations of this attempt were the different participants between meetings that contributed to the different workshops. Depending on the country, overrepresentation of a specific country may have occurred which may not have been reflective of a wide range of practices. However, to mitigate this, at the start of each following meeting the previous flow diagrams were reviewed to ensure the present attendees could either modify and/or approve our recommendations. Another limitation is the lack of evidence on many topics. References were added where possible. The more evidence-based ESMO guidelines [16] are not a consensus-based guideline and advice on referral of patients for expert review is not included. The latter is really important if we are to improve patient outcomes and the lack of instructions when to refer patients into the expert centres is a clear disadvantage of the ESMO guidelines. Moreover, the flow diagrams presented here are concise and clear and can serve as a basis for patient care pathways. The latter are being widely implanted in healthcare systems around the world.

Guideline development is an on-going process. Therefore, an update of these practical guidelines will continue annually with a planned new publication every 3–5 years depending on the progress in the field.

Conflict of interest statement

None of the authors has a conflict of interest. There was no funding for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.02.011.

Appendix

Co-authors of EOTTD: Miguel Henriques Abreu, Jocelyne Attia, Kirsty Balanchandran, Alice Bergamini, Pierre Adrien Bolze, Lotte Boog, Leigh Bowman, Antonio Casado, Patrick Chien, Raffaella Cioffi, John Coulter, Sarah Delcominette, Hind Hamad Elmalik, Yalck Eysbouts, Vildana Finci, Minke Frijstein, Vilmos Fulop, Frederic Goffin, Fernando Manuel Ribeiro Gomes, Cantù Maria Grazia, Eva-Maria Grischke, Sileny Han, Mehmet Harma, Muge Harma, Su Harma, Anne Hills, Jane Ireson, Ulrika Joneborg, Saša Kadija, Janne Kaern, Catriona Kenneally, Vesna Kesic, Jacob Korach, Miroslav Korbel, Jean Pierre Lotz, Georgia Mangili, Gloria Marquina, Jerome Massardier, Amit Mayer, Ulrike Meyer-Hamme, Magdalena Miedzińska, Isa Niemann, Nelleke Ottevanger, Sinan Ozalp, Sophie Patrier, Eva Maria Roes, Ginette Rosseel, Angela Salerno, Naveed Sarwar, Franziska Siegenthaler, Kamaljit Singh, Luisa Skupin, Olesya Solheim, Lone Sunde, Grzegorz Szewczyk, John Tidy, Nataliya Tsip, Gitta Turowski, Manuela Undurraga, Erika Utracka, Emelie Wallin, Anneke Westermann, Matthew Winter, Benoit You.

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