RATIONALE FOR CENTRALIZATION AND FUTURE DIRECTIONS

135

Frédéric Goffin, MD, PhD, Leon Massuger, MD
Frédéric Kridelka, MD, François Golfier, MD

Gestational trophoblastic disease (GTD) refers to a highly heterogeneous group of gestational conditions arising from the trophoblast, and include molar pregnancies and trophoblastic tumours or neoplasia (GTN) (1, 2). All of these trophoblastic conditions are rare diseases. Hydatidiform mole (HM) is the most common form of GTD. The reported incidence varies widely in different regions of the world. In North America and Europe, rates of HM are about 0.5 to 1 per 1000 pregnancies. In addition to their rarity, they show high heterogeneity in terms of genetics, histology, clinical behaviour, and biology. Therefore, their natural history, prognosis and outcome are variable. In case of delayed diagnosis, a complex life threatening clinical situation may be challenging to manage, i.e. extensive vaginal hemorrhage from the primitive uterine disease or from metastatic lesions in the abdomen, the chest, or the brain.

In this context of rare and heterogeneous diseases, very few randomized trials have been conducted and as a consequence, recommendations to practioners and clinicians are determined through consensus rather than based on level I evidence (3, 4, 5).

It is widely recognized that difficulties are often seen at the level of diagnosis, management and treatment.. The benefits of organized regional or national registration and the establishment of reference centers for Trophoblastic Diseases have been reported by many authors in different countries (6-8).

In this chapter, we aim to review the most relevant information pertaining to the centralization of care for GTD in Europe and worldwide, and how this centralization may benefit GTD patient outcomes.

The benefits of centralization and of referal to experienced high-volume centers have been debated over decades and have been profusely published by many authors in different countries (9-12). Recently, the Cochrane published a systematic review which aimed to assess the effectiveness of centralisation of care for patients with gynaecological cancer. A meta-analysis of three studies assessing over 50,000 women, demonstrated that teaching centres or regional cancer centres may prolong survival in women with any gynaecological cancer compared to community or general hospitals. The largest of these studies included all gynaecological malignancies and assessed 48,981 women. The findings were considered highly consistent allowing the authors to conclude that consistent evidence suggests that women with gynaecological cancer who received treatment in specialised centres had longer survival than those managed elsewhere (11).

In a recent comprehensive review, Minig et al highlight the role of gynecologic oncologists (GO). It has been demonstrated that specialized physicians working in multidisciplinary teams to treat women with gynecological cancers are able to obtain the best clinical and oncological outcomes. This model of care assumes that care of most cancers is improved by centralising care within highly specialised services that include a multidisciplinary team comprising expert surgeons, radiologists, pathologists, medical oncologists and radio-oncologists, palliative care physicians and specialised nursing staff and other health professionals (9, 10, 13-15).

Ovarian cancer represents the best example of how a well-prepared specialist can positively modify the clinical and oncologic outcomes of women. There are well-documented independent prognostic factors at advanced-stage disease, including tumor histology and grade of differentiation, patient's age, stage of disease, performance status, and surgical debulking. However, the latter is the only modifiable factor, which means that it is amenable for direct influence, and therefore, seems to be of the utmost importance when considering efforts aiming toward improving outcomes of this disease. This benefit of centralization for ovarian cancer patients has been reported by many authors in different countries and results in more comprehensive staging, cytoreductive surgery, appropriate use of adjuvant therapy, and better survival. Definitive surgical treatment of most invasive cancers by subspecialist gynecologic oncologists is recommended. In addition, it is recommended that these subspecialists provide care within designated gynecologic oncology centers. The recommendations also outline which services, such as radiation therapy, may be provided in other affiliated centers. Multidisciplinary team management is also endorsed (16-19).

With regards to endometrial cancer, Chan et al conducted the first large, population-based study to evaluate the influence of subspecialty care. The influence of GOs on staging, adjuvant treatment, and survival of patients with endometrial cancer was assessed. Patients with endometrial cancer treated by gynecologic oncologists were more likely to undergo staging surgery and receive adjuvant chemotherapy for advanced disease. Care provided by gynecologic oncologists improved the survival of those with high-risk cancers. The survival benefit associated with care by a GO may be explained by their better understanding of the disease process resulting in more accurate staging followed by adjuvant treatment if indicated (20).

No studies have specifically addressed the impact on survival of women with early-stage cervical cancer treated by gynecologic oncologists. One U.S. epidemiological study, however, studied 27,660 women with cervical cancer FIGO stage IIB–IVB who were treated at hospitals with different case volumes. The study showed that the median rate of survival of patients treated at the lowest and highest volume centers were 42.3 months (95% CI 39.8–44.8) and 53.8 months (50.1–57.5), respectively ($p < 0.001$). On multi-variable analysis, higher facility volume independently predicted improved survival ($p = 0.022$), increased likelihood of receiving brachytherapy ($p < 0.0005$) and chemotherapy ($p = 0.013$), as well as shorter time to radiotherapy completion ($p < 0.0005$) (21).

The reasons why centralisation of care results in better outcomes for patients are certainly the effect of higher volume, but most importantly the management of patients based on multidisciplinary team decisions, the experience and training of expert diagnostic pathologists and radiologists, dedicated support from specialist cancer nurses and oncopsychologists whereby their support might lead to better psychological outcomes for patients and their families.

Centralization for GTD

Historically, GTN was considered a highly lethal disease mainly due to the high potential for hematogenous spread. The overall survival rate has consistently increased and overall mortality has decreased since the recognition, by Bagshawe, of efficient chemotherapy regimens in the 1970's. However, there is still more that can be done to increase adherence to guidelines, in particular with regards to limit diagnosic pitfalls and to harmonise the management. Even if uncontrollable factors largely impact the prognosis and outcomes, such as age, tumor biology and stage at the time of diagnosis, there are other modifiable factors that lend themselves for intervention (22). In 1971, Brewer et al published data showing that the morbidity and the mortaliy of GTD was decreased if an experienced team of physicians treated patients with GTD as compared to when treatment was provided by physicians who rarely encountered such diagnoses (1971). This trends was confirmed by different authors, in differents countries (24, 25).

In the United Kingdom, a national trophoblastic disease center was established in 1972 and was then mandated by the Royal College of Obstetricians and Gynecologists and the Departments of Health to register and treat all GTD patients (Charing Cross Hospital, Sheffield and Dundee) (22).

In the Netherlands, HMs are nationally registered at the Dutch Central Registry for Hydatidiform Mole (DCRH M) residing at the Radboud University Medical Centre in Nijmegen. Created in 1977, this voluntary registry serves as an epidemiological database and provides a national hCG assay service to gynaecologists. Additionally, in the Netherlands a unique nationwide network and archive was established in 1971 under the name of PALGA (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief), in order to facilitate the optimal use of histopathology and cytopathology data for research and quality control (26, 27).

In France, a voluntary reporting center was initiated by Golfier in Lyon since 2000 which, subsequently inspired and supported the creation of a referal GTD centers in Switzerland in 2009 and then in Belgium in 2012 (8, 25, 28-29).

Recognized trophoblastic centers also exist in the US (Boston, Chicago, Dallas and others), and in many other countries like Denmark, Ireland, Hungary, Canada, Brazil, China, Philippines. Unlike the UK, no other countries have a legal mandate for registration (6, 30).

GTD is a unique condition that is well suited for centralized care as the development of a unique biomarker (hCG) has allowed for specialist teams to screen all GTD patients for prospective problems. Unfortunately, with the exception of a few countries most other European countries lack a registration system for GTD. Therefore, in 2009 a european network of clinicians and researchers working in the field of GTD has been created to improve the knowledge and management of patients with GTD. The European Organisation for Treatment of Trophoblastic Disease (EOTTD) is dedicated to optimize diagnosis, treatment, follow-up and research in Gestational Trophoblastic Disease (GTD) (31).

Experience, such as that found at regional gestational trophoblastic disease treatment centers, improves outcomes in the management of malignant gestational trophoblastic disease. Any woman for whom initial therapy for invasive mole has failed or who has a choriocarcinoma diagnosis should be referred to a physician or facility with training, expertise, and experience in managing gestational trophoblastic disease. In the systematic review by the Cochrane, the authors highlight that "*choriocarcinomas and other related placental disease are extremely rare. Traditionally,*

the management of such disease takes place in supra-regionalised centres in the developed world as expertise in this field is very limited outside such centres" (11, 32, 33, 34).

Referent Pathologists Improve Diagnostic Accuracy

Molar pregnancies most commonly present with vaginal bleeding in the first or early second trimester. Ultrasound is not reliable for the diagnosis of HMs (35). The diagnosis of hydatidiform moles, choriocarcinoma (CC), PSTT and ETT is made by histological examination of curettage specimens, endo-uterine biopsy, or hysterectomy specimens as described previously (36, 37).

The histological criteria for CM and PM have been refined for early forms, which are becoming more common thanks to the frequent use of ultrasonography. In the majority of cases, morphological criteria allow to identify molar pregnancy. However, the diagnosis may be challenging for general pathologists. Differentiation of CM from PM may be difficult, particularly in the first trimester (38, 39).

The differential diagnosis between PM and nonmolar abortion may also be difficult. In extra-uterine tubal (ectopic) pregnancies, molar pregnancy is overdiagnosed. Concerning GTN, a non-villous trophoblast at the exaggerated placental site may be confused with a PSTT and the atypical non-villous trophoblast of CM may be diagnosed as a CC or a PSTT (39).

The systematic use of referent pathologists is the rule before the registration of GTD cases in the ragional or national referral centers for GTD (UK, France, Switzerland and Belgium, for example). This systematic rereading of the specimens by a dedicated gyne-pathologist improves the diagnosis of trophoblastic diseases.

- In the UK experience, the expert pathologist confirmed the diagnosis of a partial mole in about 50% of cases. In a study of 132 ectopic pregnancies with an initial diagnosis of tubal HMs, only eight cases of moles (6%) were confirmed after rereading by RPs (40, 41).
- The French Reference center conducted an exhaustive study concerning the level of agreement in the histological diagnosis of HMs and GTNs between initial pathologists and referent pathologists. The rate of agreement between the initial pathologist and the RP for the 1851 HMs was only 74%, which corresponds with a moderate level of agreement. Whereas the referent pathologist confirmed most complete moles, partial moles were only confirmed in 64% of cases. These result are similar to those published previously in retrospective studies where the diagnosis of PM was confirmed in only 68% (42).

These histological difficulties have prompted the use of complementary techniques such as p57 immunolabelling or the study of ploidy in order to improve the diagnostic performance. The combination of ploidy data and histology resulted in a remarkable improvement in agreement, which increased from 60% using histology alone to 78% for histology and ploidy together.

However, histological morphological criteria do not always enable a definite diagnosis, and complementary techniques may be necessary to confirm or overturn a possible histological diagnosis. The study of ploidy by flux cytometry in particular and labelling of protein p57 by immunohistochemistry may be useful diagnostic tools when the morphology is inconclusive (43, 44). Pitfalls in the clinical and histological diagnosis of PSTT and ETT are common. In one large retroscpective series, 32% of patients were initially misdiagnosed as having an ectopic pregnancy. As far as histology is concerned, over one-third (39%) of PSTT and ETT are either not recognised initially or are not identified from pathological specimens. The contribution of a referral pathologist to the diagnosis of this type of tumour is therefore essential (45).

These data illustrate the difficulty in diagnosing GTD and the benefit of using experts in trophoblast pathology. The importance of referral pathologists with expertise in diagnosing trophoblastic diseases is essential and all efforts should be made to improve access to this type of expert in different countries.

Referent Centers Improve Patients Outcomes

GTN are unfrequent, heterogenous in terms of genetics histology, clinics and outcomes. The widespread variation in management of such cancers can present significant diagnostic and therapeutic challenges to both patients and clinicians. Awareness of the diverse disease types, clinical presentations and therapeutic options can potentially be limited in non-specialised units (24). Many authors from UK, France, the Netherlands, US and others reported their experience gained from the activities in regional or national referal centers in GTD and supported the benefits gained from a centralisation network. This specific point was recently reviewed by Kohorn leading to the conclusion that patients treated by physicians experienced in the management of trophoblastic disease have better results and survival (6, 34, 46).

Gestational choriocarcinoma is highly chemosensitive, which lends itself to high cure rates even in the presence of metastatic disease. Deaths from GTN are now rare events, with the overall cure rate exceeding 95%. The overall survival rate approaches 100% for low-risk GTN and 81–89% for high-risk GTN. Risk factors related to fatal GTN include histolopathologic diagnosis of choriocarcinoma, high initial hCG level, long duration

of disease, multiple sites and increasing number of metastases, antecedent nonmolar pregnancy, and extent of prior treatment (46).

Patients presenting with high risk characteristics should receive aggressive multiagent chemotherapy, often in combination with surgery and radiation therapy, to maximize their chance for cure. Exposure to inadequate first-line chemotherapy probably contributes to the development of chemoresistant disease. With regards to inadequate initial therapy, Neubauer et al showed that despite all patients who died presenting with FIGO Stage III or IV disease, only two-thirds of patients received multiagent chemotherapy as their first-line treatment. Furthermore, approximately one third of patients presented to the referal center after being treated at an outside facility. These results echo findings from earlier case studies demonstrating that there is still a need to refer to patients with GTN to specialized treatment centers, especially patients with high-risk GTN, so that they receive appropriately aggressive, multimodality therapy (47).

The challenge currently is to provide all patients with appropriate therapy for the greatest chance of cure. Centers specialized in treatment of GTN may also be more adapted at applying salvage chemotherapy, often in conjunction with surgical resection of sites of persistent tumor in a timely fashion which results in improved survival (3,4).

On the other hand, it should not be underestimated that treatment failures are complex and are not ony related to drug resistance, but may also be related to treatment toxicities that may result in patients death as a direct result of toxicity to the chemotherapy. Therefore, appropriate risk classification is essential to start the right initial therapy and to prevent therapy resistance. Multiagent chemotherapy regimens are then proposed to patients who present with high risk disease or to those who develop resistance to single agent chemotherapy in order to avoid overtreatment and undue toxicities (48, 49). In a retrospective review of the French activity, Golfier et al reported that 29% of the GTN patients who required chemotherapy received, when treated outside of the referal centers, unadapted treatments in terms of cytotoxic regimens, doses, schedules or number of consolidation cycles. For example, 8,3% of the patients with low-risk GTN were initialy treated with multiagent chemotherapy and 10% of the high-risk patients were initially treated with single agent chemotherapy (25).

In addition to improved treatment, *earlier diagnosis* plays a important role in improved survival, because longer time interval between the antecedent pregnancy and the start of treatment is associated with higher rates of metastatic disease and higher hCG levels but also with lower survival rates.

Referent Centers May Impact Surgical Management

The management of molar pregnancies requires uterine evacuation by suction, ideally under sonographic guidance to ensure uterine vacuity (3). In the past, when persistent trophoblastic disease after molar evacuation, a second curettage was frequently performed. The decision to treat early with chemotherapy versus attempted cure with repeated uterine evacuation remains an area of debate. The pro's highlight the potential of surgery alone to cure patients with persistent GTN, making the hypothesis that a second curettage would act as a "debulking" effect which would result in less patients needing chemotherapy for their PTD and if chemotherapy is needed, less courses of chemotherapy. The con's argue that repeated procedures may be more harmfull than beneficial since most patients in this situation will requires chemotherapy and, since repeated uterine curetage may be associated with complications such as bleeding, uterine perforation, post-evacuation infection, uterine synechia (50).

In UK, the Charing Cross team suggest that the referring teams discuss this issue with reference center prior to repeated evacuation. The Charing Cross referal center shows the results of an audit of second evacuations suggesting that repeated curetage is rarely of benefit when the hCG level is >1500 IU/L (http://www.hmole-chorio.org.uk/clinicians_info_pre_cxh.html).

In their Editorial, Garner et al recognized that in countries where organized regional and national registries exist, patient follow-up is efficient, and loss to follow-up is quite uncommon. Therefore, a systematic surveillance based on hCG monitoring is feasible in such practice settings allowing to achieve a high cure rate whilst exposing the minimum number of patients to cytotoxic therapy or unneeded surgery. Elsewhere where organized registeries are not available, follow-up may not be entirely reliable, a lower threshold for treatment is one method to avoid adverse outcomes from loss to follow-up. The criteria for diagnosis of postmolar GTN are, accordingly, less stringent (51).

GTN mostly affects women in their reproductive years. They are among the most curable malignancies thanks to an intrinsic sensitivity to chemotherapy. Surgical treatments are however still useful for the removal of resistant disease, to control lifethreatening hemorrhage or to treat PSTT. When there is no fertility desire, hysterectomy is a valid option to treat mole or GTN confined to the uterus. It has also been suggested that when ressources linked to organized referal centers are available, the use of repeated uterine evacuation may be limited, unneeded hysterectomy in case of fertility desire may be avoided but timely surgical procedures are proposed in case of reistant disease (52).

In conclusion, improvements in survival through the last decades were attributed to development of sensitive hCG assays to monitor disease, identification of high-risk factors that allowed individualization of treatment, and aggressive use of multiagent chemotherapy regimens to treat high-risk patients but also to the involvement of specialized treatment centers in treatment plans. This observation led the American College of Obstetricans and Gynecologist to support the view that any woman for whom initial therapy for invasive mole has failed or who has a choriocarcinoma diagnosis should be referred to a physician or facility with training, expertise, and experience in managing gestational trophoblastic disease such as that found at regional gestational trophoblastic disease treatment centers.

Current guidelines result in an overall recommendation that treatment of most invasive gynecologic cancers including GTD should be performed by subspecialists in designated GOC working working in multidisciplinary teams.

Future Directions

The establishment of the European Organisation for the Treatment of Trophoblastic disease (EOTTD) provides a wonderful platform to improve the management of patients with GTD throughout Europe. Currently, only a small number of european countries have units that offer specialised/centralised care. In the vast majority of countries care for these patients is still provided by individual non-subspecialised physisians that try to do their best to deliver the most optimal management. The management of GTD is based on three important pillars; (1) pathology, (2) hCG measurement and (3) clinical management. In most countries post evacuation pathology is not seen by a reference pathologist. From several recent research papers we have learned that initial histopathological diagnosis is incorrect in a relatively large number of cases leading to suboptimal management in women all over Europe.

With the help of the European Society of Gynecologic Oncology (ESGO), EOTTD has already initiated teaching modules in a few countries. These teaching modules are given as a kind of symposia consisting of lectures given by specialists from all three management pillars. During these symposia we try to initiate the establishment of local centres of expertise.

EOTTD is also working on the development of an international database for european patients with trophoblast disease. This database will fascilitate mainly epidemiological research for every member of the society that is interested to do so. This research will provide more accurate information on incidence, management and prognosis of GTD in our part of the world. It will also be the basis to start discussions on how to improve our management.

We aim to create one or more centres of expertise in all countries throughout Europe. In these centres we would like to see experts on all three parts of management (pathology, hCG and managemetn). During the anual EOTTD meetings collegues from all european centres will meet and discuss new management strategies and results form GTD research. To establish centres in every european country will take a number of years. In the meantime we would like to create a surrogate type of european specialised care by providing ways to contact already existing experts for all three parts of management that can be found on the website of EOTTD. These experts can be contacted by anyone that needs information for the management of there patients with GTD. In this way we hope to create the best possible management for all these mainly young women with GTD in europe.

References

1. WHO. World health organization classification of tumors. In: Tavassoli FA, Devilee P (eds). Pathology and Genetics. Tumours of the Breast and Female Genital Organs. Lyon, IARC Press, 2003;250–255.
2. Genest DR, Berkowitz RS, Fisher RA, Newlands ES, Fehr M- Gestational trophoblastic disease. In Tavassoli FA, Devilee P (Ed.), WHO Classification of Tumours. Pathology and genetics of tumors of the breast and female genital organs. IARC Press, Lyon, 2003, 250-254.
3. Bolze P-A, Attia J, Massardier J, Seckl MJ, Massuger L, van Trommel N, et al. Formalised consensus of the European Organisation for Treatment of Trophoblastic Diseases on management of gestational trophoblastic diseases. Eur J Cancer. Elsevier Ltd; 2015 Sep 1;51(13):1725–31.
4. Mangili G, Lorusso D, Brown J, Pfisterer J, Massuger L, Vaughan M, et al. Trophoblastic Disease Review for Diagnosis and Management: A Joint Report From the International Society for the Study of Trophoblastic Disease, European Organisation for the Treatment of Trophoblastic Disease, and the Gynecologic Cancer InterGroup. Int J Gynecol Cancer. 2014 Nov;24(9 Suppl 3):S109–16.
5. Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C, et al. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2013 Sep 27;24(suppl 6):vi39–vi50.
6. Kohorn E, Worldwide Survey of the Results of Treating Gestational Trophoblastic Disease, J Reprod Med, 2014; 59(3):145-153.
7. Agarwal R, et al Management and survival of patients with FIGO high-risk gestational trophoblastic neoplasia: the U.K. experience, 1995-2010. J Reprod Med. 2014 Jan-Feb;59(1-2):7-12
8. Golfier F, Raudrant D, Frappart L.— First epidemiological data from The French Trophoblastic Disease Reference Centre. *Am J Obstet Gynecol*, 2007, 196, 1-5.
9. Minig L, et al.The Relevance of Gynecologic Oncologists to Provide High Quality of Care to Women with Gynecological Cancer. Front Oncol. 2016 Jan 14;5:308

10. Fung-Kee-Fung M, Int J Gynecol Cancer. 2015 May;25(4):551-8. An organizational guideline for gynecologic oncology services.
11. Woo YL et al. Centralisation of services for gynaecological cancer. Cochrane Database Syst Rev. 2012 Mar 14;3
12. Woo YL et al. Centralisation of services for gynaecological cancers - a Cochrane systematic review. Gynecol Oncol. 2012 Aug;126(2):286-90.
13. Vernooij F, et al. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. *Gynecol Oncol* (2007) 105(3):801–12.
14. du Bois A, et al. Variations in institutional infrastructure, physician specialization and experience, and outcome in ovarian cancer: a systematic review. *Gynecol Oncol* (2009) 112(2):422–36.
15. Fung-Kee-Fung M, et al. The optimal organization of gynecologic oncology services: a systematic review. *Curr Oncol* (2015) 22(4):e282–93
16. Cowan RA et al, Is It Time to Centralize Ovarian Cancer Care in the United States? Ann Surg Oncol. 2016 Mar;23(3):989-93.
17. Fung-Kee-Fung et al. An organizational guideline for gynecologic oncology services. . Int J Gynecol Cancer. 2015 May;25(4):551-8.
18. European Society of Gyencological Cancer (ESGO). *Document of Quality Indicators of Surgery in Advanced Stage Ovarian Cancer* (2015). Available from: https://drive.google.com/file/d/0B9BpaJiYFz9oNE1PemlKcVY5T1U/view
19. Cliby et al, Ovarian cancer in the United States: contemporary patterns of care associated with improved survival. Gynecol Oncol. 2015 Jan;136(1):11-7.
20. Chan JK et al. Influence of gynecologic oncologists on the survival of patients with endome-trial cancer. *J Clin Oncol* (2011) 29(7):832–8. doi:10.1200/JCO.2010.31.2124
21. Lin JF et al, Impact of facility volume on therapy and survival for locally advanced cervical cancer. Gynecol Oncol. 2014 Feb;132(2):416-22.
22. Seckl M et al. Gestational trophoblastic disease. Lancet. 2010 Aug 28;376(9742):717-29.
23. Brewer et al, Gestational trophoblastic disease. A comparative study of the results of therapy in patients with invasive mole and with choriocarcinoma. Am J Obstet Gynecol 1971;109:335-340
24. Lybol C et al. Fatal cases of gestational trophoblastic neoplasia over four decades in the Netherlands: a retrospective cohort study. BJOG. 2012 Nov;119(12):1465-72.
25. Golfier F et al, Evaluation of treatment relating to gestational trophoblastic tumor registered to the French Trophoblastic Disease Reference Center (TDRC) in Lyon from 1999 to 2005. Gynecol Obstet Fertil. 2007 Mar;35(3):205-15.
26. Eysbouts Y et al, Trends in incidence for gestational trophoblastic disease over the last 20years in a population-based study. Gynecol Oncol. 2016 Jan;140(1):70-5.
27. Lybol C et al. Centralised registration of gestational trophoblastic disease and trends in incidence. Acta Oncologica, 2012;51:3, 415-416.
28. http://mole-chorio.hug-ge.ch/
29. Delcominette S et al. Belgian register and reference centers for gestational trophoblastic diseases. Rev Med Liege. 2015 Nov;70(11):550-6.
30. Faaborg L, Niemann I, et al. Acta Oncol. 2015 Jun 24:1-6. A 30-year experience in using oral methotrexate as initial treatment for gestational trophoblastic neoplasia regardless of risk group.
31. European Organisation for Treatment of Trophoblastic Disease. 2011. Available from: http://eottd.org/
32. Soper JT et al , Diagnosis and treatment of gestational trophoblastic disease: ACOG Practice Bulletin No. 53. Gynecol Oncol. 2004 Jun;93(3):575-85.
33. Sun et al. Clinical Presentation of Complete Hydatidiform Mole and Partial Hydatidiform Mole at a Regional Trophoblastic Disease Center in the United States Over the Past 2 Decades. Int J Gynecol Cancer. 2016 Feb;26(2):367-70.
34. Lurain et al. Results of treatment of patients with gestational trophoblastic neoplasia referred to the Brewer Trophoblastic Disease Center after failure of treatment elsewhere (1979-2006). J Reprod Med 2008;53:535-40.
35. Sebire et al. The diagnostic implications of routine ultrasound examination in histologically confirmed early molar pregnancies. Ultrasound Obstet Gynecol 2001;18:662–665.
36. Petts J et al, Histopathological and immunohistochemical features of early hydatidiform mole in relation to subsequent development of persistent gestational trophoblastic disease. J Reprod Med. 2014 May-Jun;59(5-6):213-20.
37. Sebire N et al, Immunohistochemical staining for diagnosis and prognostic assessment of hydatidiform moles: current evidence and future directions. J Reprod Med. 2010 May-Jun;55(5-6):236-46;
38. Sebire N et al , Updated diagnostic criteria for partial and complete hydatidiform moles in early pregnancy. Anticancer Res 2003;23:1723–1728.
39. Wells M. The pathology of gestational trophoblastic disease: recent advances. Pathology 2007;39:88–96.
40. Paradinas F, The diagnosis and prognosis of molar pregnancy: the experience of the National Referral Centre in London. Int J Gynaecol Obstet 1998;60:57–64.
41. Sebire N et al, Overdiagnosis of complete and partial hydatidiform mole in tubal ectopic pregnancies.Int J Gynecol Pathol 2005;24:260–264.
42. Golfier F et al, Contribution of referent pathologists to the quality of trophoblastic diseases diagnosis. Hum Reprod. 2011 Oct;26(10):2651-7
43. Kipp B et al, Comparison of fluorescence in situ hybridization, p57 immunostaining, flow cytometry, and digital image analysis for diagnosing molar and nonmolar products of conception. Am J Clin Pathol 2010;133:196–204.
44. Fisher et al, Clinical utility of selective molecular genotyping for diagnosis of partial hydatidiform mole; a retrospective study from a regional trophoblastic disease unit. J Clin Pathol. 2014 Nov;67(11):980-4
45. Moutte A et al, Placental site and epithelioid trophoblastic tumours: diagnostic pitfalls, Gynecol Oncol. 2013 Mar;128(3):568-72.

46. Neubauer NL et al, Fatal gestational trophoblastic neoplasia: An analysis of treatment failures at the Brewer Trophoblastic Disease Center from 1979-2012 compared to 1962-1978. Gynecol Oncol. 2015 Aug;138(2):339-42.
47. Hoekstra A et al, Gestational trophoblastic neoplasia treatment outcomes. Obstet. Gynecol. 112 (2008) 251–258.
48. Lurain JR. Causes of treatment failure in gestational trophoblastic disease. J Reprod Med 1987; 32: 675-9
49. Mazur MT, Lurain JR, Brewer JI. Fatal gestational choriocarcinoma. Clinicopathologic study of patients treated at a trophoblastic disease center. Cancer 1982; 50: 1833-46.
50. van Trommel N et al, The curative effect of a second curettage in persistent trophoblastic disease: a retrospective cohort survey. Gynecol Oncol. 2005 Oct;99(1):6-13.
51. Garner E et al. The curative effect of a second curettage in persistent trophoblastic disease: a retrospective cohort survey. Gynecol Oncol. 2005 Oct;99(1):3-5.
52. Pisal N et al, Role of hysterectomy in management of gestational trophoblastic disease. Gynecol Oncol. 2002 Nov;87(2):190-2.