TREATMENT OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

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Introduction

Gestational trophoblastic diseases (GTD) refer to a heterogeneous group of disorders arising from the trophoblastic epithelium of the placenta after normal or abnormal fertilization. The WHO classification of GTD includes hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). The malignant forms of GTD are collectively known as gestational trophoblastic tumors or neoplasia (GTN) (1). GTN can occur after any gestation including miscarriages and term pregnancies, but often arises after molar pregnancies. They show varying potential for local invasion and metastases and are generally extremely sensitive to chemotherapy (2). Currently, GTNs are among the most curable of all solid tumors. The overall survival rate exceeds 90% and it is close to 100% for low-risk GTN (3).

Diagnosis of GTN

The diagnosis of post-molar GTN is based, mostly, on clinical and biological rather than histological diagnostic criteria. The FIGO standardized hCG criteria for the diagnosis of postmolar gestational trophoblastic disease include (4):

1. hCG plateau for 4 consecutive values over 3 weeks (days 0, 7, 14, 21)
2. An hCG level increase of more than 10% on three values recorded over a 2-week duration (days 0, 7, and 14)
3. hCG persistence 6 months after molar evacuation;

GTN may also be diagnosed in case of histological diagnosis of choriocarcinoma, or presence of metastatic disease.

Women with GTN complicating non-molar pregnancies usually have subtle signs and symptoms of disease, which renders the diagnosis more difficult. GTN has the ability to spread and give metastasis in virtually every body site, most commonly the lung, vagina, liver, and brain. Histological confirmation of metastases should be avoided since the punction may cause excessive bleeding (5). For any woman presenting, in her reproductive age, with metastatic disease of unknown origin, hCG should be checked to exclude a gestational GTN (6).

Pretherapeuthic Workup of GTN

In 2000 a new FIGO staging/scoring system was elaborated to allow worldwide comparison of management of GTN (7,8). Once the diagnosis of GTN is established, a systematic assessment for local and distant spread is mandatory. Along with history/physical examinations and laboratory studies, radiologic examinations will image the pelvis (ultrasonography (US) or magnetic resonance), the chest (chest X-ray or computerized tomography (CT)), the abdomen (US or CT scan) and the brain (magnetic resonance imaging or CT scan). This throughout work-up allows scoring the patient according to the 2000 FIGO staging/scoring system (Table 1), taking into account eight variables from which a value from 0 to 4 is assigned. The score varies between 0 and 25 at the maximum. The clinical outcomes of patients treated for GTN correlate with this score that identifies reliably patients at risk for failure of single agent chemotherapy. Anatomical staging alone is not adequate. The FIGO stage (Table 2) is designated by a Roman numeral followed by the modified WHO score designated by an Arabic numeral, separated by a colon. PSTTs and ETTs are classified separately.

Use of the FIGO staging/scoring system is essential for determining initial therapy for patients with GTN to allow the best possible outcomes with the least morbidity. The current scoring defines two categories of patients: those deemed at low-risk (score equal or less than 6) and those who are at high-risk (score of 7 or higher) (5,9).

Table 1. FIGO 2000 Scoring System for Gestational Trophoblastic Neoplasia

Scores	0	1	2	4
Age	<40	≥40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval from index pregnancy (months)[a]	<4	4-<7	7-<13	≥13
Pre-treatment serum hCG (IU/mL)	$<10^3$	10^3-$<10^4$	10^4-$<10^5$	$\geq 10^5$
Largest tumor size (including uterus)	-	3-<5cm	≥5cm	
Site of metastases	Lung	Spleen, kidney	Gastro-intestinal	Liver, brain
Number of metastases[b]	-	1-4	5-8	>8
Previous failed chemotherapy	-	-	Single drug	2 or more drugs

The total score for a patient is obtained by adding the individual scores for each prognostic factor. Low risk, ≤6; high risk, ≥7.
FIGO, International Federation of Gynecology and Obstetrics ; hCG, human chorionic gonadotropin; IU/mL international units per milliliter;
[a]The interval is calculated from the end of pregnancy (term, molar or non-molar abortion) to the first day of chemotherapy.
[b]The number of metastases is considered but not the number of metastatic sites. Metastases must be counted on chest X-ray but not on computed tomography.

Table 2. FIGO Anatomical Staging

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

Treatment of Low-Risk Gestational Trophoblastic Neoplasia (FIGO score ≤6)

Chemotherapy

Patients with FIGO low-risk GTN (score of 6 and lower) are treated with single-agent chemotherapy. Several protocols (Table 3) have been used, which in mostly non randomized, retrospective studies have yielded fairly comparable overall results (1,5,10). The variability in primary remission rates reflects differences in drug dosages, schedules and routes of administration, as well as patient selection criteria. In general, the weekly intramuscular (IM) or intermittent intravenous (IV) infusion methotrexate and the biweekly single-dose dactinomycin protocols are less effective than one of the 5-day methotrexate or dactinomycin protocols and the 8-day methotrexate-folinic acid regimen.

Despite these differences in primary remission rates with initial chemotherapy, almost all patients are eventually cured with most being able to preserve fertility.

Stomatitis is the most common toxicity; alopecia and nausea are uncommon side effects.

Toxicity to methotrexate necessitating a switch to another agent occurs in less than 5%.

Factors found to be associated with resistance to initial methotrexate chemotherapy were high pre-treatment hCG levels, non molar antecedent pregnancy, and clinicopathologic diagnosis of choriocarcinoma.

Several studies, mostly retrospective studies, three randomized trials and one systematic Cochrane review have studied the regimens for treatment of low-risk GTN (10,11). Primary remission rates of patients treated with a variety of chemotherapy regimens for non metastatic gestational trophoblastic disease are similar. The complete

Table 3. Single-Agent Regimen for GTN

8-day methotrexate / folinic acid	Methotrexate (1.0-1.5 mg/kg) intramuscular on days 1, 3, 5, 7 with folinic acid rescue 15 mg given 24 or 30 h later on (days 2, 4, 6, 8) repeated every 14 days.
5-day methotrexate	Methotrexate intravenous 0.4 mg/kg on days 1 to 5 (maximum, 25 mg/day) repeated every 14 days
Weekly methotrexate	Methotrexate (50 mg/m^2) intramuscular repeated weekly
5-day dactinomycin	Dactinomycin (10-12 mg/kg or 0.5 mg total dose) intravenous daily for 5 days repeated every 14 days
Pulsed dactinomycin	Biweekly dactinomycin (a single 1.25 mg/m^2 IV dose every 2 weeks)

response rate to the initial single-agent chemotherapeutic drug range from 50% to 80%. The complete response to sequential single-agent chemotherapy is superior to 90% and about 10% of patients reach remission with the use of multiagent chemotherapy and/or surgery. Regardless of the treatment protocol used, chemotherapy is continued until hCG values have returned to normal and at least 2 courses are administered after hCG level returns to normal values (1,5,12).

Patients whose hCG levels reach a plateau or increase during therapy should be switched to an alternative single agent regimen. If metastases appear or alternative single agent chemotherapy fails, the patient should be treated with multiagent regimens. In the first year after completing therapy, the risk of relapse is less than 5% among patients successfully treated for low-risk GTN and is exceedingly low after that (13-15).

Surgery

If fertility preservation is not desired, total hysterectomy (with ovarian preservation) may be performed for low-risk GTN, especially if GTN is limited to the uterus. Hysterectomy may avoid chemotherapy or shorten the duration of chemotherapy. Hysterectomy may also become necessary in case of chemotherapy-resistant disease in the uterus or to treat severe uterine hemorrhage (16-18).

Follow-up After Remission

After hCG normalization, patients should undergo serial determinations of hCG levels at 2-week intervals for the first 3 months of remission and then at 1-month intervals until monitoring has shown 1 year of normal hCG levels. The risk of recurrence after 1 year of remission is very low (< 1%). Patients are counseled to use a reliable form of hormonal contraception during the first year of remission.

In summary, cure rate for low-risk metastatic GTN approaches 100% with the use of initial single-agent methotrexate or dactinomycin chemotherapy. Approximately 20-30% of low-risk patients will develop resistance to the initial chemotherapeutic agent, but >90% will be cured by the use of sequential single agent chemotherapy. Eventually, approximately 10% of patients will require multiagent chemotherapy with or without surgery to achieve remission.

Treatment of High-Risk Gestational Trophoblastic Neoplasia (FIGO score ≥7)

Patients with a 2000 FIGO score of ≥7 (Table 1) are at high risk of developing resistance to single agent treatment and so should be initially treated with multiagent chemotherapy (1,2,4,6,9). While different drug associations can be used, EMA-CO, an etoposide-based regimen with methotrexate, dactinomycin, cyclophosphamide and vincristine, is currently the most validated regimen worldwide (Table 4). Several groups have reported complete response rates around 70-80% and overall survival around 75-90% in high-risk patients treated with EMA-CO, mainly in the pre-FIGO 2000 scoring system era (19-21). This regimen has a well known mainly hematologic short-term toxicity (19). If any neutropenia-associated delay is observed, granulocyte colony stimulating factor (G-CSF) support should be used. Chemotherapy is continued until weekly normal hCG values are reached and 2 to 4 more courses (for 4 to 8 weeks) of EMA-CO are then given after the first normal hCG level (1,9) Initial treatment of FIGO high-risk patients with cisplatin combinations has also been reported, but significant cumulative toxicity is often observed before the whole number of consolidation courses is administered, thus compromising the ability to deliver adequate therapy.

Table 4. EMA-CO and High Dose EMA-CO

EMA-CO	Day 1 • Etoposide 100 mg/m^2 iv • Dactinomycin 0.5 mg iv • Methotrexate 300 mg/m^2 iv Day 2 • Etoposide 100 mg/m^2 iv • Dactinomycin 0.5 mg iv • Folinic acid 25 mg peros 12 hourly x 4 doses Starting 24 hours after methotrexate Day 8 • Vincristine 1 mg/m^2 (maximum, ^{2} mg) • Cyclophosphamide 600 mg/m^2
High-dose EMA-CO	Day 1 • Etoposide 100 mg/m^2 iv • Dactinomycin 0.5 mg iv • Methotrexate 1000 mg/m^2 iv Day 2 • Etoposide 100 mg/m^2 iv • Dactinomycin 0.5 mg iv • Folinic acid 50 mg peros 6 hourly x 4 doses Starting 24 hours after methotrexate Day 3-7 • Folinic acid 25mg peros 6 hourly Day 8 • Vincristine 1 mg/m^2 (maximum, 2 mg) • Cyclophosphamide 600 mg/m^2

EMA-CO: etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine ; iv, intravenous ; repeated every 14 days.

Management of brain metastasis

Patients with brain metastases at presentation are FIGO high-risk GTNs with a higher risk of demise either

from early-death associated with brain haemorrhage or late death from resistance to treatment. Reported cure rates with brain metastases at presentation are 50-95%, depending on symptoms as well as type of brain and other metastatic localizations (22,23). An adapted "high-dose EMA-CO" regimen where perfusion of MTX is increased to 1 g/m^2 is the strong basis for treatment of GTN patients with brain metastases (Table 4) (22). To reduce early or late deaths from brain localizations, several experienced groups have advocated treatment strategies concomitant to "high-dose EMA-CO" that need further validation. Thus, whole brain irradiation has been advocated with the purpose of both its tumoricidal and haemostatic activity and has been associated with the complete elimination of death (1,24). Surgical excision with stereotactic irradiation has also been used in selected patients. Similarly, intrathecal MTX has been used to augment central nervous system concentration of MTX (22). More recently, initiating chemotherapy with low-dose etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 on days 1 and 2 repeated weekly for 1 to 3 weeks has been associated with virtual elimination of early deaths in patients with very advanced disease, including brain metastases (25). A FIGO score of ≥13 has been recently advocated to become a consensual criterion for prediction of GTN patients with increased risk of death and particularly early death, where such induction chemotherapy should be further evaluated. Five-year mortality rate was 38% in patients with a FIGO of ≥13 while it was 12% in the whole high-risk group with a FIGO score of ≥7 (3).

Management of Liver Metastasis

Patients with liver metastases at presentation are also FIGO high-risk GTNs with an even higher risk of demise either from early-death associated with haemorrhage or late death from resistance to treatment (26). When excluding early deaths, survival was reported as high as 70% of patients with liver metastases (26). As these patients with liver metastases are almost always included in the FIGO score ≥13 group, induction chemotherapy with etoposide 100 mg/m^2 with cisplatin 20 mg/m^2 could be an excellent indication.

Resistance to Polychemotherapy

Approximately 30% of patients with FIGO high-risk GTN will have an incomplete response to first-line multiagent chemotherapy or will relapse from remission and require second line chemotherapy (27,28). Such FIGO high-risk patients who have developed resistance to EMA-CO or other etoposide-containing protocols should be treated with drug combinations employing a platinum agent. The EMA-EP regimen (etoposide and cisplatin alternating weekly with etoposide, methotrexate and dactinomycin), is considered the most appropriate therapy for such patients (29). Its significant severe hematologic toxicity is however a clear limitation. TP-TE (alternating paclitaxel and cisplatin with paclitaxel and etoposide), a paclitaxel-based protocol with lower toxicity (30), is currently under investigation in a randomized trial. In FIGO high-risk patients with failure of different lines of multiagent chemotherapy, high-dose chemotherapy with peripheral autologous stem-cell transplantation or peripheral stem cell support may be of use in highly specialized centres (31). Published data about targeted cancer therapies are currently very limited in the field of GTN even if promising theoretical arguments could be further developed for multi-drug-resistant disease (9).

Surgery

While surgery of metastases is not routinely indicated for FIGO high risk GTN (6), adjuvant surgical procedures may be necessary in selected patients, either at the time of initial treatment with multiagent chemotherapy or at the time of resistance or relapse as part of salvage therapy. Hysterectomy may be mandatory in some cases to control heavy bleeding at presentation even if selective angiographic artery embolization of the uterine arteries should be an available alternative, at least in young women when childbearing considerations have not been fulfilled. Emergency surgery for uterine suturing or partial hysterectomy may also be necessary in case of a hemoperitoneum from rupture of a subserosal myometrial location of a trophoblastic tumour. Such an emergency surgery may be of use for bowel location with hemoperitoneum or occlusion. Emergency brain surgery should also be part of the available means in case of life-threatening intracranial bleeding from metastases. Thoracic surgery may be of use in removing active isolated lung locations of chemotherapy resistant disease in selected patients with persistent or recurrent high-risk GTN (32). Care should be taken not to operate on patients with persisting lung images while hCG levels have returned to normal with chemotherapy. Such persistent images are considered as conjunctive and vascular residues with no tumour cells that could be a misleading indication for surgery (6).

PSTT and ETT

Total hysterectomy is the reference treatment for PSTT and ETT confined to the uterus (FIGO stage I) because of the relative resistance of these tumours to chemotherapy (6,9). Before indicating such a radical surgery in a young woman, histologic diagnosis of PSTT or ETT should be reviewed by a referent pathologist before implementing treatment (6). Indication for chemotherapy in FIGO stage I PSTT seems to be limited to the subgroup of patients with a long interval ≥48 months between antecedent pregnancy and development of tumour. In a multivariate analysis, this duration has been identified as the only predictive factor for survival of PSTT. Combined surgery

and chemotherapy seem to be the best approach for FIGO stage II - IV PSTT and ETT (33). EP-EMA and TP-TE are the usual protocol used although the best regimen is not yet defined due to the rarity of such trophoblastic tumours. The survival rate is approximately 100% for stage I disease while it decreases to around 50-60% for metastatic disease. Cure of PSTT with long interval ≥48 months from antecedent pregnancy seems to be around 2% only.

References

1. Lurain JR. Gestational trophoblastic disease II: classification and management of gestational trophoblastic neoplasia. Am J Obstet Gynecol. Elsevier; 2011 Jan;204 (1):11–8.
2. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. Lancet. Elsevier; 2010;376 (9742):717–29.
3. Bolze P-A, Riedl C, Massardier J, Lotz J-P, You B, Schott A-M, et al. Mortality of gestational trophoblastic neoplasia with a FIGO score of 13 and higher. Am J Obstet Gynecol. Elsevier; 2015 Sep 30;0 (0).
4. FIGO Oncology Committee. FIGO staging for gestational trophoblastic neoplasia 2000. FIGO Oncology Committee. Int J Gynaecol Obstet. 2002 Jun;77 (3):285–7.
5. 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.
6. 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.
7. Ngan HY, Bender H, Benedet JL, Jones H, Montruccoli GC, Pecorelli S, et al. Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. International Journal of Gynecology and Obstetrics. 2003 Oct;83 Suppl 1:175–7.
8. Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. International Journal of Gynecological Cancer. 2001 Jan;11 (1):73–7.
9. 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.
10. Alazzam M, Tidy J, Osborne R, Coleman R, Hancock BW, Lawrie TA. Chemotherapy for resistant or recurrent gestational trophoblastic neoplasia. Alazzam M, editor. Cochrane Database Syst Rev. Chichester, UK: John Wiley & Sons, Ltd; 2012;12:CD008891.
11. Osborne RJ, Filiaci V, Schink JC, Mannel RS, Alvarez Secord A, Kelley JL, et al. Phase III trial of weekly methotrexate or pulsed dactinomycin for low-risk gestational trophoblastic neoplasia: a gynecologic oncology group study. J Clin Oncol. American Society of Clinical Oncology; 2011 Mar 1;29 (7):825–31.
12. Lybol C, Sweep FCGJ, Harvey R, Mitchell H, Short D, Thomas CMG, et al. Relapse rates after two versus three consolidation courses of methotrexate in the treatment of low-risk gestational trophoblastic neoplasia. Gynecol Oncol. Elsevier Inc; 2012 Jun 1;125 (3):576–9.
13. Taylor F, Short D, Winter MC, TIDY J, Savage PM, Sarwar N, et al. A retrospective study to evaluate single agent methotrexate treatment in low risk gestational choriocarcinoma in the United Kingdom. Gynecol Oncol. Elsevier Inc; 2015 Feb 1;136 (2):258–63.
14. Taylor F, Grew T, Everard J, Ellis L, Winter MC, TIDY J, et al. The outcome of patients with low risk gestational trophoblastic neoplasia treated with single agent intramuscular methotrexate and oral folinic acid. Eur J Cancer. Elsevier; 2013 Oct;49 (15):3184–90.
15. Chapman-Davis E, Hoekstra AV, Rademaker AW, Schink JC, Lurain JR. Treatment of nonmetastatic and metastatic low-risk gestational trophoblastic neoplasia: factors associated with resistance to single-agent methotrexate chemotherapy. Gynecol Oncol. 2012 Jun;125 (3):572–5.
16. Eoh KJ, Chung YS, Yim GW, Nam EJ, Kim S, Kim SW, et al. Role of surgical therapy in the management of gestational trophoblastic neoplasia. Obstet Gynecol Sci. 2015;58 (4):277–7.
17. Massardier J, Mathe M, Bolze PA, Hajri T, Devouassoux-Shisheboran M, Schott A-M, et al. Hysterectomy in case of low-risk gestational trophoblastic neoplasia. Oncologie. 2014 Jun 6;16 (6):285–90.
18. Soper JT. Role of surgery and radiation therapy in the management of gestational trophoblastic disease. Best Practice & Research Clinical Obstetrics & Gynaecology. 2003 Dec;17 (6):943–57.
19. Bower M, Newlands ES, Holden L, Short D, Brock C, Rustin GJ, et al. EMA/CO for high-risk gestational trophoblastic tumors: results from a cohort of 272 patients. Journal of Clinical Oncology. 1997 Jul;15 (7):2636–43.
20. Turan T, Karacay O, Tulunay G, Boran N, Koc S, Bozok S, et al. Results with EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) chemotherapy in gestational trophoblastic neoplasia. International Journal of Gynecological Cancer. Blackwell Publishing Inc; 2006 May;16 (3):1432–8.
21. Escobar PF, Lurain JR, Singh DK, Bozorgi K, Fishman DA. Treatment of high-risk gestational trophoblastic neoplasia with etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine chemotherapy. Gynecol Oncol. 2003 Dec;91 (3):552–7.
22. Rustin GJ, Newlands ES, Begent RH, Dent J, Bagshawe KD. Weekly alternating etoposide, methotrexate, and actinomycin/vincristine and cyclophosphamide chemotherapy for the treatment of CNS metastases of choriocarcinoma. Journal of Clinical Oncology. 1989 Jul;7 (7):900–3.
23. Evans AC, Soper JT, Clarke-Pearson DL, Berchuck A, Rodriguez GC, Hammond CB. Gestational trophoblastic disease metastatic to the central nervous system. Gynecol Oncol. 1995 Nov;59 (2):226–30.
24. Yordan EL, Schlaerth J, Gaddis O, Morrow CP. Radiation therapy in the management of gestational choriocarcinoma metastatic to the central nervous system. Obstetrics & Gynecology. 1987 Apr;69 (4):627–30.

25. Alifrangis C, Agarwal R, Short D, Fisher RA, Sebire NJ, Harvey R, et al. EMA/CO for high-risk gestational trophoblastic neoplasia: good outcomes with induction low-dose etoposide-cisplatin and genetic analysis. Journal of Clinical Oncology. American Society of Clinical Oncology; 2013 Jan 10;31 (2):280–6.
26. Bakri YN, Subhi J, Amer M, Ezzat A, Sinner W, Tweijry A, et al. Liver metastases of gestational trophoblastic tumor. Gynecol Oncol. Elsevier; 1993 Jan;48 (1):110–3.
27. Lurain JR, Nejad B. Secondary chemotherapy for high-risk gestational trophoblastic neoplasia. Gynecol Oncol. Elsevier; 2005 May;97 (2):618–23.
28. Powles T, Savage PM, Stebbing J, Short D, Young A, Bower M, et al. A comparison of patients with relapsed and chemo-refractory gestational trophoblastic neoplasia. Br J Cancer. Nature Publishing Group; 2007 Mar 12;96 (5):732–7.
29. Newlands ES, Mulholland PJ, Holden L, Seckl MJ, Rustin GJ. Etoposide and cisplatin/etoposide, methotrexate, and actinomycin D (EMA) chemotherapy for patients with high-risk gestational trophoblastic tumors refractory to EMA/cyclophosphamide and vincristine chemotherapy and patients presenting with metastatic placental site trophoblastic tumors. Journal of Clinical Oncology. 2000 Feb;18 (4):854–9.
30. Wang J, Short D, Sebire NJ, Lindsay I, Newlands ES, Schmid P, et al. Salvage chemotherapy of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE). Annals of Oncology. 2008 May 13;19 (9):1578–83.
31. Lotz JP, Machover D, Malassagne B, Hingh B, Donsimoni R, Gumus Y, et al. Phase I-II study of two consecutive courses of high-dose epipodophyllotoxin, ifosfamide, and carboplatin with autologous bone marrow transplantation for treatment of adult patients with solid tumors. Journal of Clinical Oncology. 1991 Oct;9 (10):1860–70.
32. Tomoda Y, Arii Y, Kaseki S, Asai Y, Gotoh S, Suzuki T, et al. Surgical indications for resection in pulmonary metastasis of choriocarcinoma. Cancer. 1980 Dec 15;46 (12):2723–30.
33. Schmid BC, Reilly A, Oehler MK. Management of nonpregnant women with elevated human chorionic gonadotropin. Case Rep Obstet Gynecol. Hindawi Publishing Corporation; 2013;2013 (1):580709–3.