Gestational Trophoblastic Neoplasia, FIGO 2000 staging and classification

HYS NGAN, H BENDER, JL BENEDET, H JONES, GC MONTRUCCOLI, S PECORELLI
(FIGO Committee on Gynecologic Oncology)

Gestational trophoblastic diseases are composed of a spectrum of abnormal trophoblastic proliferation ranging from the benign mole to malignant choriocarcinoma with an intermediate entity based on clinical rather than histological diagnostic criteria. The benign mole may proceed to the intermediate form, which – if left untreated – may end up in death. This intermediate entity bears different names such as malignant mole, gestational trophoblastic tumor, persistent/malignant gestational trophoblastic disease that is further divided into non-metastatic, metastatic and gestational trophoblastic neoplasia. In the FIGO Committee on Gynecologic Oncology 2000 Report, the term gestational trophoblastic neoplasia (GTN) was recommended.

HISTORY OF STAGING

FIGO staging is essentially anatomically based. The spread of choriocarcinoma roughly followed the basic concept of FIGO staging. In the FIGO 1982 GTN staging, Stage I is confined to the uterus; Stage II is spread to pelvis and vagina; Stage III is spread to lung and Stage IV to other distant metastatic sites. Song et al[1] reported that all brain metastases have co-existing lung metastasis. This assumption suggested that the first stage of distant spread was in the lung, hence lung metastasis was assigned an earlier stage than brain. Problems were found with this staging system when a reliable tumor marker, human chorionic gonadotropin hormone (shCG) was used in the diagnosis and monitoring of GTN and histological differentiation of invasive mole and choriocarcinoma was not possible. Also, after the first report of cure of choriocarcinoma with chemotherapy alone, surgical resection and histological assessment become an unusual practice. The majority of GTN were clinically diagnosed. Very soon, clinicians found that other risk factors affect the prognosis of patients with GTN. A patient with Stage III GTN may have the same prognosis as an earlier stage GTN. Anatomical staging alone is not adequate. Different countries or societies used different mix of anatomical and clinical factors in staging GTN, such as types of antecedent pregnancy, interval of treatment from antecedent pregnancy, blood groups of couple, size and number of metastatic lesions, age and so on. A working group on WHO classification in 1983 proposed to unify the prognostic factors used in GTN and adopted 9 prognostic factors[2] from Bagshawe's scoring system[3]. In 1992, the FIGO Committee on Gynecologic Oncology – after looking into the prognostic significance of various prognostic factors – had simplified the 9 factors to 2 only, and incorporated these into the FIGO staging[4]. Retrospective analysis comparing the FIGO 1992 and WHO classification showed similar efficacy in discriminating low- and high-risk patients[5,6].

The International Society on the Study of Gestational Trophoblastic Diseases raised the concern that the 2 prognostic factors may not represent the most significant independent factors. Indeed, different multivariate analysis on prognostic factors came up with different sets of independent prognostic factors[7–11]. Possible reasons are the use of different diagnostic criteria, different investigative tools, different risk group classification which affect choice of chemotherapy and the different chemotherapeutic regimens used in different centers. It is for this reason, after several international seminars, meetings and workshops held at meetings of ISSGTD, International Gynecologic Cancer Society and FIGO co-ordinated by Dr. E Kohorn[12,13], that four major consensus statements were reached, recommended to the FIGO Committee on Gynecologic Oncology and adopted in 2000.

The first consensus statement regards terminology, as already mentioned at the beginning of this paper. To avoid confusion, the term GTN is recommended for the group of abnormal gestational trophoblastic proliferation that required treatment for potential or proven malignancy.

The second consensus statement regards the diagnostic criteria of GTN following a mole. It would be impossible to have a meaningful staging when there is variation in defining what constitutes a disease.

Criteria for the Diagnosis of Post Hydatidiform Mole Trophoblastic Neoplasia (GTN)[14]

(1) GTN may be diagnosed when the plateau of human chorionic gonadotropin (hCG) lasts for 4 measurements over a period of 3 weeks or longer, that is day 1, 7, 14, 21.
(2) GTN may be diagnosed when there is a rise of hCG of three weekly consecutive measurements or

Correspondence to: FIGO Annual Report Editorial Office, European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy
fax: +39-0257489872, e-mail: figo@ieo.it

Table 1
FIGO 2000 staging and classification of GTN

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

Modified WHO Prognostic Scoring System as Adapted by FIGO

Scores	0	1	3	4
Age	<40	⩾40	–	–
Antecedent pregnancy	mole	abortion	term	–
Interval months from index pregnancy	<4	4 –<7	7– <13	⩾13
Pretreatment serum hCG (iu/l)	$<10^3$	10^3–$<10^4$	10^4–$<10^5$	⩾10^5
Largest tumor size (including uterus)	–	3–<5 cm	⩾5 cm	–
Site of metastases	lung	spleen, kidney	gastro-intestinal	liver, brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	single drug	2 or more drugs

Format for reporting to FIGO Annual Report. In order to stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III, and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, e.g. Stage II:4, Stage IV:9. This stage and score will be allotted for each patient.

longer, over at least a period of 2 weeks or more days 1, 7, 14.

(3) GTN is diagnosed when the hCG level remains elevated for 6 months or more.

GTN is diagnosed if there is a histological diagnosis of choriocarcinoma.

The third consensus statement regards the recommendation of investigative tools. Many new investigative tools give much better resolution and can pick up small metastasis not visible before. The prognostic implication of this small metastasis has not been thoroughly investigated. Since GTN differs from other solid tumor where cytology or histology confirmation of metastatic lesion on imaging is recommended and the implication of metastatic tumor is ominous, one has to be careful in interpreting the significance of "metastasis" in GTN. It is hoped that even different countries elect to use different methods in investigation for the spread of GTN, the method used should be recorded to facilitate further comparison and analysis.

Investigative Tools to Diagnose Metastases[14]

(1) Chest X-rays are appropriate to diagnose lung metastases (an appropriate diagnostic tool to detect lung metastasis) and are used for counting the number of lung metastases to evaluate the risk score. Lung CT may be used.

(2) Liver metastases may be diagnosed by ultrasound or CT scanning.

(3) Brain metastases may be diagnosed by MRI or CT scanning.

The final consensus statement regards the revision of the staging of GTN (Table 1).

As mentioned before, the anatomically-based FIGO staging has its merit as shown by the study on choriocarcinoma. However, it is obviously not adequate for GTN without histological assessment. Based on current analysis, 2 modifications of the WHO scoring system were recommended to be adopted in the FIGO staging. One was to remove blood group of the patient as a factor, and hence the 2000 staging has only 8 prognostic factors. The second was to change the score attributed to liver metastasis from 2 to 4. It is hoped that after reaching a standardization of both diagnostic criteria and investigative tools, future analysis by using the same staging and classification would be more meaningful. The true significant independent factors could then be identified, and there is a possibility that the number of factors may be further reduced. Members' countries are encouraged to send in their data

to our Committee such that a critical mass is achieved in order to reach significant statistical power to identify the most significant independent prognostic factors using multivariate analysis.

A further recommendation related to staging is the use of 2 risk groups instead of 3 as recommended by WHO. A total score of 6 or less is considered as low risk[14].

Finally, it should be pointed out that the revised 2000 FIGO GTN staging and classification have taken 2 major steps away from the conventional FIGO staging. The first is the introduction of a scoring system on prognostic factors. The second is the concept of re-staging in relapse where a full re-assessment of spread and previous chemotherapy response are used in re-staging. Since GTN behave differently from other solid gynecological cancers, such new approach may be justifiable and the experience learned may be helpful in introducing this change to other cancers.

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