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THE FIGO 2002 STAGING AND RISK FACTOR SCORING SYSTEM FOR GESTATIONAL TROPHOBLASTIC DISEASE. UPDATE AND CRITICAL DISCUSSION: 2015

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7.1 INTRODUCTION

The prior chapter 6 presents an updated history of the staging and risk factor scoring system of gestational trophoblastic neoplasia (GTN). This chapter discusses the present problems with this system. In 2002 the International Federation of Obstetrics and Gynecology (FIGO) following recommendation of its cancer committee, ratified a revised classification system for GTN. What was promulgated was a combined FIGO anatomic staging system with a revised World Health Organization (WHO) risk factor scoring system [1,2]. This had been field tested by Hancock et al [3]. Ten years later, the FIGO Cancer Committee reported [4] that the title of the Gynecologic Cancer Reports would be changed to "FIGO Cancer Reports". These reports have provided the results of treating gynecologic cancers, lately including GTN, from member countries for more than 50 years. They used to be known as the "Stockholm reports" and were published every 3 years. Also the FIGO committee now proposes to publish clinical guidelines specifically for GTN [5]. In fact such guidelines were published by ISSTD in 2002 and that text is now available on line at isstd.org [6]. Since that time some of the problems of diagnosis and management of GTN have changed significantly. Let us examine these issues

Now, most physicians concerned with the management of GTN are using the 2002 FIGO system, although there are exceptions from some major trophoblast centers. For example there is reluctance to use the term "neoplasia" for post molar trophoblastic neoplasia requiring chemotherapy and several investigators persist in using terms such as "invasive mole" or "trophoblastic tumor" or "malignant mole" [7]. The term neoplasia was introduced because it does not necessarily commit to the diagnosis of cancer in a situation where the diagnosis of neoplasia may be based on the pattern of human chorionic gonadotropin (hCG) measurement rather than histologic confirmation. Nevertheless this is the first time there is an agreed unified system of classifying trophoblastic disease that is being widely used. The idiosyncratic and individual selection of the factors that prevented comparison of data from different centers has largely disappeared. We are all beginning to speak the same language.

Some serious problems however remain and require solution. The FIGO Cancer Committee retained the system of staging used for the other gynecologic cancers in the FIGO system and agreed to combine this with the actual numerical risk factor score. This replaced the grouping into "a" as low risk and "b" as high risk. By using the "raw" risk factor score to stage each patient, basic information was retained. If the patient was "grouped" at the time of staging, this basic information was lost and subsequent analysis

of subgroups would no longer be possible. Perhaps this was justified in 1992 but was counterproductive in 2002 and is certainly counterproductive now, in this age of computer technology.

One of the prerequisites of any staging system is to define the inclusion criteria precisely. With trophoblastic disease this is an issue of specific importance. GTN was variously defined by different treating physicians. It is now accepted that neoplasia after mole is diagnosed when there had been a plateau of 4 values of hCG over 3 weeks (days 1, 8, 15 and 22 or longer) or a rise of hCG for 3 values over 2 weeks (days 1, 8 and 15 or longer) [5]. It is of course also diagnosed when histologic invasive mole or choriocarcinoma is found at the time of the initial curettage. Previously the Charing Cross Group in London and the Sheffield Trophoblastic Disease Center waited many weeks before initiating chemotherapy in post hydatidiform mole patients. In the United States, the Gynecologic Oncology Group and the National Cancer Institute had been diagnosing GTN after only 3 values of plateau or 2 weeks of rise. They have now ceased to do this. Many experts believe that these criteria had invalidated several prospective randomized studies. The adoption of the agreed criteria for the FIGO staging and risk factor scoring system was preceded by discussion by a consortium of the International Society for the Study of Trophoblastic Disease (ISSTD), the International Gynecologic Cancer Society (IGCS) and the Society of Gynecologic Oncology (SGO) who agreed on these definitions [5]. Not only were the principles of diagnosing neoplasia agreed on but also the methods for diagnosing metastases. This again was a step forward. The other changes that were accepted that differ from the 1983 WHO and subsequent FIGO classifications was that the risk score for the ABO blood group was eliminated and the risk factor for liver metastases was upgraded from 2 to the highest risk factor of 4.

Now that the system has been in place for more than 12 years some problems have arisen that need to be solved expeditiously. Hopefully this will be achieved so that patient therapeutic morbidity may be reduced. In 2002 it was decided to eliminate the middle risk group of the Charing Cross-WHO classification because this group was variably treated with single agent or combination chemotherapy. Presently, there is still a low risk group of GTN with a score of 6 or less and a high risk group with a score of 7 or greater. Experience is showing that eliminating the middle risk group was a mistake. Several studies show that patients with a risk factor of 5 or 6 frequently may not respond to single agent chemotherapy [8, 9] and are likely better treated by 2 agents right from the beginning rather than waiting until a single agent has failed to be effective. It is of concern that these findings, are already a few years old and official proposals for change are only just beginning to be discussed. In the meantime such patients are having effective therapy delayed because they are categorized as "low risk".

7.2 THE FIGO 2002 STAGING AND RISK FACTOR SCORING SYSTEM

The FIGO staging and risk factor scoring system for trophoblastic disease as it was accepted by FIGO in 2002, is still presently in use in 2014 and is presented below. It is important to recognise that Placental Site and Epithelioid Trophoblastic Tumors are categorized separately from other gestational trophoblastic neoplasia.

7.2.1 THE 2002 CRITERIA FOR THE DIAGNOSIS OF POST HYDATIDIFORM MOLE TROPHOBLASTIC NEOPLASIA (GTN)

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 days 1,7,14,21.

2. GTN may be diagnosed* when there is a rise of hCG on three consecutive weekly measurements, over a period of two weeks or longer, days 1,7,14.
3. GTN is diagnosed if there is histologic diagnosis of choriocarcinoma.
4. GTN is diagnosed when the hCG level remains elevated for 6 months or more **.

*The actual level of hCG is determined by the individual investigator. It is important that an hCG assay is used that also detects abnormal variants of hCG, frequently present in GTN.

** This criterion should not be eliminated; such findings needs investigation. A diagnosis of GTN may not be appropriate as it would not apply to patients with false positive hCG [10] nor to those with unexplained low level real hCG and those without clinical or imaging evidence of GTN [11]

7.2.2. CRITERIA FOR METHODS USED TO DIAGNOSE METASTASES IN TROPHOBLASTIC NEOPLASIA.

1. Chest x-ray is appropriate to diagnose lung metastases and it is chest x-ray that is used for counting the number of lung metastases to evaluate the risk factor score. Lung CT may be used but does not influence the risk factor score because lung micro-metastases, were they to be counted, would likely increase the risk score to its maximum of 8 without adding clinical risk. This is a clinical reality though “scientifically” inappropriate. The practice appears to be justified.
2. Liver metastases may be diagnosed by CT scanning or by ultrasound. Contrast enhanced CT scanning is more accurate.
3. Brain metastases may be diagnosed by contrast enhanced MRI or CT scanning. MRI is more accurate.
4. To diagnose intra-abdominal metastases CT scanning is preferable to ultrasound.

7.2.3. FIGO STAGING OF GTN.

Stage I Disease confined to the uterus

Stage II GTN extends outside the uterus but is limited to the genital structures (adnexa, vagina, broad ligament).

Stage III GTN extends to the lungs with or without genital tract involvement.

Stage IV All other metastatic sites.

7.2.4. FIGO Scoring.

FIGO SCORING	0	1	2	4
Age	< 40	≥ 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from	<4	4 – <7	7 – <13	≥ 13

index pregnancy				
Pre-treatment serum hCG (IU/L)	<103	103 – <104	104 – <105	≥ 105
Largest tumor size (including uterus) cm	<3	3 – <5	≥ 5	-
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

7.3. PROCEDURE FOR FIGO STAGING AND RISK FACTOR SCORING FOR GTN

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, or IV. This is then separated by a colon from the sum of all the actual risk factor scores, expressed in Arabic numerals. This stage and score will be allotted for each patient. For purposes of reporting, patients are divided into high risk and low risk groups. The low risk group, at present, will have a score of 0 to 6 and the high risk group will have a score of 7 or higher. As just mentioned, it is my opinion that this practice be returned to 3 risk groups - low, medium, and high - as soon as possible.

7.3.1. EXAMPLES OF LOW RISK AND HIGH RISK STAGING/SCORING ARE PRESENTED

Example of Low Stage: Low Risk Factor Score

A 45 year old patient has a hydatidiform mole evacuated uneventfully. The hCG decreases from a pre-evacuation value of 80,000 mIU/ml to 1000 mIU/ml 4 weeks after the D&C but then persists between 800 and 1000 mIU/ml for 4 weeks. Clinical examination shows no abnormality or evidence of metastases. Ultrasound of the uterus shows a 2cm lesion in the myometrium. Chest X ray is negative. This patient is staged FIGO stage I : 2. The two risk factors present are the patient's age and the hCG of 1000 mIU/ml i.e. 103 - 104. Each risk factor has a score of one.

7.3.2. EXAMPLE OF HIGH STAGE: HIGH RISK FACTOR SCORE

A 41 year old patient has bleeding after her 3rd successful pregnancy. Curettage shows histologic choriocarcinoma. Ultrasound shows a 5 cm lesion in the myometrium and chest X ray shows multiple (more than 8) lung nodules, 1 to 2 cm in size. Brain MRI shows a 3 cm lesion in the right frontal lobe of the brain. This patient is staged FIGO IV:13 because she is aged 41 (1) and is post full term pregnancy (2), has a brain metastasis (4), has more than 8 metastases to the lung (4) and has a 5 cm lesion in the

uterus (2). The histologic choriocarcinoma does not add to the risk score by the FIGO system.

7.4 FURTHER DISCUSSION AND COMMENTS.

The 2002 FIGO staging and risk factor scoring system has now been in use for several years. However no formal prospective analysis has been performed. This seems an opportunity lost. During this time the FIGO Reports on Gynecologic Cancers did not use the system for gestational trophoblastic neoplasia so that its various components have presently only been validated in clinical practice and journal manuscripts but not in comprehensive reports from many countries. Nevertheless there seems to be "progress", as it is the first staging system with agreed inclusion criteria. If these continue to be adhered to it should become apparent which of the risk factors are significant by statistical analysis. This will allow revision to be based on valid factors. The staging component may in fact not be essential for therapy planning but has been retained for historic reasons and because everyone likes it. Some of the shortcomings of the classification have been discussed. One of the more serious is that there is no mechanism for recording patients with Hydatidiform mole when it presents. Recording such patients as stage 0 would ensure that they are followed diligently until the hCG becomes negative and, conversely recognizing neoplasia early from the rising or plateauing hCG. It would help ensure conscientious follow up. The practice would provide data on the incidence of molar pregnancy that does not progress to GTN. Also, placental site trophoblastic tumor and its non-malignant counterparts appear to "get lost" and are not well represented. This is relevant because these pathologic conditions may be difficult to distinguish with assured accuracy.

The other serious problem is the time in the course of the disease when the staging is implemented. Because FIGO does not recognize hydatidiform mole for staging purposes, staging only occurs when the patient presents with persistent or rising hCG and/or metastases appear. Also, if the disease does not respond to therapy there is presently no mechanism in the FIGO system for recording such changes. Each new physician who sees the patient, stages the disease as if she had just got the disease, even if the clinical picture has changed significantly since the initial presentation. A solution to this problem is to use a "dynamic" staging and risk-factor scoring system described in section 7.4.3, 7.4.4..

The 2012 Report from The FIGO Cancer Committee on Gestational Trophoblastic Neoplasia [5] suggests that FIGO may be prepared to make changes such as have been suggested in this chapter also in the past. However no definite recommendations were presented.

7.5 THE FUTURE OF STAGING AND RISK FACTOR SCORING IN GESTATIONAL TROPHOBLASTIC DISEASE.

Because the current staging and risk factor scoring system for Gestational Trophoblastic Disease has no place for hydatidiform mole the denominator of disease incidence is not recorded. Surely this is a major epidemiologic deficiency in the system. And surely that is a mistake. Hydatidiform mole should be included as stage 0 in the FIGO staging of gestational trophoblastic disease. GTN is different from other gynecologic cancers because the diagnosis of neoplasia may be dependent on hCG values and may be accepted without histologic confirmation. As some 20% complete hydatidiform moles evolve to neoplasia it would appear logical and sensible to include

hydatidiform mole as stage 0 in the classification of GTN. Computer technology allows the inclusion of much more “raw” data than was previously possible and that is desirable!

Another “basic rule” of all the FIGO cancer classifications is that the initial, “primary” staging remains unchanged and this applies to the FIGO 2002 staging and risk factor scoring system for gestational trophoblastic neoplasia also. That is not realistic because disease does change and either becomes cured or advances or occasionally remains stable. All such events may now be recorded accurately by developing a “dynamic” staging and risk factor scoring system [12] for gestational trophoblastic disease. The initial stage and score is retained. If the disease progresses, such change may be recorded. For the purists among us regression and cure may also be recorded. The previous history of the case is not discarded as the disease changes.

7.5.1 SUGGESTED DYNAMIC STAGING AND RISK FACTOR SCORING FOR HYDATIDIFORM MOLE.

Let us begin with hydatidiform mole. With a dynamic staging and scoring system this would be stage 0. It may well be useful to record whether the mole is complete or partial by adding “c” or “p” to the zero. Furthermore, because of the difficulty in distinguishing the type of mole by histology in the early weeks of pregnancy, the classification should insist that the suffix is only added if ploidy or P57 immuno-histo-chemistry has been performed to ascertain the type of mole [13,14,15]. When patients with partial mole, diagnosed only by histology, are determined to require chemotherapy more detailed assessment nearly always shows that the mole was in fact complete. Some investigators say that this is not necessary because all such patients are cured. Even so, if definitive confirmation in patients with alleged histologic partial mole who develop GTN is not done, that report may be scientifically inaccurate because of the error associated with even expert histologic assessment [16]. This issue becomes more frequent because of the earlier diagnosis of mole in pregnancy associated with ultrasound diagnosis of fetal death and evacuation of the uterus in early pregnancy when the classical histologic features of mole may still be absent. DNA genotyping seems to be the most accurate method of diagnosis [11] and is not significantly more expensive than the other methods of differential diagnosis.

In addition, a decision will also need to be made whether the risk factors associated with high-risk mole [17] (as opposed to high risk trophoblastic neoplasia) should also be recorded. Thus one may note uterine size as being greater than 4 weeks of gestational age (U), persistent bleeding after mole evacuation (B), High hCG (hCG and the actual value), presence of theca-lutein cysts (TLC) and pulmonary embolization of molar tissue (PE). Perhaps such a recording system may be unwieldy but it would certainly provide precise information.

7.5.2. THE DYNAMIC STAGING AND SCORING FOR TROPHOBLASTIC NEOPLASIA.

The staging of post-molar trophoblastic neoplasia and neoplasia after apparent miscarriage or choriocarcinoma is equally simple. The basic staging follows the FIGO 2002 regulations but if the disease progresses, more information may be added. The objection that the initial cancer staging must always remain with that patient and must never be changed appears antiquated. Using computer technology we have the opportunity to change the staging and risk factor scoring of patients. The initial staging is not lost and a more realistic descriptive summary of the patient’s disease is obtained. The definition of high-risk neoplasia and low-risk neoplasia is maintained with a dividing

score at 6 or less, or 7 or greater, the latter requiring multiple-agent chemotherapy [8, 9]. This hopefully will also change with re-institution of three risk groups.

The time when risk factor scoring is determined has not been mandated. At present it is usual that each new consultation for any patient is associated with yet another staging and the previous assessment is usually ignored and lost. A detailed computerized staging system would allow changes in staging and scoring if new disease develops so that the timing of staging is no longer relevant.

7.5.3. EXAMPLES OF DYNAMIC STAGING AND SCORING HYDATIDIFORM MOLE.

The mole is evacuated and P57 histochemistry [13] or ploidy [14,15] confirms a complete mole. The stage: score would be 0c:1; that is stage of mole = 0, c for complete and age is the only risk factor. That is the primary staging. Hitherto this has not been done at all because mole was not counted by the FIGO system. The patient's hCG fails to regress and then climbs to 40,000 mIU/ml over 4 weeks. The patient now has "neoplasia" and is staged as Ic:2. A score of one is allotted for the age and one for the level of hCG (see table, section 7.2.5., page 12). The patient is given single agent chemotherapy but the hCG continues to climb and 4 small lung metastases appeared on chest X-ray. CT of the abdomen and MRI of the brain were negative for other metastases. The stage: score now is IIIc:7; one for age, 2 for level of hCG, 2 for number of lung metastases by chest X-ray and 2 for failed single agent chemotherapy. Such a sequence may be represented as: 0c:1 -> Ic:2 -> IIIc:7. Whether it is decided to add more clinical information will need intense discussion.

7.5.4. THE PROBLEM OF INVASIVE MOLE.

Until two years ago the Japanese Gynecologic Cancer Society classified invasive mole as a separate entity in their staging system on the basis of the pattern of hCG regression but has now accepted the FIGO system. In Mongolia, India, Indonesia, but rarely in the United States and Europe, GTD may present as intra-abdominal bleeding due to massive invasive mole penetrating the full thickness of the myometrium so causing hemoperitoneum. This is a clinically dramatic presentation and is clearly life threatening, but nevertheless, is pathologically and, in the staging system, histophysiologically the same process as

histologic postmolar neoplasia that presents with only an elevated hCG after mole evacuation. Should this really be classified as a separate entity or subclassified within GTN? In order to solve this serious problem in the clinical classification of trophoblastic disease, it is suggested that additions are made to the risk factor scoring of invasive mole similar to those proposed for stage 0 trophoblastic disease. This may be achieved by adding to stage I - GTN, the degree of myometrial invasion as seen by imaging and indicated by "m" for

myometrium, followed by "0" for no myometrial invasion on imaging, "s" for superficial invasion, "i" for intermediate invasion, and "f" for full myometrial invasion. Then an added "M" (capital/upper case) may indicate molar histology while "CH" would indicate histologic choriocarcinoma. Thus, a patient with post-full term pregnancy choriocarcinoma with half penetration of the myometrium would be recorded as: I:m.i.CH.

7.5.5. DISCUSSION AND CONCLUSION.

A dynamic staging and risk factor scoring system for GTD would provide a “real time” accounting of the disease process. This would be achieved by adapting the 2002 FIGO staging and risk factor scoring system so that hydatidiform mole is included and that changes in the risk factor scoring are permitted to correspond to the changing status of the patient. This proposal presumes that there will be rigorous adherence to the definitions for terminology set out by the Society of Gynecologic Oncologists guidelines for classifying gynecological tumors [18] and also, to the criteria for the diagnosis of trophoblastic disease and trophoblastic neoplasia promulgated by FIGO. The suggestion was first published in 2007 – is interest beginning to stir?

7.6. FALSE POSITIVE HCG AND QUIESCENT GESTATIONAL TROPHOBLASTIC DISEASE

The question also needs to be raised whether the “syndromes” of False Positive hCG and Quiescent Gestational Trophoblastic Disease (QGTD) should be included in the Classification of Trophoblastic Disease. False positive hCG [10,19] is associated with an erroneous assay for hCG in a patient who has no hCG but is thought to have GTN because of this finding. The problem is associated with lack of neutralization of heterophil antibody by the assay method. Although it is an erroneous diagnosis it has become sufficiently common to warrant recognition as a clinical entity.

The syndrome of Quiescent Gestational Trophoblastic Disease (QGTD) [11, 20] is recognized when there has been a pregnancy event, most frequently a molar pregnancy, and low levels of hCG persist for months if not years. The definition of QGTD requires that real hCG is present for at least 3 months, that there is no evidence of tumor by clinical examination or by sophisticated imaging and that chemotherapy and even surgery are ineffective in making the hCG negative. In some 20% of patients the disease becomes activated after a period of months or years, hyperglycosylated hCG (hCG-H) becomes detectable in serum and the neoplasia is now sensitive to therapy. The reason for the quiescence is that the number of cytotrophoblast cells is too small to produce detectable hCG-H but there are sufficient syncytiotrophoblast cells to produce detectable hCG. In patients in whom the disease becomes reactivated the cytotrophoblast cells multiply sufficiently to produce detectable hCG-H and this may precede the appearance of overt clinical disease by weeks or months. Unfortunately many of these patients have been actively treated, without benefit, during the quiescent stage so that when the disease does become active, treatment modalities may have become exhausted. As this has become a significant clinical problem it is suggested that QGTD should also be included in the clinical classification of Trophoblastic Disease.

7.7 OVERALL CONCLUSION

Members of the International Society for the Study of Trophoblastic Disease and other physicians treating gestational trophoblastic disease need to address several issues discussed in this chapter in order that this so treatable disease may be managed more efficiently. It is less expensive to solve these problems promptly than to compromise with accepting non-scientific methodology and not providing patients with the most efficient methods of achieving expeditious cure.

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