6
STAGING AND CLASSIFICATION SYSTEMS

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6.1 INTRODUCTION

It is universally recognized that an accurate and precise staging and classification system for gestational trophoblastic neoplasia (GTN) is essential to enable clinicians to assess the prognosis or the risk of patients, to individualize and to optimize their treatment. There have been a variety of staging and classification systems developed by different centres and some are still being used. This makes meaningful comparison of treatment results and evaluation of new treatment protocols difficult and hampers the improvement in the management of the disease.

During the 2000 Fédération Internationale de Gynéologie et d'Obstétrique (FIGO) Oncology Committee meeting held in Washington, a revised staging system was proposed and the details of the revised FIGO staging (Table 6.1) were published in 2002 [1]. It was also recommended that gestational trophoblastic neoplasia (GTN) should replace terms like gestational trophoblastic tumor, persistent gestational trophoblastic disease (GTD), residual GTD and malignant GTD. Also, placental site and epithelioid trophoblastic tumours were specifically excluded. Other new features of this staging system are the recommendation of the investigative tools for staging and the definition of metastases. This new staging system for GTN incorporates the classical anatomical staging with other prognostic indicators identified by Bagshawe [2] and others [3-5] and which have been documented to be clinically useful in managing patients with GTN. In this chapter, we shall review the historical background leading to the formulation of the 2000 FIGO staging and we shall try to compare its effectiveness in prognostic prediction with that of the World Health Organization (WHO) scoring system.

6.2 HISTORICAL REVIEW

6.2.1 MORPHOLOGICAL/HISTOLOGICAL

CLASSIFICATION

For many centuries, morphological /histological classification was the only classification. In 1276, it was first recorded that the Countess of Henneberg delivered 365 'children' [6]. From the description of the 'children', the pregnancy was clearly a hydatidiform mole. In 1840, Wilton [7] published a report on a patient with chorioadenoma destruens who had a perforated uterus resulting in fatal intraperitoneal hemorrhage. In 1877 the first case of choriocarcinoma was described by Chiari [8]. Sänger [9] proposed the first morphological classification in 1893 (Table 6.2). Two years later, Marchand [10] proposed to call this group of diseases chorionepithelioma malignum and he classified the diseases into typical and atypical forms and related the different forms to the prognosis of the patients.

Table 6.1 FIGO 2000 Anatomical Staging and scoring

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

FIGO SCORING	**0**	**1**	**2**	**4**
Age	< 40	≥ 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy	<4	4 – <7	7 – <13	≥ 13
Pre-treatment serum hCG (IU/L)	$<10^3$	10^3 – $<10^4$	10^4 – $<10^5$	≥ 10^5
Largest tumor size (including uterus) cm	<3	3 – <5	≥ 5	-
Site of metastases	Lung	Spleen,	Gastro-intestinal	Liver,

		Kidney		Brain
Number of metastases	-	1 – 4	5 – 8	> 8
Previous failed chemotherapy	-	-	Single drug	2 or more drugs

Table 6.2 Sänger's classification for GTD

1. Decidual sarcoma with participation of chorionic elements:
   a. Diffuse, ulcerated type
   b. Nodular, non-ulcerated type
   c. Mixed nodular—ulcerative type
2. Decidual sarcoma with participation of chorionic elements, following hydatidiform mole
3. Interstitial, destructive hydatidiform mole

Ewing [11] categorized the diseases into syncytial endometritis, chorioadenoma destruens (invasive mole) and choriocarcinoma in 1910, which formed the basis of classifications used by many centers nowadays. Since then, many workers, notably Novak, Ishizuka, Hertz, Park and Driscoll, reported their findings on the morphology and histology of the different groups and their variants, and the clinico-pathological behaviors had also been widely investigated. Nevertheless, the diagnostic difficulty remained a problem in many studies. In 1967, the International Union Against Cancer (UICC) led by Ishizuka and Brewer produced a monograph compiling a clinical and morphological classification [12] (Table 6.3). Another morphological classification, including the diagnosis of invasive mole, was adopted by the GTN Registration Committee of the Japan Society of Obstetrics and Gynecology for reporting their GTN data [13] (Table 6.4). If the histological diagnosis was not available, patients would be classified as 'clinical invasive mole' or 'clinical choriocarcinoma' based on a choriocarcinoma risk score system.

It becomes clear that GTN consists of a group of related conditions ranging from benign to malignant forms with different prognosis and they can develop following any type of pregnancy. However, in recent decades, the diagnosis of GTN is mainly established by the human chorionic gonadotropin (hCG) levels and clinical presentations, and surgery is seldom required. Therefore under many circumstances the exact histological diagnosis is not

known at the onset of the disease. In other words, it implies that the management plan cannot be made prospectively based on this type of morphological / histological classification. It was also known that histological grade of the lesion, i.e. the degree of differentiation and proliferation of the trophoblasts, did not correlate well with the behavior of the tumor and hence histological grading could not be used to predict patients' outcomes. It became obvious that a different classification was needed. In fact, since early 1980s to 90s, many centers apart from Japan had started to adopt a clinical classification or had used a clinical classification in addition to a morphological system.

6.2.2 ANATOMICAL STAGING SYSTEM

Clinicians are used to stage gynecological malignant diseases based on anatomical criteria. In 1982, the FIGO Oncology Committee proposed an anatomical staging system for GTN (Table 6.5) and encouraged its use for the report of GTN data universally. This system was based on the classification system formulated by Song et al which is still being used in some centers in China [14] (Table 6.6). However, it was soon found that the prognosis of patients varied greatly even within the same stage. Besides, a number of clinical features had also been recognised as a prognosticator other than the anatomical extent of the disease. The 1982 FIGO anatomical staging was therefore not universally accepted as expected.

Table 6.3 UICC 1967 classification for GTD

A.	Gestational
B.	Non-gestational
I.	CLINICAL DIAGNOSIS
	1. Non-metastatic
	2. Metastatic
	a. Local (pelvic)
	b. Extrapelvic (specify location)
	3. Other required information
	a. Evidence
	i. Morphological
	ii. Non-morphological
	b. Antecedent pregnancy. Specify duration

i. Normal
ii. Aborted
iii. Molar

c. Previous treatment
i. Untreated
ii. Treated. Specify

II. MORPHOLOGICAL DIAGNOSIS

1. Hydatidiform mole
   a. Non-invasive
   b. Invasive
2. Choriocarcinoma
3. Uncertain[a]
4. Other required information
   a. Diagnostic basis. Specify
      i. C = Curettage
      ii. U = Excised uterus
      iii. N = Necropsy
      iv. 0 = Other
   b. Date of diagnosis (with respect to date of onset of treatment)
   c. Subsequent change in morphological diagnosis. Specify diagnostic basis as in II.4a

[a]'Syncytial endometritis' is not considered neoplasia.

Table 6.4 Registration Committee, Japan Society of Obstetrics and Gynecology Classification for GTD

1. Total (or complete) hydatidiform mole
2. Partial hydatidiform mole
3. Invasive (or destructive) hydatidiform mole
4. Choriocarcinoma
5. Persistent trophoblastic disease
   a. Post-molar persistent hCG
   b. Clinical invasive (or destructive) mole
   c. Clinical choriocarcinoma

Table 6.5 1982 FIGO anatomical staging system for GTD

Stage	
I.	Confined to the uterus corpus
II.	Metastases to pelvis and vagina
III.	Metastases to lung
IV.	Distant metastases

Table 6.6 Song's classification for GTD

Stage		
I.		Disease confined to the uterus
II.	A	Disease extends to adnexa and parametria
	B	Disease extends to vagina
III.	A	Disease extends to lung and metastases less than 3 cm in diameter or mottling in less than half of one lung
	B	Disease extends to lung and metastases bigger than 3 cm in diameter or mottling in more than half of one lung
IV.		Disease extends to other organs, e.g. brain, liver, kidney and bowel

Reproduced with permission from Song *et al,* Trophoblastic tumours: diagnosis and treatmen published by People Health, Beijing.

6.2.3 CLINICAL CLASSIFICATION

For a long time, it was well known that GTN patients with metastases had a worse prognosis than those without. The early methods for detection of metastasis were physical examination, chest X-rays, electro-encephalogram, arteriogram and the detection of an increased level of hCG in the cerebrospinal fluid. These methods would only detect late or large (>2 cm in diameter) metastasis. Therefore, large tumor volume rather than the site of the metastasis appeared to be a more important adverse prognostic factor. As mentioned before, delegates at the 1965 UICC Conference held in the Philippines agreed to incorporate a clinical classification into a morphological classification [12] (Table 6.3) which divided the patients into non-metastatic and metastatic groups. In the same year, Ross and his co-workers [15] identified

some clinical features that were associated with poor prognosis, including high hCG level, duration of disease longer than four months, and the presence of brain and/or liver metastasis.

Table 6.7 Hammond's Southeastern Trophoblastic Disease Center Clinical Classification for GTD

I. Non-metastatic GTD

II. Metastatic GTD
   A. Good prognosis
      1. Urinary hCG <100000 IU/24 h urine or <40 000 lU/L serum
      2. Symptoms present for less than 4 months
      3. No brain or liver metastases
      4. No prior chemotherapy
      5. Pregnancy event is not term delivery (i.e.mole, ectopic spontaneous abortion)

   B. Poor prognosis
      1. Urinary hCG >100000 IU/24 h urine or >40 000 lU/L
      2. Symptoms present for more than 4 months
      3. Brain or liver metastases
      4. Prior chemotherapeutic failure
      5. Antecedent term pregnancy

In 1973 Hammond et al [16] reported the treatment results of their patients based on a clinical classification that divided patients into non-metastatic and metastatic groups, where the metastatic GTN patients were further divided according to good and poor prognosis depending on the hCG level, duration of symptoms before treatment, previous failure of chemotherapy and antecedent pregnancy (Table 6.7). Since then, the majority of US centers have used a clinical classification similar to Hammond's.

In 1986, the Dutch Working Group for Trophoblastic Tumors had devised a classification system similar to Hammond's system (Table 6.8) [17] and has been widely used in the Netherlands. It also included extra-uterine metastasis in more than one site as a poor prognostic factor.

History has shown that these clinical classifications are largely accurate in predicting patients' outcomes. They can be used

prospectively to guide the choice of chemotherapeutic regimen, i.e. single or multiple agents. However, the relative importance of each factor is not taken into consideration. Hence, a prognostic scoring system allocating different weight to different prognostic factors might provide more prognostic information for an individual patient.

Table 6.8 Classification by the Dutch Working Group for GTN

Low-risk GTN
Demands all of the following conditions:

1. Antecedent pregnancy: hydatidiform mole, abortion
2. No metastases or metastases in both of the following conditions:
   a. One organ site
   b. Site in the small pelvis, vagina or lung
3. No previous chemotherapy
4. Interval between evacuation and start of chemotherapy less than 12 months

High-risk GTN
Demands one or more of the following conditions:

1. Failure of previous chemotherapy
2. Metastases in one or more of the following organs:
   a. Brain
   b. Liver
   c. Spleen
   d. Kidney
   e. Gastrointestinal tract
3. Metastases in more than one site (outside the uterus)
4. Antecedent pregnancy: term
5. Interval between end of antecedent pregnancy and start of chemotherapy more than 12 months

6.2.4 PROGNOSTIC SCORING SYSTEM

In 1976, Bagshawe [2] found that the treatment response of his patients were influenced by a few parameters, including the outcome of the antecedent pregnancy, disease burden as reflected by the urine hCG level, interval between the antecedent pregnancy and the start of chemotherapy, ABO groups of the couple, extent of mononuclear cell tumor infiltrate, size of tumor, site of metastases

especially brain, age and parity of the patient. Together with other variables like the number of metastases, patient's immune status and response to he previous chemotherapy, he then suggested a weighted prognostic scoring system which divided patients into high-, medium- and low-risk groups (Table 6.9). Unfortunately, Bagshawe's prognostic score could not be calculated for patients in certain developing countries where GTN was prevalent because some investigation tests were not available. In 1983, a WHO Working Group [18] modified and simplified the Bagshawe system (Table 6.10) which becomes widely used by centers in developing countries. It is easy to use and can effectively reflect the prognosis of the patients.

Subsequently, the Charing Cross also derived a similar scoring system which divided patients into low- (0 – 5), medium- (6 – 9) and high- (>9) risk groups [19] (Table 6.11).

Table 6.9 Bagshawe's prognostic scoring system for GTD (1976**)**

Score	*0*	*10*	*20*	*40*
Age (years)	<39	>39		
Parity	1, 2, >4	3 or 4		
Antecedent pregnancy	Mole	Abortion	Term	
Histological diagnosis (AP)	Invasive mole	Not known	Choriocarcinoma	
Interval (AP to start of chemotherapy) in months	<4	4-7	7-12	>12
HCG (plasma IU/L or urine IU/day)	10^3-10^4	<10^3	10^4-10^5	>10^5
ABO groups (patient x husband)	A x A O or A x B O or A x AB	O x O A x O O x A B x B AN x B	B x O or A AB x O or A	
No. of metastases seen	None	1-4	4-8	>8
Site of metastases	Not detected Lungs Vagina	Spleen Kidney	Gastrointestinal tract Liver	Brain
Largest tumor mass diameter	3 cm	3-5 cm	5cm	
Lymphocytic infiltration of tumor	Marked	Moderate or unknown	Slight	
Immune status	Reactive	Unknown	Unreactive	
Relapse after previous			Yes	

chemotherapy

Modified 1983; see Table 12.1

Table 6.10 WHO prognostic scoring system for GTD

	0	*1*	*2*	*4*
Age	≤39	>39		
Antecedent pregnancy	Mole	Abortion	Term pregnancy	
Interval	<4	4-6	7-12	>12
Pretreatment hCG (log)	<3	3-4	4-5	>5
ABO group (female x male)		O x A A x O	B AB	
Largest tumor (cm)		3-5	5	
Site of metastasis		Spleen, kidney	Gastrointestinal tract, liver	Brain
Number of metastases identified		1-4	4-8	>8
Previous chemotherapy failed			Single drug	2 or more drugs

<4, low risk; 5-7, medium risk; >7, high risk.
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Table 6.11 Charing Cross prognostic scoring system for GTD

	0	*1*	*2*	*6*
Age	≤39	>39		
Antecedent pregnancy	Mole	Abortion or unknown	Term	
Interval to treatment (months)	<4	4-6	7-12	>12
Pretreatment hCG (log)	<3	3-4	4-5	>5
ABO group (female x male)		A x O O x A O or A x unknown	B x A or O AB x A or O	
Number of metastases		1-4	4-8	>8
Site of metastasis	None, lungs, vagina	Spleen, kidney	Gastro-intestinal tract, liver	Brain
Largest tumor (cm)	<3	3-5	>5	
Previous chemotherapy			Single drug	2 or more drugs

0-5, low risk; 6-9, medium risk; >9, high risk.

6.3 REVISED FIGO STAGING SYSTEM 1992

6.3.1 BACKGROUND

Despite having implemented these clinical classifications, WHO prognostic score and the FIGO staging systems, for years, there was no agreement on the best system and none had been shown to be remarkably superior to the others. And although many parameters had been attributed to the patients' prognosis, the relative importance of each of them was still debatable and some even found to be insignificant [5,17,20-24]. Unfortunately, different evaluation criteria and chemotherapeutic regimens were used in these studies. In general, the WHO score was found to be more predictive of prognosis than the FIGO anatomical staging [5, 22-25].

The FIGO Oncology Committee met in Singapore during the XIIIth World Congress of Obstetrics and Gynaecology and decided to add substages based on the hCG level and interval from the antecedent pregnancy to diagnosis to its anatomical staging (Table 6.12) [26]. The revised FIGO was simple, easy for clinicians to remember and use, and the risk factors could be assessed from the patient's history and the hCG levels. It had also been adopted by the UICC in the TNM (tumor, node, metastasis) staging system [27].

6.3.2 EVALUATION OF THE 1992 REVISED FIGO STAGING SYSTEM

Ngan et al studied 207 GTN patients and found that revised FIGO staging correlated well with the WHO risk score and substaging was necessary to discriminate patients' risk within a stage especially in stages III and IV [23]. However, occasionally there would be patients with localized disease but large tumor volume or long history and these patients should be regarded as medium or high risk.

Soper et al compared the Hammond clinical classification, WHO scoring system and the modified FIGO staging system [3]. While it was found that certain prognostic factors were not independently prognostic like hCG level and tumor size, all three systems could categorise the patients into low and high risks with comparable efficiency and the FIGO substages could discriminate the different

prognostic groups in stage III patients.

A later study by Goldstein et al [27] comparing the FIGO 92 staging with WHO prognostic score also echoed that both could reliably predict treatment outcomes and could facilitate the clinicians to select the optimal treatment protocols.

Nevertheless, Lurain et al reported that their proposed Brewer score, based on factors like diagnosis of choriocarcinoma, number and sites of metastasis, previous failed chemotherapy, together with the WHO score, had a better predictability of patients' outcomes compared to the Hammond clinical classification and the revised FIGO 92 staging systems [5].

Table 6.12 FIGO 1992 Anatomical Staging

Stage	
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 known genital tract involvement
Stage IV	All other metastatic sites

Substage	
A	No risk factor
B	One risk factor
C	Two risk factors

Risk factors	
1	hCG higher than 100 000 U/l
2	Duration to diagnosis more than 6 months

6.4 REVISED FIGO STAGING SYSTEM 2000

6.4.1 BACKGROUND

The 1992 FIGO staging has the advantage of simplicity and yet incorporating significant risk factors. However, clinicians treating GTN preferred to have a more comprehensive risk scoring system based on the WHO classification, which has been used by many

centres and had been shown to have a good correlation with the prognosis. However, factors like blood group were considered to have no prognostic significance and hence this was removed from the current WHO prognostic scoring system. Also, multivariate analysis showed that liver metastasis carried a poor prognosis similar to that of brain metastasis and hence liver metastasis was given a score of 4 instead of 2 [3-5, 29, 30]. Placental site trophoblastic tumor would be reported separately. This modified WHO prognostic scoring system was thus recommended in the 2000 staging system (Table 6.1).

The traditional WHO scoring system divided the patients into low, medium and high-risk groups and single or multiple agents had been used for the medium group [23, 27]. The current WHO scoring system divided the patients into just the low and high-risk groups using 7 as the cut-off [31], recommending single agent for low-risk patients and multi-agents for high-risk patients. This 2-tier classification might help to reduce the number of patients being assigned into the high-risk group without compromising their outcomes.

6.4.2 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 and will be changed when a new clinical event like recurrence arises. It is hoped that this new staging system combining both anatomic and non-anatomic factors may gain widespread acceptance, improve patient management and serve as an example for other disease sites which may begin to incorporate tumor markers, chromosomal changes and other non-anatomic prognostic factors into their staging systems.

6.4.3 CRITERIA IN THE DIAGNOSIS OF GTN

Another difficulty challenging clinicians in managing GTN is the criteria of establishing the diagnosis of GTN. In the US, a persistent serum hCG level over 3 weeks would warrant treatment

by chemotherapy. In other places, 4 or more weeks of persistently raised serum hCG level would be used. Hence, the FIGO committee recommended that the diagnosis of GTN would be made with the following criteria:

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

However*, in a large review of 13960 patients with molar pregnancy, only 76 patients (<1%) had persistently raised hCG of >5 IU/L six months after evacuation [32]. 66 of them did not receive chemotherapy and the hCG spontaneously returned to normal in 65 patients (98%), while 10 patients received chemotherapy and 8 (80%) returned to normal. Therefore, this indication has been omitted in the recent FIGO and UK guidelines [33, 34].

6.4.4 INVESTIGATIVE TOOLS IN STAGING

Physical examination is needed to check if there is any systematic involvement like lung, liver, vaginal metastasis or adnexal mass. The serum hCG level is taken as a part of the scoring requirement and treatment baseline. Doppler ultrasound of the pelvis is needed to exclude any pregnancy or retained products of conception, and to measure the uterine volume and the size of any intrauterine lesion. There is also emerging evidence that pulsatility index of the uterine artery can predict the resistance to methotrexate especially for those at WHO score 5 – 6 though it has not been incorporated into the scoring system [35, 36]. Chest x-ray is crucial to rule out pulmonary metastasis and to count the number of chest lesions. Routine computed tomography (CT) of the chest is still controversial, because micro-metastases can occur up to 40% [37] and replacing chest x-ray by CT scan does not alter the outcomes [37, 38]. Lesions <2 cm may also regress spontaneously [38].

Ultrasound or CT is used to look for liver metastasis. The FIGO recommends whole-body CT scan if lung metastasis is present [33]. CT or magnetic resonance imaging (MRI) of the brain is not routinely performed unless the patients have neurological symptoms or lung metastasis. If the imaging does not show any brain metastasis but there is clinical suspicion, cerebrospinal fluid (CSF) can be aspirated to measure the hCG level. A CSF:serum hCG ratio of greater than 1:60 suggests central nervous system metastasis.

6.4.5. EVALUATION OF THE 2000 REVISED FIGO STAGING SYSTEM

A study conducted in Thailand reviewed 124 patients and retrospectively classified them with the 1992 and 2000 FIGO staging systems and the original and modified WHO scoring systems [40]. Considering stage I, II and III with score ≤ 7 (in 1992 FIGO and original WHO scoring systems) ≤ 6 (in 2000 FIGO and modified WHO scoring systems) as low risk, only one patient previously regarded as high risk in the old systems was re-classified as low risk and the correlation of risk categorization between the old and new combined systems was 97.9%.

On the other hand, El-Helw et al compared the Sheffield-modified Charing Cross scoring system (SCCSS) with the revised FIGO 2000 / WHO systems [41], and they found that there were fewer patients falling into the high risk group using the newer systems (9.3% Vs 7.1%). Comparing with the patients in 1973 – 2000, those treated in 2000 – 06 tended to have a lower complete response rate in both low- and high-risk groups, as well as a higher proportion of patients requiring second-line chemotherapy. Besides, only 7 out of 19 patients (37%) with score 6 by the FIGO 2000 system could achieve a complete response to methotrexate / folinic acid. The authors thus proposed to lower the current cut-off score for low-risk group from 6 to 5, or increase the risk score allocated to hCG level of $>10^5$ IU/L from 4 to 6.

Whether the FIGO 2000 / modified WHO system has down-staged a certain group of patients still needs further evaluation. But it is unquestionable that a universally accepted staging and scoring system is essential to allow comparison of results across different centres. In a questionnaire survey, the usage of FIGO staging was only 55% and 77% in year 2006 and 2005 [42]. One example of the advantage of such international collaboration could be seen in the 26th FIGO annual report where raw data of 483 patients from 40 centres were collected and merged for a large-scale analysis, By

selecting those patients whose survival data were available, it was found that the 5-year survival of 200 stage I patients was 97.3%, which was similar to the 195 low-risk patients whose risk scores were less than 7 [43]. As for the 17 stage IV patients, the 5-year survival was 61.9% while it was 79.5% for 62 high-risk patients. Using 12 as a cut-off to further divide the high-risk group into two groups, the 5-year survival of the 43 intermediate-risk patients with score between 7 and 12 was 84.3%, and was only 68.4% in 19 high-risk patients with score >12.

6.5 SUMMARY AND CONCLUSION

A historical review of various staging and classification systems for GTD was presented. An attempt was also made to evaluate the 1992 and 2000 revised FIGO staging systems. It is obvious that the current staging and scoring system is not flawless posing challenges in the management of this disease especially in those with score 5-6 and the ultra-high risk group. A further modification and improvement of the system deems necessary. However, given that GTN is a rare disease, this can never be achieved without a universal usage of the current systems and international collaboration so that a larger sample size can be gathered for meaningful analysis.

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