

## ORIGINAL ARTICLE

# Can the FIGO 2000 scoring system for gestational trophoblastic neoplasia be simplified? A new retrospective analysis from a nationwide dataset

Y. K. Eysbouts<sup>1\*</sup>, P. B. Ottevanger<sup>2</sup>, L. F. A. G. Massuger<sup>1</sup>, J. Int'Hout<sup>3</sup>, D. Short<sup>4</sup>, R. Harvey<sup>4</sup>, B. Kaur<sup>5</sup>, N. J. Sebire<sup>5</sup>, N. Sarwar<sup>4</sup>, F. C. G. J. Sweep<sup>6</sup> & M. J. Seckl<sup>4</sup>

Departments of <sup>1</sup>Obstetrics and Gynecology; <sup>2</sup>Medical Oncology; <sup>3</sup>Health Evidence, Section Biostatistics, Radboud University Medical Centre, Nijmegen, The Netherlands; Departments of <sup>4</sup>Medical Oncology; <sup>5</sup>Pathology, Charing Cross and Hammersmith Campuses, Imperial College London, London, UK; <sup>6</sup>Department of Laboratory Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands

\*Correspondence to: Dr Yalcke K. Eysbouts, Department of Obstetrics and Gynecology, Radboud University Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel: +31-24-361-4725; E-mail: yalcke.eysbouts@radboudumc.nl

**Background:** Worldwide introduction of the International Federation of Gynaecology and Obstetrics (FIGO) 2000 scoring system has provided an effective means to stratify patients with gestational trophoblastic neoplasia to single- or multi-agent chemotherapy. However, the system is quite elaborate with an extensive set of risk factors. In this study, we re-evaluate all prognostic risk factors involved in the FIGO 2000 scoring system and examine if simplification is feasible.

**Patients and methods:** Between January 2003 and December 2012, 813 patients diagnosed with gestational trophoblastic neoplasia were identified at the Trophoblastic Disease Centre in London and scored using the FIGO 2000. Multivariable analysis and stepwise logistic regression were carried out to evaluate whether the FIGO 2000 scoring system could be simplified.

**Results:** Of the eight FIGO risk factors only pre-treatment serum human chorionic gonadotropin (hCG) levels exceeding 10 000 IU/l (OR = 5.0; 95% CI 2.5–10.4) and 100 000 IU/l (OR = 14.3; 95% CI 4.7–44.1), interval exceeding 7 months since antecedent pregnancy (OR = 4.1; 95% CI 1.0–16.2), and tumor size of over 5 cm (OR = 2.2; 95% CI 1.3–3.6) were identified as independently predictive for single-agent resistance. In addition, increased risk was apparent for antecedent term pregnancy (OR = 3.4; 95% CI 0.9–12.7) and the presence of five or more metastases (OR = 3.5; 95% CI 0.4–30.4), but patient numbers in these categories were relatively small. Stepwise logistic regression identified a simplified risk scoring model comprising age, pretreatment serum hCG, number of metastases, antecedent pregnancy, and interval but omitting tumor size, previous failed chemotherapy, and site of metastases. With this model only 1 out of 725 patients was classified different from the FIGO 2000 system.

**Conclusion:** Our simplified alternative using only five of the FIGO prognostic factors appears to be an accurate system for discriminating patients requiring single as opposed to multi-agent chemotherapy. Further work is urgently needed to validate these findings.

**Key words:** gestational trophoblastic neoplasia, classification, staging, FIGO, risk factors

## Introduction

Gestational trophoblastic disease (GTD) comprises a group of pregnancy-related disorders including the premalignant complete and partial hydatidiform moles through to the malignant invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) [1].

The malignant counterparts are often collectively referred to as gestational trophoblastic neoplasia (GTN). Fortunately, with the introduction of effective chemotherapy, GTN has become highly curable with overall survival rates approaching 99% [1–4].

Cure for non-PSTT/ETT forms of GTN can often be achieved with single-agent chemotherapy comprising either methotrexate (with or without folinic acid rescue) or actinomycin D. However,

some patients require multi-agent chemotherapy most commonly comprising etoposide, methotrexate, actinomycin D alternating weekly with cyclophosphamide and vincristine (EMA/CO) to achieve long-term remission [4]. Over the years, several important predictors of unfavorable prognosis such as serum human chorionic gonadotropin (hCG) levels and site of metastases have been proposed [2, 5, 6] to stratify patients between single- or multi-agent therapies. These factors have formed the basis of a number of different clinical scoring systems [5, 7], used to distinguish GTN patients as either having a low-risk or high-risk of developing resistance to single-agent chemotherapy.

To help facilitate comparison of datasets between international treatment centers, a renewed scoring system was introduced in 2000 [8, 9]. The new International Federation of Gynaecology and Obstetrics (FIGO) 2000 risk scoring system was based on a combination of anatomic and pathophysiological features of the disease and was developed with the effort of a number of international societies including the International Society for the Study of Trophoblastic Diseases, the International Gynaecologic Cancer Society, and FIGO [9, 10].

The worldwide introduction of the FIGO 2000 has provided an opportunity to reach agreement on classification and subsequent treatment of patients with GTN. However, the system is quite elaborate and comprises an extensive set of risk factors, several of which relate to tumor bulk and may therefore not be independently prognostic [2, 6, 11]. A greater number of factors involved will likely result in an increased variability in scoring and classification. Especially in a low-incidence disease like GTN, however, global unification is essential to optimize management.

In this study, 15 years following the introduction of FIGO 2000, we decided to reevaluate all prognostic factors involved in the FIGO 2000 scoring system to determine whether simplification of this system is feasible.

## Materials and methods

### Patients

All patients diagnosed with GTN between January 2003 and December 2012 were identified from the electronic database of the Trophoblastic Disease Centre at Charing Cross Hospital in London. Patients with a histopathological diagnosis of PSTT or ETT were excluded, resulting in 813 GTN patients of which 725 were low-risk and 88 were high-risk by FIGO 2000 scoring. Uni- and multivariable analyses were conducted for 705 of 725 low-risk patients because this was the total number of cases where their response to single-agent therapy was known. The remaining 20 patients had FIGO score 6 disease and either wanted high-risk treatment or were advised to start high-risk treatment because of a very high pretreatment serum hCG typically in excess of 400 000 IU/L [12].

### Management protocols

Before treatment all patients were assigned to low- or high-risk groups in accordance with the FIGO 2000 scoring system for GTN (supplementary Table S1, available at *Annals of Oncology* online). Low-risk patients received single-agent methotrexate with folinic acid rescue (50 mg i.m. methotrexate (MTX) on days 1, 3, 5, and 7 and folinic acid 15 mg orally on days 2, 4, 6, and 8). In patients developing resistance or unmanageable toxicity, therapy was changed to either single-agent actinomycin D (ActD) or multi-agent chemotherapy comprising etoposide,

methotrexate, and actinomycin D alternating weekly with cyclophosphamide and vincristine (EMA/CO). The decision to use ActD as opposed to EMA/CO was based on the serum hCG level at the point of resistance. Patients with an hCG  $\leq 300$  IU/L received ActD, whereas those with  $> 300$  IU/L were given EMA/CO as described previously [13]. ActD was given as 0.5 mg i.v. on days 1–5 every 2 weeks [13]. Patients with disease resistant to ActD received EMA/CO chemotherapy subsequently. High-risk patients received multi-agent chemotherapy with EMA/CO as the first-line therapy. In patients presenting with very advanced disease, induction low-dose etoposide and cisplatin was given before commencing either EMA/CO or EP/EMA (etoposide and cisplatin alternating weekly with etoposide, methotrexate, and actinomycin D). Appropriate adaptation for occult or overt CNS disease was provided as described previously [14, 15]. Disease response and resistance to therapy were assessed by serum hCG measurements undertaken twice weekly until hCG was normal and then weekly until 6 weeks after completion of chemotherapy using the Charing Cross hCG radioimmunoassay as described previously [4].

### Statistical analysis

The predictive value of the prognostic factors for chemoresistance to MTX or ActD was assessed in low-risk patients using univariate and multivariable logistic regression.

Thereafter, a backward stepwise (Wald) logistic regression was carried out for all patients to evaluate whether simplification of the original FIGO system was feasible. To minimize the number of low-risk patients unnecessarily subjected to the more aggressive multi-agent chemotherapy with consequent toxicity, simplified models were only considered if at least 98% of patients had concordant FIGO classification. Guided by the previous results, a small set of modified FIGO models that best resembled classification of the original FIGO 2000 was constructed. Finally, with receiver operating characteristic (ROC) curves, the discriminating power of the alternative models in comparison to the original FIGO classification was evaluated. All statistical analyses were carried out with SPSS for windows 22.0.

## Results

Patient characteristics of the 813 patients with GTN are shown in Table 1. Twenty-eight percent of low-risk patients eventually needed salvage multi-agent chemotherapy after initial MTX/FA with or without subsequent ActD. One death associated with acute renal failure occurred as a result of complications during multi-agent therapy for widespread disease.

Table 2 shows the results of the univariate and multivariable analyses carried out for low-risk patients treated with single-agent chemotherapy. Site of metastases and previous failed chemotherapy were not included in the analysis as all patients with widespread metastases or previous failed chemotherapy were classified as high-risk patients and therefore not treated with single-agent therapy. Tumor size, antecedent term pregnancy, interval and pretreatment serum hCG were significant predictors for single-agent resistance in univariate analysis. In multivariable analysis, pretreatment serum hCG levels exceeding 10 000 IU/L (OR = 5.0; 95% CI 2.5–10.4) and 100 000 IU/L (OR = 14.3; 95% CI 4.7–44.1), interval exceeding 7 months since antecedent pregnancy (OR = 4.1; 95% CI 1.0–16.2), and tumor size of over 5 cm (OR = 2.2; 95% CI 1.3–3.6) were all identified as independent predictive factors for resistance to single-agent therapy. An increased risk was apparent for antecedent term pregnancy (OR = 3.4; 95% CI 0.9–12.7) and the presence of five or more

Table 1. Patient characteristics<sup>a</sup>

Patient characteristic	Low-risk patients (N=725)		High-risk patients (N=88)	
	Mean (SD)	Min-max	Mean (SD)	Min-max
Age (years)	32.2 (8.0)	14–56	34.7 (9.2)	15–62
Pretreatment <sup>10</sup> log serum hCG (IU/l)	3.8 (1.1)	1–7	4.9 (1.1)	2–7
Interval (months)	1.8 (2.1)	0–35	10.5 (33.2)	0–242
Duration of treatment (months) <sup>b</sup>	1.9 (2.2)	0–15	2.8 (1.6)	0–10
FIGOscore	2.7 (1.6)	0–6	10.3 (3.9)	7–23
Antecedent pregnancy	Number	Percentage	Number	Percentage
Hydatidiform Mole	696	96.0	36	40.9
Miscarriage	17	2.3	4	4.5
Term	12	1.7	48	54.5
Tumor size (cm)				
<3	304	41.9	11	13.7
3–5	240	33.1	13	16.3
>5	152	21.0	56	70.0
Site of metastases				
Vagina	4	0.6	4	5.0
Lung	56	7.7	46	57.5
Liver	–	–	6	7.5
Brain	–	–	12	15.0
Other	–	–	5	6.3
Number of metastases				
None	662	91.4	23	28.7
1–4	58	8.0	23	28.7
5–8	4	0.6	7	8.8
>8	–	–	27	33.8

<sup>a</sup>For some patients scoring on one or more of the FIGO criteria was unavailable.

<sup>b</sup>Duration of treatment is defined in months until normalization in serum hCG levels was reached.

metastases (OR = 3.5; 95% CI 0.4–30.4). However, numbers in these categories were relatively small.

Using stepwise backward (Wald) logistic regression, FIGO criteria lacking significant independent value were eliminated, identifying three simplified models. In these models, 4 (model 2) or 5 (models 1 and 3) of the original 8 FIGO criteria were sufficient for identical risk classification in 99% of patients (Table 3). The discriminating power of these simplified FIGO scoring systems was compared with the original FIGO 2000 using ROC analysis. In models 1 and 2, six and seven patients, respectively, were classified differently. In model 3, with the elimination of tumor size, site of metastases, and previous failed chemotherapy, classification for one patient changed from low-risk to high-risk. None of these patients had >4 metastases or metastases outside the lungs. Supplementary Table S2, available at *Annals of Oncology* online, shows the characteristics of all eight cases with a different risk classification when using one of the simplified alternatives in comparison to the FIGO 2000.

## Discussion

The FIGO 2000 comprises a weighted prognostic scoring system resulting in a calculated total score and subsequent classification of GTN patients with low-risk and high-risk of resistance to single-agent chemotherapy. Most prognostic factors relate to

tumor bulk, it is therefore questionable whether all these factors are required for adequate classification of patients [16]. Furthermore, with the use of interrelated factors the actual weight for certain items could be overrepresented using FIGO 2000.

With use of uni- and multivariable logistic regressions, a smaller selection of risk factors could be identified as significant predictors for single-agent resistance [1–4]. In concordance with other studies, both tumor size and pretreatment serum hCG emerge as important prognostic variables in our analysis [5, 11]. As all patients with GTN likely undergo imaging with pelvic ultrasound, tumor size can be derived quite easily in a non-invasive manner. In some cases, the volume of a trophoblastic tumor however may not represent the proportion of viable cells due to variations in the extent of necrosis and hemorrhage [17]. Serum hCG is a disease-specific tumor marker, associated with burden of disease and is easily measured quantitatively. hCG levels of over 10 000 and 100 000 IU/L in particular reflect strong relations to treatment failure in low-risk patients. As commercially available assays for quantification of serum hCG concentrations use different sets of antibodies and often a different standard, assay results strongly depend on the type of assay used. Although the effect is probably modest with high hCG levels, problems may occur with monitoring of response and follow-up in the lower range of hCG levels [1, 17, 18].

While antecedent term pregnancy and interval since diagnosis have been associated with poor prognosis in univariate analyses,

**Table 2. Univariate and multivariable analyses of prognostic factors for single-agent resistance**

Variable	Rate of single-agent resistance (%)	OR (95% CI) <sup>a</sup>	
		Univariate	Multivariable
Age (years)			
<40	159/572 (27.8%)		
≥40	34/133 (25.6%)	0.9 (0.6–1.4)	0.9 (0.6–1.5)
Antecedent pregnancy			
Hydatidiform Mole	183/677 (27.0%)		
Miscarriage	4/17 (23.5%)	0.8 (0.3–2.6)	0.6 (0.1–2.4)
Term	6/11 (54.5%)	3.2 (1.0–10.7) <sup>a</sup>	3.4 (0.9–12.7)
Interval (months)			
<4	179/617 (29.0%)		
4–6	9/73 (12.3%)	0.3 (0.2–0.7) <sup>a</sup>	1.1 (0.5–2.7)
7–12	5/14 (35.7%)	1.4 (0.4–4.1)	4.1 (1.0–16.2) <sup>a</sup>
>12	0/1 (0%)	–	–
Pre-treatment serum hCG (IU/l)			
<1000	19/167 (11.4%)		
1000–10 000	28/187 (15%)	1.4 (0.7–2.6)	1.6 (0.8–3.5)
10 000–100 000	127/324 (39.2%)	5.0 (3.0–8.5) <sup>a</sup>	5.0 (2.5–10.4) <sup>a</sup>
>100 000	19/27 (70.4%)	18.5 (7.1–48.0) <sup>a</sup>	14.3 (4.7–44.1) <sup>a</sup>
Tumor size (cm)			
<3	55/302 (18.2%)		
3–5	61/232 (26.3%)	1.6 (1.1–2.4) <sup>a</sup>	0.9 (0.6–1.4)
≥5	71/142 (50.0%)	4.5 (2.9–7.0) <sup>a</sup>	2.2 (1.3–3.6) <sup>a</sup>
Number of metastases			
None	172/644 (26.7%)		
1–4	19/56 (33.9%)	1.4 (0.8–2.5)	1.4 (0.7–2.6)
5–8	2/4 (50.0%)	2.7 (0.4–19.6)	3.5 (0.4–30.4)
>8	0/0 (0%)	–	–

<sup>a</sup>*P* < 0.05.

they however lose their significant prognostic value in some multivariable analyses [2, 6, 19]. For interval, the resulting hazard ratio appears nonlinear and results likely depend on the chosen cutoff time. A sensible cutoff point will probably be beyond 12 months since diagnosis, as suggested by Powles et al. [20]. In our study, only few patients had an interval exceeding 7 months, and likewise an increased risk of single-agent resistance was seen. In patients with antecedent term pregnancies, we observed an increased risk of single-agent resistance, but even in this rather large cohort of patients, numbers in this subcategory remain small. Although choriocarcinoma could be considered a surrogate marker for antecedent term pregnancy, the latter term is preferred as histological confirmation is not always available. Problems with correct identification of the antecedent pregnancy and interval subsequently can particularly occur when a patient has experienced an abortion without histological examination previously.

The effect of advanced age in GTD incidence has been evaluated regularly [21–23]. Its possible effect on the development of

GTN and survival however has been under debate [2, 5, 6, 11]. In line with the majority of studies, age was not identified as an independent prognostic factor in the present study. However, treatment often differs with advanced age because hysterectomy is a reasonable treatment option when fertility preservation is not desired and a reduction of toxicity from chemotherapeutic regimens may be profitable. Furthermore, considering all factors required for staging, age is probably one with the least possible uncertainty [17].

For both site of metastases and number of metastases, measurements are highly dependent on the used imaging technology used. For practical purposes and uniformity, simple investigation tools such as X-ray provide adequate clinical guidance [17]. Only few patients with a high number of metastases (five or more) exist, possible implications on prognosis therefore remain unclear. Furthermore, there is wide consensus on the effects of widespread metastases on single-agent resistance and survival [2, 5, 6, 11]. In this cohort, however, patients with widespread metastases were all characterized by a total FIGO score of over 10. Simultaneous presence of other prognostic factors has obviated the occurrence of misclassification in this group.

We however have to keep in mind that the present FIGO score, whereas only designed for stratifying patients between low- and high-risk treatments is also used to identify patients at greatest risk of early death within 4 weeks of commencing therapy and late death from multidrug-resistant disease. These ultrahigh-risk patients, present with widespread metastatic disease, reflected by a very high FIGO score (>12), are at significant risk for pulmonary, i.p., or intracranial hemorrhage and may benefit from low-dose induction chemotherapy. Furthermore, those with liver metastases with or without brain metastases are at increased risk of late death [15]. Removal of criteria that reflect these factors in a simplified system would hinder identification of these patient groups [14]. Consequently, the new system will need to be carefully evaluated with sufficient patient numbers in the high- and ultrahigh-risk groups.

Consensus exists on the concept of restaging in case of relapse with full reassessment of spread of disease and previous chemotherapy response. Failure to respond to single-agent therapy already justifies the start of a different single-agent regimen or multi-agent therapy depending on hCG value. Confusion may however exist on the definition of failed chemotherapy. It would therefore be helpful to provide a clear definition on failed chemotherapy with the revised FIGO 2000 (i.e. rise of serum hCG after two chemotherapy cycles).

It appears that only a small proportion of FIGO 2000 prognostic factors is needed to differentiate patients with low versus high-risk of single-agent resistance. This could lead to a relatively straightforward system with a small subset of easily retrievable factors, ideally reducing variability in scoring and improving agreement between centers. A simplified model with age, pretreatment serum hCG levels, number of metastases, antecedent pregnancy and interval alone resulted in an identical risk classification as the original FIGO 2000 in all but 1 of the 194 low-risk patients that needed to switch to high-risk therapy. Tumor size, previous failed chemotherapy, and site of metastases did not provide much added value.

After 15 years of experience with the worldwide accepted FIGO 2000, the present study provides a useful overview of its design

**Table 3. Alternative scoring systems and their performance with FIGO 2000 compared**

Model	AUC <sup>a</sup>	True-positive <sup>b</sup>	True-negative <sup>b</sup>	False-positive <sup>b</sup>	False-negative <sup>b</sup>	Sensitivity	Specitivity	Identical classification
Original FIGO 2000	1.000	694	73	0	0	1.00	1.00	100%
Model 1								
Age								
Antecedent pregnancy								
Pretreatment serum hCG								
Tumor size								
Number of metastases	0.999	693	70	2 <sup>1,2 c</sup>	4 <sup>5,6,7,8 c</sup>	0.99	0.97	99.1%
Model 2								
Age								
Antecedent pregnancy								
Pretreatment serum hCG								
Number of metastases	0.998	720	71	4 <sup>1,2,3,4 c</sup>	3 <sup>5,7,8 c</sup>	1.00	0.95	99.2%
Model 3								
Age								
Antecedent pregnancy								
Interval								
Pretreatment serum hCG								
Number of metastases	1.000	722	73	1 <sup>4 b</sup>	0	1.00	0.99	99.9%

<sup>a</sup>Risk classification according to the FIGO 2000 was considered 'gold standard'.

<sup>b</sup>For every alternative scoring system the number of discordant patients and corresponding case numbers are highlighted.

<sup>c</sup>Allowing for the fact that the FIGO 2000 was already used in this particular data, the AUC, sensitivity and specificity for the original FIGO 2000 were consequently calculated at 1.0.

and performance in a large nationwide cohort. Although the number of patients with resistance to single-agent therapy in the low-risk group made us inquisitive on possible improvements in the performance of FIGO 2000, exploration of possible improvement in classification is challenging when only the prognostic factors currently employed in the FIGO 2000 are considered. Doppler ultrasonography, used to measure uterine vascularity through pulsatility index, has been suggested as an independent prognostic factor for resistance to single-agent chemotherapy [24]. Further improvement by including novel variables such as Doppler pelvic ultrasonography should be considered. A renewed evaluation, preferably through international research collaboration, would be needed to further validate these findings and refine FIGO 2000 into a straightforward classification system we could all embrace.

## Conclusion

The total FIGO score is determined by a summation of scores for eight prognostic factors. The majority of factors relate to tumor bulk and are not independently prognostic for single-agent resistance. Our simplified alternative using only five of the FIGO prognostic factors remains an accurate system for discriminating patients requiring single as opposed to multi-agent chemotherapy. This simplified alternative would ideally reduce variability in scoring and improve agreement between centers. However, further validation is required to ascertain how this system performs in distinguishing ultrahigh-risk and high-risk patients.

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