

Is maintenance chemotherapy always necessary in gestational trophoblastic neoplasia? A retrospective cohort analysis

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ABSTRACT

Objectives: Gestational trophoblastic neoplasia (GTN) is a rare but highly curable group of gestational tumors. Current risk stratification relies on the International Federation of Gynecology and Obstetrics (FIGO) staging and WHO scoring systems, yet both have shown limited accuracy in predicting relapse or chemoresistance. The necessity of routine maintenance chemotherapy following remission - particularly in low-risk patients - remains controversial.

Methods: We conducted a retrospective cohort study of 25 patients with GTN treated between 2006 and 2022. Demographic, clinical, and treatment-related data were analyzed. Outcomes of interest included methotrexate (MTX) resistance, relapse, and the use of maintenance chemotherapy. Follow-up duration and disease outcomes were assessed descriptively.

Results: The median age at diagnosis was 28 years. Most patients (76%) had FIGO stage I disease; 44% were classified as high-risk. MTX resistance occurred in two patients (8%), both low-risk. Only one relapse was observed, occurring five years after remission. Maintenance chemotherapy was given to 64% of patients. Notably, none of the eight patients who did not receive maintenance therapy - including four high-risk cases - experienced relapse. No clear difference in outcomes was observed between stage I and stage III patients.

Conclusions: In this real-world cohort with long-term follow-up, maintenance chemotherapy did not appear necessary to prevent recurrence, even in select high-risk patients. Additionally, the FIGO/WHO systems showed limited prognostic discrimination. These findings support the need for individualized, response-adapted management strategies and underscore the limitations of current risk models in GTN.

Keywords: Maintenance chemotherapy, gestational trophoblastic neoplasia, FIGO stage

Gestational trophoblastic neoplasia (GTN) is a rare but highly curable group of gestational tumors, characterized by abnormal trophoblastic proliferation and elevated serum human chorionic gonadotropin (hCG) levels. With timely diagnosis and

appropriate treatment, cure rates exceed 90%, even in metastatic disease [1]. Risk stratification typically relies on the International Federation of Gynecology and Obstetrics (FIGO) anatomical staging system and the World Health Organization (WHO) prognostic scoring

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system: low-risk patients (WHO score <7; FIGO stage I–III) are generally treated with single-agent methotrexate (MTX), while high-risk cases require multi-agent chemotherapy such as the etoposide-methotrexate-actinomycin D/cyclophosphamide-vincristine (EMA/CO) regimen [2, 3].

However, two aspects of GTN management remain controversial. First, the necessity of maintenance chemotherapy after remission is debated, especially in low-risk patients with inherently low relapse rates [4, 5]. Second, the prognostic accuracy of the FIGO/WHO system is increasingly questioned, with studies showing minimal differences in disease-free survival (DFS) across stages and relapse occurring even in low-risk patients [3-6].

Recent reviews have further highlighted the limitations of the FIGO 2000 system, citing methodological inconsistencies, ambiguous risk weighting, and failure to incorporate radiologic or molecular predictors. Jin-Kai *et al.* [6] proposed replacing this one-size-fits-all approach with task-specific prognostic models tailored to distinct clinical goals, such as predicting chemotherapy resistance or recurrence. These evolving perspectives support a shift toward more individualized, response-adapted strategies in GTN management.

In this study, we analyzed a 16-year cohort of GTN patients to evaluate relapse, while addressing two unresolved questions in GTN care - whether maintenance chemotherapy is essential for preventing recurrence, and whether FIGO staging accurately reflects clinical risk in long-term survivors.

METHODS

Study Design and Data Collection

This retrospective cohort study included all patients diagnosed with GTN between January 2006 and June 2022. Of 31 identified cases, 25 with complete data and adequate follow-up were included in the final analysis.

GTN was diagnosed based on clinical, biochemical, radiologic, and/or histopathologic findings. Included cases comprised postmolar GTN - defined by persistently elevated or rising β -hCG beyond six months after molar evacuation - and histologically

confirmed choriocarcinoma, invasive mole, placental site trophoblastic tumor (PSTT), or epithelioid trophoblastic tumor (ETT). No patients with a WHO score >13 (ultra-high-risk category) were included in this study.

Demographic, clinical, and treatment-related variables were retrospectively collected, including patient characteristics, tumor pathology, treatment modalities, and outcomes such as MTX resistance, recurrence, and final disease status.

Low-risk patients were treated with single-agent MTX, while high-risk patients received multi-agent EMA/CO chemotherapy. Maintenance chemotherapy was defined as three additional cycles of the same regimen after complete remission, at the discretion of the treating physician.

Maintenance chemotherapy decisions were individualized, based on the depth and timing of hCG normalization, initial FIGO/WHO score, metastatic burden, treatment-related toxicity, patient compliance, and physician judgment. Patients with rapid and sustained hCG decline, minimal metastatic disease, and high toxicity risk were more likely to forgo maintenance therapy. Patients were monitored weekly with serum β -hCG until three consecutive values were below 5 mIU/mL, followed by monthly surveillance for at least six months. MTX resistance or progression was defined per FIGO 2002 criteria as a >10% rise over three values, plateau over four weeks, or persistent elevation beyond six months.

Risk Stratification and Staging Systems

Anatomical staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) 2002 criteria, which classifies gestational trophoblastic neoplasia (GTN) into four stages based on the anatomical extent of disease:

- Stage I:** Disease confined to the uterus.
- Stage II:** GTN extending to the genital structures (adnexa, vagina, or broad ligament).
- Stage III:** Pulmonary metastases, with or without uterine involvement.
- Stage IV:** Metastases to distant organs such as liver or brain.

Prognostic scoring was conducted using the FIGO/WHO 2000 risk scoring system, which integrates clinical, biochemical, and metastatic parameters

to predict resistance to single-agent chemotherapy. This composite score assigns numerical values (0, 1, 2, or 4 points) to the following eight prognostic (Table 1):

The cumulative score stratifies patients into risk groups as follows:

Low-risk: Total score 0-6

High-risk: Total score ≥ 7

Ultra-high-risk (optional classification): Score ≥ 13 or presence of extensive metastatic disease [2, 4, 5].

Accordingly, in our study, patients with FIGO stage I-III disease and a WHO score of 0-6 were classified as low-risk, whereas those with FIGO stage IV and/or a score ≥ 7 were classified as high-risk.

Ethical approval

All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. The study protocol was approved by the Ethics Committee of Ankara City Hospital (approval number: E1/2997/2022; date: 02/11/2022).

Statistical Analysis

All analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY). Continuous variables were reported as medians with ranges or interquartile ranges (IQRs), and categorical variables as counts and percentages. Primary outcomes included remission, recurrence, and MTX resistance. Follow-up duration was calculated from

diagnosis to last clinical contact. Median follow-up and its 95% confidence interval (CI) were estimated using the non-parametric bootstrap method with 1,000 resamples. The observed follow-up range was also reported.

RESULTS

Twenty-five patients were included in the study, with a median age of 28 years. The most common presenting symptom was abnormal uterine bleeding, followed by asymptomatic β -hCG elevation. GTN developed after a molar pregnancy in slightly more than half of the cases. Most patients were diagnosed within four months of the antecedent pregnancy.

Invasive mole was the predominant histologic subtype. According to FIGO staging, most patients had stage I disease, and all metastases ($n = 6$) were limited to the lungs. Based on WHO/FIGO criteria, 56% of patients were classified as low-risk and 44% as high-risk (Table 2).

Chemotherapy was initiated in all but one patient, who underwent primary hysterectomy with subsequent remission. MTX was the first-line treatment in all low-risk and in selected high-risk patients. MTX resistance occurred in two cases, both successfully managed with multi-agent therapy. One relapse was documented five years after achieving initial remission.

Maintenance chemotherapy was administered in 64% of cases. Importantly, none of the eight patients

Table 1. Prognostic scoring

Risk Factor	Score 0	Score 1	Score 2	Score 4
Age (years)	<40	≥ 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval from index pregnancy (months)	<4	4-6	7-12	>12
Pretreatment 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, kidney	Gastrointestinal tract	Brain or liver
Number of metastases	0	1-4	5-8	>8
Previous failed chemotherapy	None	-	Single-agent	Multi-agent

Table 2. Baseline characteristics of patients with gestational trophoblastic neoplasia (n=25)

Characteristic	Data
Age at diagnosis (years)	28 (19-49)
Gravidity	3 (1-9)
Parity	1 (0-6)
Serum β -hCG at GTN diagnosis (IU/L)	8.5×10^5 (3.4×10^2 - 1.2×10^7)
Presenting symptom	
Vaginal bleeding	12 (48.0%)
Asymptomatic (elevated hCG only)	9 (36.0%)
Amenorrhea	2 (8.0%)
Abdominal pain	2 (8.0%)
Antecedent pregnancy	
Molar pregnancy	13 (52.0%)
Complete mole	7 (28.0%)
Partial mole	6 (24.0%)
Non-molar pregnancy	12 (48.0%)
Abortion	3 (12.0%)
Ectopic pregnancy	2 (8.0%)
Term pregnancy	7 (28.0%)
Histologic subtype	
Invasive mole	23 (92.0%)
Choriocarcinoma	2 (8.0%)
FIGO anatomic stage	
Stage I	19 (76.0%)
Stage II	0 (0.0%)
Stage III	6 (24.0%)
Stage IV	0 (0.0%)
WHO/FIGO prognostic risk score	5 (2–10)
Low-risk (score <7)	14 (56.0%)
High-risk (score $\geq$ 7)	11 (44.0%)
Site of metastasis	
No metastasis	19 (76.0%)
Lung only	6 (24.0%)

Data are shown as n (%) or median (range)

who did not receive maintenance therapy - including four classified as high-risk - experienced relapse. This finding raises questions about the necessity of routine consolidation therapy in certain patients.

At a median follow-up of 30.7 months (95% CI: 27.7–55.5), all patients were alive and disease-free.

No treatment-related deaths or severe adverse events were reported (Table 3).

No significant difference in long-term outcomes was observed between patients with FIGO stage I and III disease, suggesting limited prognostic discrimination in this cohort.

Table 3. Treatment characteristics and outcomes

Parameter	Data
First-line treatment	
Upfront hysterectomy	1 (4.0%)
Methotrexate	17 (68.0%)
EMA/CO regimen	7 (28.0%)
Maintenance chemotherapy	
Yes	16 (64.0%)
No	8 (32.0%)
Methotrexate resistance	2 (8.0%)
Recurrence	1 (4.0%)
Outcome	
Alive and disease-free	25 (100.0%)
Follow-up duration (months)	Median: 30.7 (95% CI: 27.7-55.5); range: 4.4-194.9

Data are shown as n (%). Follow-up duration is presented as median with 95% confidence interval and range. Treatment characteristics and clinical outcomes of patients with gestational trophoblastic neoplasia (GTN). First-line therapies included single-agent methotrexate (MTX) in weekly or 3-day regimens, multi-agent EMA/CO, or primary surgery. Maintenance chemotherapy was defined as three additional cycles following remission. All patients were alive and disease-free at last follow-up.

DISCUSSION

This 16-year retrospective cohort provides real-world insight into two unresolved questions in GTN management: whether post-remission maintenance chemotherapy is essential and how accurately the FIGO/WHO risk stratification systems predict long-term outcomes.

Several studies have questioned the discriminatory power of the FIGO and WHO scoring systems in guiding therapeutic decisions. Powles *et al.*, in a large retrospective series of 1708 cases, identified 60 relapses and 11 chemoresistant cases, noting that relapses occurred even among low-risk patients and that prognostic scores poorly predicted survival after relapse, especially in ultra-high-risk disease [6]. Similarly, Osborne *et al.* [7] evaluated 216 low-risk GTN patients enrolled in a randomized trial and observed methotrexate resistance in patients with WHO scores of 5–6, suggesting inadequate discrimination within the low-risk group. A meta-analysis including 901 complete responders by Albright *et al.* [8] reported a 4.1% relapse rate, with markedly higher mortality in patients with ultra-high-risk scores (≥ 13), despite comparable treatment regimens [8]. In their comprehensive guideline, Seckl

et al. [9] also noted the limited prognostic performance of anatomical staging alone and recommended incorporating clinical judgment and hCG kinetics.

Our own findings further support these concerns. No significant difference in long-term outcomes was observed between patients with FIGO stage I and III disease, and both instances of methotrexate resistance occurred in patients classified as low-risk. These results challenge the reliability of current staging and scoring systems in capturing the true biological heterogeneity of GTN.

Importantly, recent work by Jin-Kai *et al.* [6] offers a deeper critique of the FIGO 2000 framework. The authors argue that the system was originally developed to describe general prognosis, not to inform clinical decisions such as predicting resistance or recurrence. They also demonstrate that the WHO score relies on arbitrarily assigned weighting and lacks statistical grounding, which may lead to risk misclassification. Their findings highlight the need for task-specific, biologically informed prognostic models tailored to discrete clinical endpoints [6]. This aligns closely with our observations and reinforces the need for refined stratification tools that integrate clinical, biochemical, and potentially molecular variables.

The second area of controversy—maintenance chemotherapy—remains unsettled. Expert consensus often favors continued treatment for several weeks post-remission, particularly in high-risk patients [9]. However, this practice is based largely on retrospective data rather than prospective validation. Albright *et al.* [8] reviewed over 2,100 high-risk patients and found limited evidence supporting uniform consolidation, despite its widespread adoption. Our study contributes to this debate by showing that none of the eight patients who did not receive maintenance therapy—including four high-risk cases—developed relapse during long-term follow-up.

This finding is supported by several reports questioning the need for three-cycle consolidation protocols. In the MITO-9 study, a multicenter retrospective analysis of 333 low-risk GTN patients treated with first-line methotrexate across six institutions in Italy. Following hCG normalization, patients were grouped according to the number of consolidation cycles received—two, three, or more than three—and relapse rates were assessed. Notably, no relapses occurred among patients with FIGO scores ≤ 2 who received only two consolidation cycles. In contrast, relapse rates increased to 2.2% and 10.2% among those receiving three and more than three cycles, respectively, regardless of FIGO subscore [10]. Conversely, Mitric *et al.* [11] conducted a retrospective analysis of 94 patients across two Canadian academic centers and demonstrated excellent outcomes with standardized three-cycle consolidation following care centralization in Canada. Several institutions, including Braga *et al.* [12], continue to advocate for three consolidation cycles following remission in both low- and high-risk GTN patients. Lybol *et al.* [13] also reported lower relapse with three versus two methotrexate cycles (4.0% vs. 8.3%, $P=0.006$). However, Couder *et al.* [14], in a large cohort of 465 patients, found that the number of consolidation cycles was not independently predictive of recurrence; rather, antecedent term pregnancy and the need for ≥ 5 MTX cycles were stronger indicators.

Taken together, these findings - including those from our cohort - underscore the need to move beyond rigid, uniform maintenance protocols. Personalized, response-adapted strategies based on dynamic treatment indicators may provide safer and more effective post-remission care. In line with this, Jin-Kai *et al.* [6] proposed integrating innovative tools such as slope

modeling, time-series analysis, and machine learning into future prognostic models. Similarly, a recent systematic review protocol highlighted the absence of high-quality evidence supporting universal consolidation and advocated for individualized management in postmolar GTN [15].

Limitations

This study has several limitations. Its retrospective design limits causal inference and introduces potential selection bias. The small sample—especially in subgroup analyses—diminishes statistical power. Additionally, being a single-center study may limit generalizability. Nonetheless, the findings provide meaningful real-world insights and raise clinically relevant questions for future prospective research.

CONCLUSION

Our real-world data support two central insights in GTN management. First, maintenance chemotherapy may be safely omitted in selected—including some classified as high-risk—without compromising long-term outcomes. Second, the FIGO/WHO scoring systems showed limited prognostic accuracy in predicting relapse or resistance. These findings emphasize the need for individualized, response-adapted risk models that integrate clinical dynamics and data-driven predictors. Prospective multicenter studies are warranted to validate these strategies and guide optimal post-remission care.

Ethical Statement

This study was approved by the Ankara City Hospital Clinical Research Ethics Committee No. 1 (decision no.: E1/2997/2022; approval date: 02.11.2022). The study was conducted in accordance with the principles of the Declaration of Helsinki and with good clinical practice guidelines. The requirement for informed consent was waived due to the retrospective design of the study and the use of anonymized clinical data.

Data Availability

All data generated or analyzed during this study are included in this published article. Additional datasets that support the findings of this study are

available from the corresponding author upon reasonable request.

Authors' Contribution

Study Conception: EA, DU; Study Design: EA, DU; Supervision: DU; Funding: MB, ÖB, EA; Materials: EH; Data Collection and/or Processing: MB, EH; Statistical Analysis and/or Data Interpretation: ÖB, EA; Literature Review: ÖB, EA; Manuscript Preparation: EH; and Critical Review: EH.

Conflict of interest

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Generative Artificial Intelligence Statement

Portions of the manuscript were developed with the assistance of ChatGPT-4o (May 2024 version), a large language model developed by OpenAI. This tool was employed solely to enhance linguistic clarity, improve academic expression, and ensure stylistic consistency. All medical content, statistical analyses, and scientific interpretations were independently generated by the authors. The final version of the manuscript was thoroughly reviewed and approved by all authors.

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