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# First-line hysterectomy for women with low-risk non-metastatic gestational trophoblastic neoplasia no longer wishing to conceive☆,☆☆

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## HIGHLIGHTS

- Hysterectomy cures 82.4% of low-risk non-metastatic GTN patients no longer wishing to conceive.
- A FIGO score of 5–6 and choriocarcinoma are independent risk factors for the failure of hysterectomy.
- Reference treatment of young patients with low-risk non-metastatic GTN is chemotherapy.

## ARTICLE INFO

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## ABSTRACT

*Background.* Low-risk gestational trophoblastic neoplasia (GTN) patients (FIGO score ≤6) are generally treated with single agent chemotherapy (methotrexate or dactinomycin) resulting in a 5-year mortality rate of 0.3%. However, despite these encouraging survival rates, chemotherapy is associated with significant adverse events in most patients. Although it is generally accepted that patients who no longer wish to conceive may be treated by hysterectomy for a hydatidiform mole, the evidence to support this strategy in low-risk GTN patients is lacking.

*Objectives.* To describe the survival, efficacy, and tolerance associated with first-line hysterectomy in low-risk non-metastatic GTN patients.

Study design.

Seventy-four of 1072 low-risk GTN patients treated in the French Center underwent first-line hysterectomy. Patients data with successful first-line hysterectomy were retrospectively compared to those requiring further salvage chemotherapy.

*Results.* First-line hysterectomy was followed by hCG normalization in 61 patients (82.4%, 95% confidence interval [CI] 71.8–90.3) without any further salvage chemotherapy, whereas 13 patients required salvage chemotherapy. After multivariate analysis, a FIGO score of 5–6 (exact OR 8.961, 95%CI 1.60–64.96), and the presence of choriocarcinoma (exact OR 14.295, 95%CI 1.78–138.13) were associated with the risk of requiring salvage chemotherapy.

*Conclusion.* Hysterectomy as a first-line treatment is effective without salvage chemotherapy in 82.4% of women with low-risk non-metastatic GTN and can be presented as an alternative to single-agent chemotherapy when childbearing considerations have been fulfilled. In young patients, this therapeutic option should not be considered because single-agent chemotherapies are curative in nearly 100% of patients while maintaining fertility.



☆ This study was conducted in the French Reference Center for Trophoblastic Diseases, Lyon, France.

☆☆ **Condensation**: First-line hysterectomy is curative for 82.4% of patients with low-risk non-metastatic GTN no longer wishing to conceive.

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## 1. Introduction

Gestational trophoblastic diseases (GTDs) encompass placental pre-malignant (complete and partial hydatidiform moles) and malignant (invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor) entities [1–3]. The latter, which are also called gestational trophoblastic neoplasia (GTN), may be diagnosed by pathological examination or abnormal changes in serum human chorionic gonadotropin (hCG) levels during post-molar follow-up as defined by the International Federation of Gynecology and Obstetrics (FIGO) criteria [4]. Post-molar malignant transformation is usually observed after 0.5–3% and 15–20% of partial and complete hydatidiform moles, respectively [2]. Although protocols vary among centers, there is general agreement among international experts that GTN patients should be treated according to FIGO score, with monochemotherapy for low-risk patients (FIGO ≤6) and polychemotherapy for high-risk patients (FIGO ≥7) [4–6]. Most centers use methotrexate or dactinomycin for low-risk GTN [7], whereas EMA-CO (etoposide, methotrexate, and dactinomycin alternated weekly with cyclophosphamide and vincristine) is the most prescribed protocol in high-risk GTN patients [6]. Recent data on low-risk and high-risk GTN patients managed with this strategy showed a 5-year mortality rate of 0.3% (95% confidence interval [CI] 0.07–1.06%) and 12% (95% CI 7.49–18.9), respectively [8].

Despite the encouraging survival rates resulting from decades of chemotherapy optimization and centralized care for patients with rare tumors, many patients experience serious adverse side effects from chemotherapy [9]. In GTN patients treated with an 8-day methotrexate regimen, 4.2% had severe (grade 3 or 4) blood/bone marrow toxicity and metabolic/laboratory toxicity, including 1.4% with grade 4 toxicities [10]. Moreover, a greater proportion of GTN patients treated with EMA-CO have leukemia, melanoma, meningioma, and head and neck secondary malignancies compared to a national age-matched population. However, all protocols are associated with an increased risk of early menopause [11].

Although it is generally accepted that patients no longer wishing to conceive may be treated for a hydatidiform mole by hysterectomy, evidence to support this strategy in low-risk GTN patients is lacking. Here, we present a retrospective study on survival, efficacy, and tolerance of first-line hysterectomy performed on patient demand in patients with low-risk GTN without future reproductive desire between 1999 and 2016 at the French Reference Center for Trophoblastic Diseases (FRCTD).

## 2. Patients and methods

This study was carried out at the FRCTD in Lyon, which has been receiving voluntary declarations of GTD cases since 1999. The Center provides pathological review, supports local clinicians in charge of patients when choosing treatment according to the FIGO score, and organizes prospective follow-up [12, 13]. In most cases, patients are treated by their referring physician in their original hospital.

For this study, explicit information was provided by the FRCTD to physicians in charge of each patient regarding the global recommendation of monochemotherapy for the treatment of low-risk GTN, and that the morbidity associated with hysterectomy is not negligible. All patients had an effective uterine evacuation prior to their hysterectomy. The surgical approach for hysterectomy (laparoscopic, laparotomy, or vaginal) was chosen by the local physicians, but they were asked not to morcellate the uterus and no lymph node dissection was advocated. Informed consent for prospective registration at the FRCTD was obtained from each patient, and ethical approval was obtained from the local ethics authority. Every registered patient's diagnosis was confirmed by our referring pathologists [12].

FIGO scoring and staging was determined by pelvic Doppler ultrasound, abdomen and chest computed tomography, followed by chest X-ray in the case of lung metastasis, and brain and pelvic magnetic resonance imaging [5].

The long standing use of total serum hCG as a sensitive tumor biomarker reflecting GTN chemosensitivity or for the early detection of relapses is acknowledged worldwide [6]. The total serum hCG concentration was measured by automated immunochemiluminescence analyzers in the laboratory of each patient center. Serum hCG was measured weekly until 1 month after normalization for patients who did not require further chemotherapy or until the end of the second consolidation cycle when further chemotherapy was needed. Serum hCG was then measured monthly for 12 months for single-agent chemotherapy and first-line hysterectomy alone, and for 18 months for polychemotherapy. The clinical and hCG follow-up was then eased.

Among 7625 registrations of patients at our center between 1999 and 2017, 1422 concerned a diagnosis of GTN; for 10 patients who presented two different GTNs, only the first episode was considered. Patients with pathological diagnosis of epithelioid trophoblastic tumor, placental site trophoblastic tumor, or unclassified intermediate trophoblastic tumors were not included (n = 62). 1072 patients had low-risk GTN with an interval of at least 6 months between first hCG normalization and data extraction. Patients with the following conditions were excluded from analysis: first-line chemotherapy (n = 918), any surgery different from classical total hysterectomy (partial hysterectomy, salpingo-oophorectomy, hysteroscopic resection, or vaginal metastasectomy; n = 11), hemostatic hysterectomy or hysterectomy performed in the absence of FIGO-defined GTN diagnosis criteria (n = 37), hysterectomy with concomitant chemotherapy (n = 9). Patients with lung metastasis were excluded from the study (n = 19; Fig. 1).

We identified 74 patients with low-risk GTN without any metastasis on extension work-up treated with first-line hysterectomy (Table 1). The youngest patient, who was 29 years old, had a hysterectomy performed at our center at her demand and confirmed by a collegial decision during a multidisciplinary meeting. Criteria for failure of hysterectomy alone and the initiation of subsequent chemotherapy were as follows: at least 3 weekly consecutive plateauing (<10% variation between two serum hCG) or 2 consecutive increases (>10%) in serum hCG. The same criteria were used to define chemoresistance. First-line single-agent chemotherapy was methotrexate. In cases of failed methotrexate, second line chemotherapy was dactinomycin when hCG was ≤500 IU/L or EMA-CO if hCG titers were higher. From July 2005, this hCG threshold was increased to 1000 IU/L and since July 2010, dactinomycin was given in failed methotrexate regardless hCG titers. FIGO score and stage were extracted from our database using PARADOX 9 software (Corel, Ottawa, Canada). The occurrence of severe post-operative complications (grade III) according to Clavien-Dindo was retrieved after a review of patients' medical histories [14].

The primary objective was to report the proportion of patients cured by first-line hysterectomy in a retrospective single-center national cohort. Secondary objectives included the frequency and nature of salvage chemotherapy used after failure of first-line hysterectomy and an explanatory assessment of prognostic factors.

Statistical analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC). The relationships between success of hysterectomy and the characteristics of the GTN patients were assessed by Fisher's exact test. The mean difference was tested using the nonparametric Wilcoxon-Mann-Whitney test. A univariate analysis was performed to identify predictive factors for hysterectomy failure. Exact odds ratios and CIs were estimated. Significance was set at $p < 0.05$. Multivariate analysis was performed after the selection of significant variables from univariate analysis.

## 3. Results

Among 74 low-risk non-metastatic GTN patients treated with first-line hysterectomy as the only planned treatment, 61 (82.4%; 95% CI 71.8–90.3, $p < 0.0001$) achieved hCG normalization without any further