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**Original Research Article**

# 5-Fluorouracil as first-line treatment for low-risk gestational trophoblastic neoplasia

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## Abstract

***Purpose:*** *To investigate the efficacy and prognostic factors in response to 5-fluorouracil (5-FU) in low-risk gestational trophoblastic neoplasia (GTN).*
***Methods:*** *This single-center retrospective study analyzed the hospital records of 204 LRGTN patients admitted to Department of Gynecology, Liaoning Cancer Hospital & Institute of China from 2002 to 2016 for retrieval of their clinical data, chemotherapy regimens, related side-effects, and evaluation of treatment efficacy and prognostic factors.*
***Results:*** *The median progression-free survival (PFS) was 55 months (3 - 190 months). The overall cure rate was 100 %, with no tumor-related deaths. When a single-agent regimen i.e. 5-FU, was selected for initiation of treatment for 132 patients while only 49 of them were treated with chemotherapy, the effective cure rate was 62.88 % (83/132); while the overall drug resistance r was 27.27 % (36/132). For patients with FIGO scores ≥ 4 points, the incidence of drug resistance was 71.43 % (5/7), while the incidence of III/IV myelosuppression was 10.61 % (14/132). A total of 38 patients (18.63 %) received surgical treatment in addition to chemotherapy. A comparison was made between two groups of patients with non-drug resistance, i.e., patients with unexpected GTN diagnosed postoperatively and those who received chemotherapy preoperatively. It was found that the number of courses of GTN chemotherapy for those who were unexpectedly diagnosed postoperatively was more than that for those who received chemotherapy preoperatively (p = 0.004).*
***Conclusion:*** *The single drug (5-FU) was effective in the management of low-risk (LR)-GTN. Treatment failure was related to drug resistance, high tumor score, and severe toxicity. Multi-agent regiments in combination with surgery, were an effective treatment method for GTN. For patients without metastasis and fertility requirements, surgery after chemotherapy significantly shortened the treatment cycle without increasing complications.*

***Keywords:*** *Gestational trophoblastic neoplasia (GTN), Low-risk patients, Prognosis, 5-Fluorouracil, progression-free survival (PFS)*



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## INTRODUCTION

Gestational trophoblastic neoplasia (GTN) is a trophoblastic hyperplasia disease which is characterized by invasion of the myometrium or ectopic metastasis [1]. The incidence of GTN is relatively high in the Asian population. The treatment is based on combined use of

chemotherapy and surgery. Currently, it uses the clinical staging and scoring system of International Federation of Gynecology and Obstetrics (FIGO) 2000 which was officially developed in 2002 and is still in use today. In this scoring system, GTN patients with a prognostic score ≤ 6 points are considered low-risk. The guidelines were updated in 2015 [2], with the recommendation that each national diagnosis and treatment center may adjust the inclusion criteria according to their own diagnosis and treatment experience.

The treatment of GTN is based on the FIGO prognostic score using grading and individualized treatment principles [3]. There is no consensus on the best treatment for low-risk gestational trophoblastic neoplasia (LRGTN). According to the current FIGO guidelines, single-agent chemotherapy is the first choice for low-risk GTN patients. The frequently used drugs are methotrexate (MTX), actinomycin D (Act-D), and 5-fluorouracil (5-FU) [4]. The complete remission rates of low-risk GTN reported in the literature vary greatly (50 -90 %) due to different drug doses, frequencies, administration methods, and selection criteria [5,6].

The FIGO guidelines are usually updated so as to propose further stratified management of low-risk patients. However, there is currently no high-level evidence to show which single drug or treatment produces the best effect. Different centers choose different programs which account for differences in clinical efficacy, and it also creates problems for the standard treatment of diseases. This study reviewed the clinical records of GTN in Liaoning Cancer Hospital & Institute, investigated the factors related to efficacy of 5-fluorouracil in the treatment of LRGTN, and evaluated the efficacy of 5-FU as a single-agent in the treatment of LRGTN.

## METHODS

### Clinical profiles

The clinical data of LRGTN patients admitted to our hospital from 2002 to 2016 were collected. All patients received chemotherapy, and some patients also underwent surgery at the same time. The study was approved by the Ethics Committee of Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute (approval no. 20201101-2). The study conformed to the guidelines of the Declaration of Helsinki [7]. All patients provided written informed consent.

The clinical diagnosis, staging, and prognosis scores followed the FIGO 2000 prognostic scoring system standard, with patients with scores ≤ 6 as low-risk [8]. A total of 204 patients with sufficient clinical data were followed up, up to April 2018. One patient died due to non-tumor related causes.

### Case characteristics

#### *Inclusion criteria*

Patients in the following categories were included in the study: all patients who were fully evaluated before the first chemotherapy administration, with chemotherapy program supervised by a physician with extensive experience in the treatment of GTN; patients whose assessment comprised routine physical examination, serum β-human chorionic gonadotropin (β -HCG) level, chest x-ray or lung computed tomography (CT), pelvic ultrasound, or magnetic resonance (MR), as well as patients administered primary chemotherapy treatment from 2002-01-01 to 2016-12-31.

#### *Exclusion criteria:*

They were as follows: diagnosis of epithelioid trophoblastic tumor (ETT) and placental site trophoblastic tumor (PSTT), due to unique biological behavior; and incomplete medical records.

During the course of treatment, routine blood, liver, and kidney function tests, blood β-hCG assay, and pelvic ultrasound were performed before each course of treatment. If necessary, CT/MR was performed. Routine blood testing was performed every 2-to-3 days during chemotherapy. After every 2 to 3 courses of treatment, patients with stage III disease underwent lung CT. The single-agent (5-FU) regimen was based on fasting body weight on the morning of chemotherapy, with doses of 28-30 mg/kg/day. Intravenous drip was prescribed for 8-10 days at 2-week intervals.

### Drug resistance

This was indicated by increased β-hCG level following 2 consecutive treatment courses.

### Recurrence

Patients whose β-hCG levels were re-elevated after 3 weeks of undetectable levels in the

absence of pregnancy, were deemed to have recurrence.

### Indications for withdrawal

After the β-hCG returned to normal level, 1 to 2 courses of the last effective regimen were administered. During the treatment period, if the β-hCG levels decreased slowly, or the tumor lesions were extensive, consolidation was performed with 2 to 3 courses of the last effective regiment.

### Statistical analysis

Statistical analyses were performed using SPSS version 20.0 statistical software. The independent sample non-parametric test was used for measurement data, while ratios were compared using the chi-square test. Survival analysis was performed using Kaplan Meier analysis. Statistical significance was assumed at $p < 0.01$.

## RESULTS

### Patient profile

The demographic and clinical characteristics of the study population are summarized in Table 1. The efficacy of single-agent (5-FU) in the treatment of LRGTN is summarized in Table 2. Analyses of survival in different programs are shown in Figure 1.

### Clinical characteristics

The median age of the patients was 31 years (range 18 – 63 years), and the average age was 33 years. The primary clinical manifestation was irregular vaginal bleeding. Thirty-eight patients underwent surgery as part of their treatment protocol. Fifteen patients were diagnosed with GTN after surgery at another hospital. Twenty-four patients (63.16 %) were of advanced age (≥ 40), with median PFS of 55 months (3 – 190 months), and recurrence rate was 0.98 % (2/204): one case recurred within 6 months).

For the single-agent group, a total of 133 patients were treated with single-agent chemotherapy (132 patients treated with 5-FU). There were 69 patients in stage I, 2 patients in stage II, and 62 patients in stage III. There were 81 patients with 0 - 2 points, 46 patients with 2 - 4 points, and 6 patients with 5 - 6 points, as shown in Table 1. Seventy-one patients were included in the combined chemotherapy group, amongst which subjects at stages I, II and III were 19, 2 and 50, respectively.

**Table 1:** Efficacy of single-agent (5-FU)

| Parameter | Effective (n=83) | Failing (n=49) | $\chi^2$ | *P-value* |
|---|---|---|---|---|
| ***Years*** | | | 0.525 | 0.469 |
| ≤39 | 56（60.9%） | 36（39.1%） | | |
| ≥40 | 27（67.5%） | 13（32.5%） | | |
| ***β -hCG level*** IU/L | | | 0.954 | 0.329 |
| ＜10000 | 70（64.8%） | 38（35.2%） | | |
| ≥10000 | 13（54.2%） | 11（45.8%） | | |
| ***Clinical diagnosis*** | | | 6.694 | 0.010 |
| Invasive hydatidiform mole | 67（58.3%） | 48（41.7%） | | |
| Choriocarcinoma | 16（94.1%） | 1（5.9%） | | |
| ***Clinical stages*** | | | 1.699 | 0.192 |
| I | 47（68.1%） | 22（31.9%） | | |
| II-III | 36（57.1%） | 27（42.9%） | | |
| ***Last pregnancy*** | | | 4.679 | 0.031 |
| Mole | 70（59.3%） | 48（40.7%） | | |
| abortion/term delivery | 13（92.9%） | 1 （7.1%） | | |
| ***Pregnancy*** | | | 1.120 | 0.772 |
| 1 | 15 | 12 | | |
| 2 | 23 | 12 | | |
| 3 | 22 | 14 | | |
| ≥4 | 23 | 11 | | |
| ***Delivery time*** | | | 4.860 | 0.088 |
| 0 | 27 | 24 | | |
| 1 | 45 | 17 | | |
| 2 | 11 | 8 | | |
| ***FIGO prognosis* score** | | | 0.137 | 0.711 |
| 0-3 | 73（63.5%） | 42（36.5%） | | |
| 4-6 | 10（58.8%） | 7（41.2%） | | |

**Table 2:** Chemotherapy in combination with surgery for patients with LR-GTN

| **Accidental GTN hysterectomy (surgery + chemotherapy)** | | | **Hysterectomy without fertility requirements (chemotherapy + surgery)** | | | **Local focus resection (continuous focus after chemotherapy)** | | |
|---|---|---|---|---|---|---|---|---|
| ***Diagnosis*** (stage : score) | ***Chemotherapy*** | ***Courses*** | ***Diagnosis*** (stage : score) | ***Chemo-therapy*** | ***Courses*** | ***Diagnosis*** (stage : score) | ***Chemotherapy*** | ***Courses*** |
| CC* (II:2) | ① | 4 | IM (I:2) | ① | 3 | IM (III:4) | ① | 3 |
| IM** (III:5) | ③ | 4 | IM (I:2) | ① | 2 | IM (I:2) | ① | 6 |
| IM (I:4) | ③ | 3 | IM (I:3) | ① | 2 | CC (I:2) | ① | 5 |
| CC (I:6) | ③ | 3 | IM (I:4) | ① | 3 | CC (I:6) | ② | 13 |
| IM (III:2) | ① | 3 | CC (II:6) | ① | 2 | IM (III:6) | ③ | 3 |
| CC (I:6) | ③ | 2 | IM (I:2) | ① | 2 | CC (I:5) | ④ | 4 |
| IM (III:1) | ① | 5 | IM (I:3) | ① | 4 | IM (I:2) | ① | 6 |
| IM (III:1) | ① | 4 | IM (I:4) | ① | 4 | IM (I:2) | ① | 4 |
| CC (III:5) | ④ | 5 | IM (I:4) | ① | 4 | IM (I:2) | ① | 5 |
| IM (III:5) | ③ | 4 | IM (III:6) | ③ | 4 | IM (I:3) | ② | 7 |
| IM (III:3) | ① | 5 | CC (I:1) | ① | 2 | | | |
| CC (I:3) | ① | 6 | IM (I:2) | ① | 3 | | | |
| IM (III:2) | ① | 5 | IM (I:5) | ③ | 3 | | | |
| IM (III:5) | ③ | 7 | | | | | | |
| IM (III:4) | ③ | 7 | | | | | | |

Notes: **Primary chemotherapy:**
① : 5-FU; ②: Act-D; ③: 5-FU+Act-D; ④: 5-FU+Act-D+vincristine(VCR); CC*: choriocarcinoma; IM**:invasive mole

Eleven patients had 0-2 points, 21 patients had 2-4 points, and 39 patients had 5-6 points.

***Therapeutic effect of single drug 5-FU* treatment**

With the exception of one case of Act-D, 132 patients (64.71 %, 132/204) received 5-FU as initial chemotherapy (Table 1). Ages, hCG levels, clinical diagnosis, clinical stages, last pregnancy, number of pregnancies, delivery times, and prognostic scores did not significantly affect the efficacy of 5-FU treatment ($p > 0.01$). Eighty-three patients were treated effectively, accounting for an effective rate of 62.88 % (83/132) after single-agent (5-FU) chemotherapy. Chemotherapy was changed for forty-nine patients due to single drug (5-FU) treatment failure. Among these, three patients (2.27 %, 3/132) developed grade III/IV myelosuppression and were switched to Act-D single drug regimen. The remaining forty-six patients were switched to combined chemotherapy, and all showed good treatment efficacy.

Two out of 132 patients (1.51%, 2/132) developed recurrence. Both of these patients had stage III disease with a clinical diagnosis of tumor invasion. One patient had a history of prior chemotherapy, with decrease in β -hCG level to normal, and was given 1 consolidated course of treatment after 3 months of relapse. The patient was cured with combination chemotherapy (5-FU + Act-D). The second patient had a large weight change after the initial treatment, resulting in a change in the medication plan. Recurrence developed after 3 years, but this patient was cured with combination chemotherapy (5-FU+Act-D+ VCR + etoposide).

Hysterectomy was performed in 18 of the 132 patients without fertility requirement. Locally-focused resection was performed in 5 patients due to poor effect of chemotherapy. One patient underwent hysterectomy after drug resistance.

Kaplan-Meier analysis is shown in Figure 1. PFS was not affected by initial single-agent (5-FU) treatment, whether or not the chemotherapy regimen was changed ($p = 0.157$ (> 0.01).

**Adverse events (AEs)**

Routine peripheral blood testing was performed every 2 to 3 days during treatment. Liver and kidney functions were measured before each treatment. The AEs associated with chemotherapy drugs were graded I to IV, according to the system developed by the World Health Organization (WHO). The common side effects of chemotherapy primarily involved the blood system and digestive system. The main clinical manifestations were nausea, vomiting, oral ulcer, diarrhea, and transaminase abnormality. Almost all patients developed different degrees of myelosuppression which was the most common AE.

In the single drug 5-FU treatment group, severe AEs associated with chemotherapy occurred in four patients (10.61 %, 14/132), expressed as grades III to IV leukopenia or thrombocytopenia. One case of grade III liver injury occurred, which was resolved with supportive treatment. The incidence of leukopenia was 6.06 % (8/132), while the incidence of grade IV leukopenia which primarily occurred during the second to third course of chemotherapy, was 3.79 % (5/132). One patient developed grade III thrombocytopenia (45 x $10^9$/L), after one course of treatment, which was resolved after bone marrow support treatment. One patient developed serious AEs after a course of chemotherapy with the 5-FU regimen. The manifestations were systemic reactions: grade Ⅱ fever, grade Ⅲ gastrointestinal reaction, and grade Ⅱ myelosuppression. This patient's condition improved after treatment was changed to the Act-D protocol. No patient died due to AEs of chemotherapy.

A total of 17 patients with low-risk, high-scoring (≥ 4 points) disease who underwent single-agent (5-FU) chemotherapy were included in the initial analysis; treatment protocol was changed for 7 of them (41.18 %), and 5 patients (71.43 %) were resistant. The effective cure rate for patients with low-risk, high-scoring disease was 58.8 % (10/17).

***Fertility circumstance***

For patients with LRGTN after treatment, the use of contraception was recommended for 12 months, via oral contraceptives and/or barrier contraception (condoms). With the exception of 30 cases of hysterectomy, 204 patients were followed up for 6 - 190 months. There were 9 cases of natural pregnancy (5.17 %, 9/174), leading to 3 cases of abortion and 6 cases of uncomplicated delivery. All of these patients were under 40 years of age.

**Chemotherapy in combination with surgical treatment**

Thirty-eight patients (18.63 %) underwent surgery in this study (Table 2). Out of these, 10 patients underwent surgical treatment without local remission after multiple chemotherapy treatments. Fifteen patients were treated at an outside hospital for vaginal bleeding, abdominal pain, or other symptoms, and they had a postoperative diagnosis of GTN, and were then transferred to our hospital for chemotherapy. The number of chemotherapy courses for patients with GTN diagnosed unexpectedly ranged from 3 to 7. In the other 13 patients, there was no requirement for fertility, and the number of treatment courses was in the range of 2-4.

When the two groups of patients with non-resistant factors in the surgical group were compared, the results showed that there was no significant difference in prognosis between them ($p$ = 0.751). However, the number of treatment courses differed significantly between them ($p$ = 0.004): the number of chemotherapy courses was markedly higher in subjects diagnosed incidentally with GTN after undergoing hysterectomy than in those scheduled to undergo surgery after preoperative chemotherapy.

## DISCUSSION

It is known that GTN, a group of pregnancy-linked diseases of placental trophoblasts, is characterized by invasion and destruction of peripheral blood vessels. Thus, hematogenous metastasis is very common, and the tumors are prone to metastasis and hemorrhage within the myometrium, which may be life-threatening. However, GTN is sensitive to chemotherapeutic drugs: its cure rate is greater than 90 %.

For LR-GTN, the Chinese Medical Association, FIGO, and many other authorities recommend using single-agent multi-course chemotherapy, but the regimen which is the most efficacious, remains controversial. Etoposide, MTX and Act-D (VP-16) are commonly used in countries outside China, while 5-FU and FUDR are used in China. Due to the differences in the doses of various drugs prescribed, and variations in the mode of administration, there are differences in complete remission rates of newly diagnosed LR-GTN amongst institutions. At present, a large body of clinical evidence and foreign multi-center studies suggest that Act-D single-agent chemotherapy produces a good response and a high success rate. In a retrospective study comparing the efficacy and toxicity in subjects with LR-GTN receiving the 8d/1d-MTX regimen [2], it was found that although 8d-MTX-related AEs were frequent, these events were self-limiting and had no long-term sequelae. Moreover, there was significant continuous remission rate after therapy. Ordered evaluation showed that Act-D was better than MTX (RR 0.64, 95 % CI 0.54 - 0.76), and the success rate of Act-D was higher. In a meta-analysis which included 7 trials and 4 retrospective studies on 987 patients, it was reported that Act-D regimen had better efficacy than MTX [3].

Toxicity analysis showed that 5d im MTX caused more nausea and vomitus, and more frequent level 3/4 AEs were observed. Therefore, 5d-iv Act-D was the most effective strategy. Data have revealed that VP-16 single-drug regimen has good efficacy, it is not recommended as first-line treatment due to probability of new tumor formation [4]. The complete remission rate due to 5-FU may be higher than 90%. Thus, it was the primary treatment strategy used in this research. However, in recent years, due to the relatively complicated management during chemotherapy, there are cases of patient death due to serious AEs, leading to limited clinical application of 5-FU.

In this study, the effective cure rate of 5-FU for patients with low-risk, high scoring (≥4 points) tumors was 58.8 %, but it has been reported that the number of courses and the total treatment time of subjects given Act-D were statistically less than in patients on 5-FU. In addition, Osborne *et al* [5] found that FIGO scores of 5 – 6 resulted in 42 % response rate of the Act-D single-dose regimen, while that of the MTX weekly regimen was only 9 %. In conclusion, MTX, Act-D or 5-FU may be selected as a first-line drug in accordance with the current evidence and the principle of clinical individualization, but Act-D is the first choice. For patients with FIGO score > 4, combination chemotherapy is more suitable initially.

In recent years, with the development of effective chemotherapy, the therapeutic effect of GTN has been significantly enhanced, with cure rate of LRGTN patients close to 100 %. However, 20 - 30% of LRGTN patients develop drug resistance after initial single-agent chemotherapy. Thus, they must receive second-line or even third-line salvage chemotherapy and/or surgery. This increases the risk of drug resistance and exposure to more drug toxicity.

Although there is no recognized first-line chemotherapy for LRGTN, its survival rate is close to 100 %. Thus, surgical treatment is not recommended. The purpose of surgery is as follows: to control life-threatening emergencies such as acute tumor rupture and bleeding; to shorten the treatment time and reduce the chemotherapy course for patients whose tumor focus disappears slowly or those who have no fertility requirements; to reduce the tumor load and recurrence risk after the removal of drug-resistant focus, and to improve the prognosis of patients. In a systematic review of six documents from different countries published by BMC, the conclusion clearly showed that total hysterectomy is a better treatment for hydatidiform mole patients aged 40 years or more [6]. Although the treatment of GTN is primarily based on chemotherapy, proper understanding of the indications for surgery and how to choose the appropriate time for surgery are essential [8]. Multi-drug chemotherapy in combination with surgery for patients who develop relapse improves the cure rate and reduces recurrence rate [9].

In this study, 38 patients (18.63 %) underwent surgery; 8 patients were treated with local focus resection after chemotherapy due to slow reduction of the tumor focus after treatment, so as to reduce the tumor load, without recurrence. In 15 patients diagnosed with GTN after surgery due to vaginal bleeding, abdominal pain, or other causes, and 13 patients with no fertility requirements after prior chemotherapy, the treatment without fertility-spairing required surgery was short, and the difference was statistically significant. A study has shown that 32 out of 42 subjects with drug resistance disease who were treated with surgery from 1996 to 2006 achieved complete remission. The risk factors for poor prognosis were preoperative reproductive tract and extrapulmonary metastasis, and perioperative serum β- hCG >10 IU/L [10]. Therefore, in patients with low-risk and non-metastatic disease and no fertility requirements, total hysterectomy produces a higher success rate. In addition, in cases of treatment failure, the presence of drug-resistant isolated lesions and timely surgery may shorten the course of disease and result in cure. Comprehensive literature and clinical experience recommend the following indications for total hysterectomy: (a) patient age ≥ 45 years, (b) life-threatening massive hemorrhage or uterine rupture, and (c) chemotherapy resistance in patients.

Gestational trophoblastic neoplasia (GTN) resistance is generally considered to be present when blood levels of β-HCG increase during chemotherapy; drug resistance is implicated, regardless of the presence or absence of new metastases. In a 15-year retrospective analysis of the medical records of patients with LRGTN in our hospital, the overall remission rate was approximately 100 %, which is similar to results of Kanno [11].

In this study, 132 patients were treated with 5-FU as the initial treatment program, while the 83 patients with drug-sensitive disease were treated with single-agent 5-FU for the entire

course, out of which 82 patients developed complete remission (98.8 %). It can be seen that for the patients sensitive to 5-FU, single drug treatment produced good prognosis, although drug resistance during treatment cannot be ignored. Drug resistance refers to the insensitivity of cancer cells to chemotherapy.

Studies elsewhere generally reported that factors associated with LRGTN resistance to a single drug are high prognosis score (5 - 6 points) and high hCG level (>$10^5$U/L). Similar conclusions were not reached in this study since there were few of such patients. Since greater than 85 % of 5-FU is metabolized by dihydropyrimidine dehydrogenase (DPD), the occurrence of toxic side effects may be related to the lack of DPD enzymes. Thus, if this can be detected before treatment, individualized application would be beneficial for providing more precise and patient-specific treatment. 5-Fluorouracil (5-FU)-based chemotherapy plays an important role in the treatment of gastrointestinal cancer, and research on 5-FU resistance is primarily related to the treatment of intestinal cancer. It has been pointed out that more than 1/2 of the patients have drug resistance, with most cases representing acquired drug resistance due to decreased sensitivity after continuous use of 5-FU chemotherapy [12].

The mechanism of 5-FU resistance is complex, and there are limited studies on drug resistance in GTN. The most important factor in the failure of single-agent (5-FU) chemotherapy in this study was drug resistance. The drug resistance rate was 27.27 % (36/132), which may represent acquired drug resistance (58.33 %, 21/36) after three courses of treatment. All patients who were sensitive to the 5-FU regimen had good prognosis, with the exception of some patients who developed severe AEs. Thus, if a 5-FU-sensitive/resistant gene is detected before treatment, or if the DPD activity is increased, the clinical utilization rate of the drug will be greatly improved. Compared with 5-FU, FUDR has higher drug activity and lower side effects. It can be considered a replacement for 5-FU in clinical practice.

For drug-resistant patients, it is very important to choose the right timing of surgery, and to understand the indications for surgery, in order to improve patient prognosis. It is generally accepted that surgical indications for patients with drug-resistant GTN are as follows: good condition of the patient and ability to tolerate surgery, isolated metastasis, resectable lesions, absence of active metastases beyond the surgical resection site, and preoperative blood β-hCG level as close to normal level as possible [13,14].

The patients in the low-risk gestational trophoblastic tumor PFS group initially chose treatment with chemotherapy, based on clinical diagnosis, clinical stages, nature of the last pregnancy, and prognosis scores. It seems that the single drug treatment protocol initially produced better PFS. This result may also be related to the unclear stratification of patients with choriocarcinoma and non-hypercarcinoma mole in the last pregnancy.

## CONCLUSION

Single-agent 5-FU is effective in the treatment of LR-GTN. The failed treatments were related to drug resistance, high prognosis scores and serious side effects. The combination of multiple treatments is an effective means of treating LR-GTN for patients who have no metastasis and no fertility requirements. For those who have no metastasis and no fertility desires, surgery after chemotherapy may significantly shorten the treatment cycle without increasing surgical complications. However, it should be emphasized that stratified and individualized treatment of LR-GTN is necessary.

## DECLARATIONS

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***Ethical approval***

The study was approved by the Ethics Committee of Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute (approval no. 20201101-2)..

***Availability of data and materials***

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

***Conflict of Interest***

No conflict of interest associated with this work.

### *Contribution of Authors*

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Dan Chen and Xin Zhang conceived and designed the study; and drafted the manuscript. Dan Chen, Yanfeng Yang, Yitong Li and Yining Zhao collected, analyzed and interpreted the experimental data. Dan Chen and Yanfeng Yang revised the manuscript for important intellectual contents. All authors read and approved the final manuscript.

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