Original Research

Second Curettage for Low-Risk Nonmetastatic Gestational Trophoblastic Neoplasia

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OBJECTIVE: To evaluate the efficacy and safety of second uterine curettage in lieu of chemotherapy for patients with low-risk, nonmetastatic gestational trophoblastic neoplasia (GTN) and to evaluate whether response to second curettage is independent of patient age, World Health Organization (WHO) risk score, registration human chorionic gonadotropin (hCG) level, lesion size, and depth of myometrial invasion measured on ultrasound examination.

METHODS: This was a cooperative group multicenter prospective phase II study. Prestudy testing included quantitative hCG level, pelvic ultrasonography, and chest radiography. Patients were categorized according to WHO risk scoring criteria (low risk with a score of 0–6).

RESULTS: Sixty-four women with newly diagnosed low-risk, nonmetastatic GTN were enrolled. Four patients were excluded. Twenty-four patients (40%) (lower 95% confidence limit 27.6%) were cured after second curettage. An additional two patients (3%) achieved a complete response but did not complete follow-up. Overall, 26 of 60 patients were able to avoid chemotherapy. Surgical failure was observed in 34 women (59%) and was more common in women 19 years old or younger or 40 years old or older. One case of grade 1 uterine perforation was successfully managed by observation. Four grade 1 and one grade 3 uterine hemorrhages were reported. New metastatic disease (lung) was identified in one of these women after second curettage. In three patients (surgical failures), the second curettage pathology was placental site trophoblastic tumor, and it was placental nodule in one additional patient.

CONCLUSION: Second uterine curettage as initial treatment for low-risk, nonmetastatic GTN cures 40% of patients without significant morbidity.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, https://clinicaltrials.gov/, NCT00521118.

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Low-risk gestational trophoblastic neoplasia (GTN) is a highly curable disease that typically requires five to seven cycles of single-agent chemotherapy with either methotrexate or actinomycin-D to achieve a cure. If second curettage can safely cure GTN and avoid chemotherapy for a significant number of women, it is an important advance in the care of these patients. Historically, gynecologists in a few trophoblastic treatment centers have routinely performed a second uterine curettage for patients with persistent GTN. Other expert centers have maintained that the risk of second curettage exceeds the benefit and thus limited this procedure to patients with heavy bleeding. Regardless of the indication, single-institution retrospective reports show inconsistent outcomes with success ranging from 9% to 60% and uterine perforation occurring as often as 8% of these procedures.[1–11]

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Given these widely disparate outcomes ranging from not effective to highly effective, a multicenter cooperative group trial was indicated. To address this important question, the Gynecologic Oncology Group (GOG) initiated this prospective two-stage, single-arm phase II study of second curettage, in October 2007, as first-line treatment for nonmetastatic, low-risk persistent trophoblastic disease[12] (Fig. 1). The intent of this study was to better define the efficacy and safety of second curettage in patients with persistent, nonmetastatic low-risk GTN.

MATERIALS AND METHODS

Study eligibility required potential participants to have either a complete or partial mole at their first curettage, clinical staging (pelvic ultrasonography, chest radiography, and quantitative human chorionic gonadotropin [hCG] assay), and a World Health Organization (WHO) risk score of 0–6 to enroll in the study (Tables 1 and 5). Note that because patients with GTN patients are rescored at each recurrence, a patient failing first-line therapy could remain low risk (WHO score 0–6), but these patients were not eligible for this study. Patients with a positive or a suspicious chest radiograph were not eligible. Diagnostic slides and pathology reports from the first curettage were reviewed centrally after enrollment. Patients with a first curettage diagnosis of choriocarcinoma, placental-site trophoblastic tumor, or epithelioid trophoblastic tumor were not eligible. Patients with an initial registration hCG level less than 20 milli-international units/mL were also not eligible to minimize inclusion of patients with false-positive hCG tests from circulating heterophilic antibody.[13] Prior chemotherapy was an exclusion criterion.

Before registration, all patients underwent a pelvic ultrasound examination measuring the volume of intrauterine disease in three dimensions. Lesion size was determined to be the largest of these dimensions. The maximal depth of myometrial invasion was measured in one dimension. All patients also underwent either a staging chest radiograph or, less frequently, a computed tomography scan of the chest. If the computed tomography scan of the chest was negative, it was inferred that a chest radiograph, the test of choice, would also have been negative. A quantitative hCG assay was obtained on all patients before registration. The particular assay used was not specified in the study protocol.[13,14] Patient demographics were obtained at registration and included patient age, race and ethnicity, and type of molar pregnancy. Informed consent was obtained from interested, study-eligible patients who then underwent a second uterine curettage at a GOG member institution within 14 days of registration. Local institutional review board approval of the study was obtained for all participating sites. Surgical cure was defined as achievement of a normal hCG level followed by a minimum of 6 months of continued normal hCG testing.[14] Surgical response was defined as achievement of a normal hCG level but less than 6 months of completed normal testing. Surgical failure was deemed to be a rise or plateau in the hCG level as defined by the International Federation of Gynecology and Obstetrics (2000) definition of persistent GTN or the presence of malignant trophoblast such as placental site trophoblastic tumor in the second curettings.[15] Adverse events were defined and graded using Common Terminology Criteria for Adverse Events 3.0. The pathology from both the initial and second curettages was centrally reviewed post hoc by two pathologists.

The method of evacuation was not specified but could include intraoperative ultrasound localization of residual trophoblast or directed hysteroscopic resection; patients could have had either or both procedures as well as no imaging.[5,14] Patients were then followed postoperatively with weekly quantitative hCG levels beginning 14 days after the procedure. If the hCG reached the institutional normal, the hCG level was to be obtained monthly for 6 additional months. In patients whose hCG level rose or plateaued based on the International Federation of Gynecology and Obstetrics 2000 criteria, second curettage was deemed to have failed (surgical failure) and disease was to be restaged and a new risk score determined.[15,16] Patients were to be followed for a minimum of 24 months or until cure with chemotherapy if surgical management failed.[17–19]

In the study design, a rate of surgical cure of 25% or higher was considered clinically significant and a rate of 10% or less was evidence of insufficient activity.

An optimal but flexible two-stage design with early stopping guidelines intended to limit accrual of patients to an inactive treatment was used.[20] Surgical

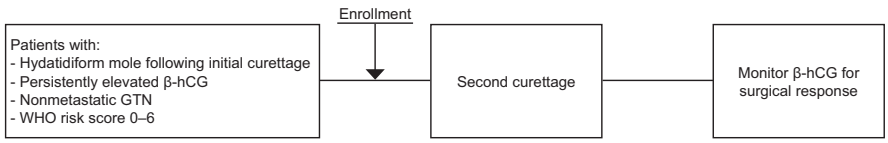

Fig. 1. The study schema (Gynecologic Oncology Group study no. 242). GTN, gestational trophoblastic neoplasia; WHO, World Health Organization.

Osborne. Second Curettage as Management of GTN. Obstet Gynecol 2016.

Table 1. Patient and Disease Characteristics

Characteristic	n (%)
Age group (y)	
10–19	4 (6.7)
20–29	21 (35.0)
30–39	29 (48.3)
40–49	4 (6.7)
50–59	2 (3.3)
Ethnicity	
Hispanic or Latina	17 (28.3)
Non-Hispanic	37 (61.7)
Not reported	6 (10.0)
Race	
Not reported	6 (10.0)
Asian	7 (11.7)
Black or African American	8 (13.3)
Native American or Alaskan Native	1 (1.7)
Native Hawaiian or Pacific Islander	1 (1.7)
White	37 (61.7)
Molar class	
Complete	54 (90.0)
Partial	6 (10.0)
WHO score	
0	12 (20.0)
1	12 (20.0)
2	16 (26.7)
3	9 (15.0)
4	6 (10.0)
5	2 (3.3)
6	3 (5.0)
Registration hCG (milli-international units/mL)	
20.1–100.0	1 (1.7)
100.1–1,500.0	19 (31.7)
1,500.1–5,000.0	10 (16.7)
5,000.1–10,000.0	7 (11.7)
10,000.1–100,000.0	20 (33.3)
100,000.1–1,000,000.0	3 (5.0)

WHO, World Health Organization; hCG, human chorionic gonadotropin.

cure reported in greater than 9 of 60 eligible patients would be interpreted as a positive study. The intention of the design was to limit type II error to 10% and type I error to 0.05. Exact confidence intervals for proportion cured accounting for interim analyses were constructed.[21,22]

The primary objective was to evaluate the efficacy and safety of second curettage in this patient population. Secondary objectives included the frequency and severity of adverse events and exploratory assessment of prognostic factors. The maximum grade of acute adverse events within a category, regardless of attribution, was tabulated for eligible patients who underwent a second curettage. The quantitative hCG level measured at registration and just before second evacuation (both as continuous variables and as discrete variables using cutoffs of 1,500 or 5,000 milli-international units/mL), the presence or absence of myometrial invasion, WHO risk score, age, and race were assessed for their relationship with response to second evacuation using standard tests for categorical variables or logistic regression and estimation of the concordance proportion.[23]

RESULTS

From October 2007 to February 2013, 64 women were registered in the study and underwent second curettage; four were subsequently deemed ineligible after central review. Three women were excluded for an initial WHO risk score of 7 (high risk) and one with an uncertain histologic diagnosis. Therefore, data from 60 women were included in this analysis.

Demographic information was collected on all patients with a representative sampling of ethnic groups and reproductive ages (Table 1). Fifty-four patients (90%) had a pretreatment diagnosis of complete mole and six (10%) with a partial mole based on central pathology review. There was one patient (2%) registered with an hCG level less than 100 milli-international units/mL and three women (5%) with an hCG level at registration greater than 100,000 milli-international units/mL. Twelve patients (20%) had a WHO risk score of zero but two had a score of 5 (3%) and three (5%) had a score of 6. The median follow-up was 24 months.

Twenty-four out of 60 women were successfully treated with second curettage and did not require chemotherapy, for a surgical cure rate of 40%. Two patients (3%) did not complete follow-up (considered a surgical response) but both had achieved a normal hCG level before being lost to follow-up; overall 28 of 60 patients were able to avoid chemotherapy. The 95% lower confidence limit for the surgical cure was 27.6%. This value is above 10% and excludes 25%, the minimal clinical effect defined in the study. Twenty-nine women (48%) developed persistent GTN as demonstrated by a rise or plateau in the hCG level or new metastatic disease (one developed pulmonary disease and endometrial stromal sarcoma) (Table 2).

When patient age at study entry was considered with respect to the extremes of reproductive age, a known risk factor for GTN, disease was cured in only one of four women younger than 19 years of age and one of six women aged 40 years of age or older. In contrast, 22 of 50 (44%) women between 20 and 39 years of age were cured by second curettage alone with 49% (24/50) treatment success when surgical responses and cures were combined (Table 3).

When the WHO risk score was 4 or less, cure was observed in 24 of 55 patients (43.6%); and when the risk score was 5 or 6, no patients were cured (0/5)

Table 2. Disease and Treatment Outcomes

Endpoint	n (%)
Reason off therapy	
Completed regimen	24 (40.0)
Disease progression	29 (48.3)
Patient refused or other	7 (11.7)
Surgical response	
Surgical cure	24 (40.0)
Surgical response	2 (3.3)
Surgical failure	29 (48.3)
Indeterminate	5 (8.3)
Disease status	
No new disease	59 (98.3)
New metastatic disease	1 (1.7)
Survival status	
Alive	60 (100.0)

Surgical cure was defined as achievement of a normal human chorionic gonadotropin (hCG) level followed by a minimum of 6 months of continued normal hCG testing results.[14] Surgical response was defined as achievement of a normal hCG level but less than 6 months of completed normal testing results. Surgical failure was deemed to be a rise or plateau in the hCG level as defined by the International Federation of Gynecology and Obstetrics (2000) definition of persistent gestational trophoblastic neoplasia or the presence of malignant trophoblast such as placental site trophoblastic tumor in the second curetting.[15]

(Table 3). When the outcomes and ultrasound findings were compared, if no evidence of residual uterine disease was observed, 7 of 17 (41%) patients had a surgical cure and, if disease was seen but no myometrial invasion was reported, the response was classified as surgical cure in 9 of 22 (41%). For patients with myometrial invasion, including the two patients who had a surgical response, the combined response was seen in 10 of 21 (48%) (Table 3).

Uterine tumor size was recorded for all but one patient (2%). Thirty-five women (59%) had a residual intrauterine tumor large enough to be seen on pelvic ultrasonography (greater than 6 mm). The volume of disease in three dimensions was obtained for all 35 women for whom residual uterine disease was observed. Myometrial invasion was not universally reported; for 38 patients (64%), specific reference to myometrial depth was absent but in almost all cases could be inferred from the radiologist's narrative. These ultrasound findings were not statistically or clinically significant.

When the registration hCG level was between 100 and 1,500 milli-international units/mL, surgical cure was reported in 53% (10/19); between 1,500 and 5,000 milli-international units/mL, surgical cure was observed in 40% (4/10); between 5,000 and 10,000 milli-international units/mL surgical cure was observed in 29% (2/7); between 10,000 and 100,000 milli-international units/mL surgical cure was observed in 40% (8/20); above 100,000 milli-international units/mL, no cures (0/3) were observed. There was one additional surgical response between 1,500 and 5,000 milli-international units/mL and one more response at a level greater than 100,000 milli-international units/mL, but these patients could not be included as surgical cures because they did not complete the 6-month follow-up (Table 3).

Several hCG cutoff levels reported in the literature were examined using the study data set. Below 700 milli-international units/mL, 43% (6/14) were cured and above 700 milli-international units/mL, 43.9% (20/46) were cured.[6] When a 1,500- milli-international units/mL cutoff was used, below that level, 50% (10/20) were cured and above 1,500 milli-international units/mL, 40% (16/40) were cured.[5] When the level from the Charing Cross report was examined, below 5,000 milli-international units/mL, 50% (15/30) were cured, whereas, above that level, 37% (11/30) were cured.[24] None of these factors were found to be statistically significantly associated with outcome (Table 3).

The degree to which hCG level might predict response to second curettage was examined using a receiver operator characteristic plot.[23] When the data from the current study were examined using the registration log-transformed hCG level, the area under the curve was 0.59 suggesting that the hCG level at registration alone was a poor discriminator of surgical cure. A logistic model with age and squared age terms was fit to predict cure. The area under the curve for this model was 0.77 suggesting that a moderate association exists between these two parameters.

Three patients (3/60) were found to have placental site trophoblastic tumor at the second curettage and were automatically classified as surgical failures. However, the hCG level normalized in one of these patients without further treatment. One patient underwent hysterectomy and the other was treated successfully with methotrexate and subsequently had a successful pregnancy.

Data on toxicity were collected prospectively. There was infrequent and generally low-grade toxicity reported including one patient with grade 3 uterine hemorrhages (defined as requiring transfusion) and one patient with grade 3 neutropenia. One uterine perforation was reported that was successfully managed by observation (Table 4).

In total, 29 of the original cohort of 64 women (45%) derived clinical benefit from the second curettage: 24 surgical cures, two surgical responses, and three instances of a pathology change to placental site

Table 3. Prognostic Features and Response Category

Characteristic	Surgical Cure		All Patients	χ^{2*} *P*
	Yes	No		
All patients	24 (40.0)	36 (60.0)	60	
Patient group				.98
Mass noted, no myometrial invasion noted	9 (40.9)	13 (59.1)	22 (36.7)	
Mass with myometrial invasion	8 (38.1)	13 (61.9)	21 (35.0)	
No mass noted	7 (41.2)	10 (58.8)	17 (28.3)	
WHO score category				.06
WHO score 4 or less	24 (43.6)	31 (56.4)	55 (91.7)	
WHO score greater than 4	0	5 (100)	5 (8.3)	
Registration β-hCG (milli-international units/mL)				.51
20.1–100.0	0	1 (100)	1 (1.7)	
100.1–1,500.0	10 (52.6)	9 (47.4)	19 (31.7)	
1,500.1–5,000.0	4 (40.0)	6 (60.0)	10 (16.7)	
5,000.1–10,000.0	2 (28.6)	5 (71.4)	7 (11.7)	
10,000.1–100,000.0	8 (40.0)	12 (60.0)	20 (33.3)	
100,000.1–1,000,000.0	0	3 (100)	3 (5.0)	
Registration hCG (milli-international units/mL) at least 700				.80
hCG less than 700	6 (42.9)	8 (57.1)	14 (23.3)	
hCG 700 or greater	18 (39.1)	28 (60.9)	46 (76.7)	
Registration hCG (milli-international units/mL) at least 1,500				.20
hCG less than 1,500	10 (50.0)	10 (50.0)	20 (33.3)	
hCG 1,500 or greater	14 (35.0)	26 (65.0)	40 (66.7)	
Registration hCG (milli-international units/mL) at least 5,000				.29
hCG less than 5,000	14 (46.7)	16 (53.3)	30 (50.0)	
hCG 5,000 or greater	10 (33.3)	20 (66.7)	30 (50.0)	
Age group (y)				.07
10–19	1 (25.0)	3 (75.0)	4 (6.7)	
20–29	5 (23.8)	16 (76.2)	21 (35.0)	
30–39	17 (58.6)	12 (41.4)	29 (48.3)	
40–49	1 (25.0)	3 (75.0)	4 (6.7)	
50–59	0	2 (100)	2 (3.3)	

WHO, World Health Organization; hCG, human chorionic gonadotropion.
Data are n (%) unless otherwise specified.
* For tests of no difference in proportion with surgical cure outcome.

trophoblastic tumor that was identified by second curettage earlier than likely would have been the case otherwise.

DISCUSSION

This study demonstrates significant utility of second curettage as first-line treatment for persistent trophoblastic neoplasia. As a multicenter, prospective clinical trial, it greatly strengthens the evidence that women with postmolar GTN can be treated safely and effectively with uterine curettage allowing 28 of 60 patients (47%) of trial participants to avoid chemotherapy. Three prior reports had suggested that between 9% and 60% of patients who undergo second curettage for persistent GTN might be saved the need for chemotherapy.[5,6,8,24] This GOG clinical trial represents the only prospective cooperative group study of this important issue.

Limitations of this GOG study are primarily based on the patient numbers and the lack of standardization that arises in multiinstitution trials. With only 60 evaluable patients, this study has limited statistical power to discern the effect of well-recognized prognostic factors such as age and hCG level on treatment effect. Furthermore, the lack of standardization across institutions for the technique for second uterine curettage, with or without ultrasound guidance, prevents comment on the ideal curettage technique.

In trophoblastic disease treatment centers around the world, second uterine curettage is viewed with mixed opinion. It has mostly been used to "debulk" residual intrauterine disease or to control excessive vaginal bleeding in patients with newly diagnosed disease. The theoretical risk of uterine hemorrhage, upper genital tract infection, or uterine perforation is often cited as a reason to avoid curettage; despite that,

Table 4. Grade of Adverse Event Using Common Terminology Criteria for Adverse Events 3.0

Adverse Event Term	No. of Patients With Maximum Adverse Event Grade			
	0	1	2	3
Fatigue	57	2	1	0
Hair loss or alopecia (scalp or body)	59	1	0	0
Nausea	58	2	0	0
Diarrhea	59	1	0	0
Perforation, uterus	59	1	0	0
Hemorrhage				
Uterus	59	0	0	1
Vagina	56	4	0	0
Leukocytes	59	1	0	0
Hemoglobin	50	6	4	0
Platelets	58	2	0	0
Neutrophils	59	0	0	1
Hypokalemia	59	1	0	0
Hyperglycemia	59	1	0	0
Hypocalcemia	58	2	0	0
Pain				
Abdominal pain not otherwise specified	55	4	1	0
Head or headache	58	1	1	0
Chest wall	59	1	0	0
Breast	59	1	0	0
Maximum grade overall	43	9	6	2

there were no surgical complications that required hysterectomy reported in the Sheffield and Netherland studies. In these previous studies, uterine perforation and grade 3 uterine hemorrhage were reported infrequently and were managed nonsurgically.[5,6] Delaying chemotherapy could theoretically lead to disease progression requiring multiagent chemotherapy; this did not occur in this trial.

The present study demonstrated that the success of second curettage could not be predicted with statistical significance on the basis of patient age, the WHO risk score, registration hCG level, or the ultrasound findings (the size or volume of intrauterine disease and the depth of myometrial invasion). The extremes of patient age may have value in predicting failure although the numbers are too small to be conclusive. Only one of four patients aged 19 years and younger was cured or responded and one of six patients aged 40 years or older was cured or responded. A model with age and squared age predicted cure with a receiver operator characteristic area under the curve of 0.77 suggested a moderate association.

When the WHO risk score was 0–4, 24 of 55 patients (44%) were cured and there was one additional

Table 5. World Health Organization Gestational Trophoblastic Neoplasia Prognostic Scoring System[15]

Scores	0	1	2	4
Age	<40	≥40	—	—
Antecedent pregnancy	Mole	Abortion	Term	—
Interval months from index pregnancy	<4	4–6	7–12	>12
Pretreatment serum β-hCG (iu/l)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Largest tumor size (including uterus)	<3	3–4 cm	≥5 cm	—
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastases	—	1–4	5–8	>8
Previous failed chemotherapy	—	—	Single drug	≥2 drugs

hCG, human chorionic gonadotropin.
Low-risk: individuals with a score 6 or less; high-risk: individuals with a score 7 or greater.
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surgical response. Of the five patients with a score of 5 or 6, none were cured but one additional patient did have a surgical response; this trend was not statistically significant in exploratory analysis (P=.06). These findings suggest that second curettage is unlikely to benefit patients with a risk score of 5 or 6 (Table 3). No clinically significant complications related to the repeat curettage were observed. The likelihood of uterine perforation was very low and was managed conservatively. The prior reports from Sheffield and the Netherlands both reported an incidence of uterine perforation less than 2% although most of the second curettages in these reports were performed in a wide range of settings ranging from referral centers to community hospitals.[14,15]

Pelvic inflammatory disease was not observed in the current study and was not reported in the earlier reports. Hemorrhage after curettage was not clinically significant in any of the reports, including the present study. As a result, second curettage for GTN should be considered a low-risk intervention, although longitudinal data on the incidence of uterine synechiae and infertility do not exist. Although outcomes in this trial indicate second curettage is a low-risk procedure, they reflect the results when performed by a physician expert in the care of GTN.

Based on central pathology review, in the present study, three patients were found to have placental-site trophoblastic tumor in the second curettage material confirming the Sheffield group's observation (histoconversion to choriocarcinoma in 5/544 women). The findings of central pathology review suggest that pathology expertise in interpretation of trophoblastic neoplasia is critical in this patient population. One additional patient had a placental nodule, a benign variant of epithelioid trophoblastic tumor, at second curettage. Because these pathology changes were not identified until the post hoc central pathology review, the three women with placental site trophoblastic tumor were treated for presumed GTN. All were cured; one was cured by the repeat curettage alone, one underwent second curettage followed by methotrexate and was cured, and a third underwent hysterectomy and was cured.

Second curettage is a simple alternative to immediate chemotherapy for patients with newly diagnosed, nonmetastatic, low-risk GTN regardless of hCG level and the amount of intrauterine disease.[25] Immediate chemotherapy may be preferred for patients with a WHO risk score of 5 or 6 and for patients at the extremes of reproductive life, specifically, 19 years of age or younger and older than 39 years of age. In this study, 47% of patients derived potential benefit from immediate second curettage and were saved the need for chemotherapy.

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