

Original Article

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Running Title: The Role of Surgery in Management of Gestational Trophoblastic Neoplasia

Is There a Role for Surgery in the Management of Gestational Trophoblastic Neoplasia?

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Abstract

Background: Gestational trophoblastic diseases are treated with chemotherapy, but some patients are resistant to it and require surgeries. The role of surgery in the management of these patients is not clearly defined. This study aimed to evaluate the role of surgery in the management of patients with gestational trophoblastic tumor (GTN).

Method: This cohort study was performed on patients with GTN referred during June 2009 to June 2019. The patients receiving hysterectomy, hysterotomy to remove uterine lesion, pulmonary lobectomy, craniotomy, and other surgical procedures were included in the study. The surgery indications were resistant to chemotherapy or hemorrhage.

Results: The survival rate of the 31 patients that entered the study was 100%. The mean age of patients was 36 years. The frequency of surgeries were as follow: hysterectomy in 21 patients (67.7%), hysterotomy in six patients (19.4%), removal of lung lesion in three patients (9.7%), and craniotomy in one patient (3.2%). Among the patients, 22 showed complete response to treatment and nine patients had relative response. The relation between response to surgery with variables, such as the type of previous pregnancy, disease pathology, the scoring of disease in World Health Organization (WHO) system, the severity of disease based on The International Federation of Gynecology and Obstetrics (FIGO) stage, and the need to chemotherapy sessions, were significant.

Conclusion: Surgery played an important role in management of patients with GTD. Previous non-molar pregnancy, stage, and WHO score based on clinical factors affected the response rate of treatment.

Keywords: Gestational trophoblastic disease, Choriocarcinoma, Invasive surgery, Trophoblastic neoplasms, Surgery

Introduction

Gestational trophoblastic neoplasia (GTN) is a rare spectrum of disorders involving human placenta. From histology perspective, it consists of a group of diseases, namely molar pregnancy (complete or partial), invasive mole, and choriocarcinoma. This group of diseases is a rare type of genital malignancies which contains less than 1% of women malignancies and has the ability of local invasion and far metastasis. It is also curable with chemotherapy even in metastatic cases.¹

Thoracotomy may play a role in the management of high-risk patients. In the case of consistent pulmonary metastasis despite chemotherapy, thoracotomy may be applied to remove the resistant lesion. However, a complete evaluation regarding metastasis in other places has to be performed before thoracotomy. Surgery may be beneficial in 2/3 of the patients with high-risk GTN. Resection of drug-resistant pulmonary metastases may be effective in selected patients.^{2,3}

In addition to the use of hysterectomy in chemotherapy-resistant patients, it is employed to control hemorrhage or infection. In cases with high tumor involvement of uterus, hysterectomy can reduce the size of trophoblastic tumor considerably and the required chemotherapy sessions.⁴⁻⁶ While trophoblastic neoplasia is a chemosensitive tumor, surgical hysterectomy, which is potentially curative in the management of metastatic gestational trophoblastic tumor (GTN), has failed to multiple chemotherapy regimen due to chemoresistant foci.⁷

In the patients, specifically in women over 40 years of age with no desire to preserve fertility and localized disease, primary hysterectomy should be taken into consideration.⁸ In chemotherapy-resistant GTN, additional hysterectomy may be beneficial, particularly once the disease is localized. For patients with widespread

metastatic GTN, the removal of chemotherapy-resistant tumor bulk of uterus via hysterectomy may have subsequent effects on survival.⁸

Craniotomy is carried out in the cases of brain metastasis with complications (increased intracranial pressure). Emergent craniotomy for tumor resection and hematoma removal was reported for acute intracerebral hemorrhage.³

The low and high incidence of GTN respectively in western countries and Southeast Asian countries, its relative frequency in Iran and the lack of information regarding their treatment reveals the necessities of conducting a research in this regard. The current work investigated the role of surgery in the management of gestational trophoblastic neoplasia.

Materials and Methods

In this cohort study, the medical records of 380 patients with GTN who had referred to gynecologic clinic or oncology department of Gheam hospital and chemotherapy department of Omid hospital from June 2009 to June 2019 were reviewed. Informed consents from the patients were obtained.

This proposal was approved by the Ethic Committee of Mashhad University of Medical Sciences with the ethics code of IR.MUMS.REC.1389.72. Moreover, 31 patients who underwent different kinds of surgery comprising hysterectomy, hysterotomy, pulmonary lobectomy, craniotomy, or other surgical procedures for GTN management, entered the study. Serial Beta Human chorionic gonadotropin (B-HCG) measurements were performed weekly following the surgery and the patients were divided into three groups based on therapeutic response:

- Complete response: when B-HCG level decreased to normal during the six weeks after surgery

- Relative response: lack of normal B-HCG level, but 50% or more reduction in its level
- Constant disease: no change in B-HCG level
- Progressive disease: increased B-HCG level despite combined chemotherapy after surgery

Relative response, constant disease, and progressive disease were considered to be treatment failure. The prognostic factors were identified for all the patients with treatment failures and also cases with successful treatment.

The results were expressed as mean \pm standard deviation and percent. The comparison was carried out with Independent T-Test and finally the chi-squared test was employed to compare qualitative parameters. All the analyses were performed with SPSS version 11.5.0 software. Differences were considered to be statistically significant when *P*-values were <0.05 .

Results

This was a descriptive study examining the clinical and laboratory characteristics of the patients with GTN undergoing surgery during the treatment process. Thirty-one patients entered the study. The survival rate of the patients after 12 months was 100%. 22 (71%) patients had complete response to the treatment and nine patients (29%) had relative response. Several characteristics of the studied patients are presented in tables 1, 2.

Among the 21 patients (67.7%) receiving hysterectomy due to the resistance to chemotherapy, 16 patients (72.7%) had complete response and five patients (55.6%) had relative response to the treatment. Subsequently, nine patients did not require postoperative chemotherapy while in others, chemotherapy continued after surgery and

all the patients finally had complete improvement.

Among the six patients receiving hysterotomy, three patients received it because of the resistance to chemotherapy, one patient due to severe vaginal hemorrhage, and two patients due to shock and bleeding following uterine rupture. In the three patients, chemotherapy continued after surgery and all the patients were cured. Three patients in our work underwent thoracotomy to remove pulmonary lesion. These patients were referred with the primary complaint of AUB and were treated through combined chemotherapy with choriocarcinoma diagnosis. The patients with resistance to chemotherapy and with pulmonary symptoms, such as dyspnea, and one case of hemoptysis were chosen for surgery. After the surgery with continued chemotherapy, the patients demonstrated the favorite response and HCG level decreased to normal. Afterwards, two patients had all of above criteria, but one patient had HCG ≥ 1000 and tumor had involved all of left hemi-thorax, for whom total left pneumonectomy was performed. In all the three patients, combined chemotherapy was continued and all the patients responded to the therapy.

Herein, one patient had high-risk GTN, in which the imaging studies showed the signs of metastasis to brain and lung. The patient received combined chemotherapy; however, due to the resistance and signs of increased intracranial pressure, the patient underwent brain metastasectomy. Pulmonary lesion was improved with further chemotherapy and the patient had overall improvement.

Based on the above tables, the relation between response to surgery (in both complete and relative response group) with variables, including the type of previous pregnancy, disease pathology, the scoring of disease in World Health Organization (WHO) system, the severity of disease based

on The International Federation of Gynecology and Obstetrics (FIGO) stage, and the need for chemotherapy sessions, were of significance. On the contrary, the association between the response to surgery with the type of surgery, reason for surgery, and HCG level prior to surgery was not significant.

Discussion

In the current research, 31 patients with GTN receiving hysterectomy, hysterotomy to remove uterine lesion, pulmonary lobectomy, craniotomy, or other surgical procedures for GTN treatment were evaluated. Among the patients, 28 (90.3%) patients had surgery because of being resistant to chemotherapy and three patients (9.7%) received surgery for hemorrhage. It seems that it is time to revise the position and indications of surgery in GTN.

Today, surgery as an additional treatment to chemotherapy plays an important role in the treatment of GTN patients.^{9, 10} In NCCN guideline 2019, the role of surgery in management GTN is highlighted.

The role of surgery in the treatment of GTN is changing on account of the new chemotherapy protocols; however, it is still the main treatment in the patients with chemotherapy-resistance GTN. The general indications of surgery in trophoblastic diseases are: uterine evacuation, hysterectomy in the patients older than forty years with no desires to preserve fertility, in special cases of invasive mole, uterine rupture, severe intravaginal or intraperitoneal hemorrhage, and local removal of uterine lesion, and its rupture through the invasive mole in the patients with a desire for pregnancy. Adjuvant surgeries, particularly hysterectomy and thoracotomy in chemo-refractory patients^{2, 7, 11} in controlling hemorrhage, to resolve bowel or urinary tract obstruction, to control

infection, or to control life threatening complication, has an important application. HCG level as a valuable parameter for the follow-ups of the patients with GTN decreased significantly after surgery in the adjuvant with chemotherapy. Therefore, it seems that the results of surgery in the adjuvant with chemotherapy were better in comparison of patient receiving chemotherapy.^{10, 12}

In the present work, the mean age of patients was 36 years old. The recurrence of disease was not observed in the studied patients and survival was 100%. The response to the treatment based on post-surgery HCG level included 22 patients (71%) with complete response and nine patients (29%) with relative response.

Feng et al.¹³ conducted a study on 61 patients with chemotherapy-resistant GTN receiving surgery. The mean age of the patients was 29 years which was less than our patients. Feng et al. defined the response to therapy as follows; Complete response: having at least six weeks of the normal level of HCG after the surgery, Relative response: HCG level higher than normal after reducing more than 50% after surgery, Progressive disease: increased HCG level following the surgery and adjuvant chemotherapy, and Constant disease: constant level of HCG or a reduction of less than 50%.⁹ Herein, the time interval for the reduction of HCG was not defined. Based on the response definition in the study by Feng, 47 patients (77%) had complete response, four patients (6.6%) had relative response, and 10 patients had constant or progressive disease. In the present study, we did not observe constant or progressive diseases in our patients. In the current work, complete response was defined as reaching the normal level of HCG during the six weeks after the surgery and relative response was defined as a more than 50% reduction in HCG level during this period. Based on our definition of response,

22 patients (71%) had complete response and nine patients (29%) had relative response; however, considering the definition by Dr. Feng, the complete response in our patients was 100% since in all the patients the HCG level decreased to normal and remained at normal level eventually.

Ghaemmaghami et al. in a study reviewed 23 patients who received surgery due to the resistance to chemotherapy (43.5%) and hemorrhage (56.5%). One recurrence followed by death was reported.¹⁴

In regard to prognostic factors, our results implied that disease pathology, WHO score, FIGO stage, and the type of previous pregnancy were prognostic factors whereas in Feng's study age HCG level before surgery, type of previous pregnancy, and extra uterine metastasis except lung were prognostic factors. In the present study, the relation of response rate with age and HCG level was not significant but the relation with type of previous pregnancy, disease stage, and distant metastasis was of significance and similar to Feng's study.

Hysterectomy

Hysterectomy plays an imperative role in the management of the patients with high-risk GTN.¹⁰

The primary hysterectomy can be considered in the patients with small extrauterine tumoral lesions or in the patients with no desire to preserve fertility. The two more common causes of hysterectomy are the uterine lesions being resistant to chemotherapy and controlling severe uterus hemorrhage.^{7,8}

In a study by Pongsaranantakul¹⁵ it was stated that most of GTN patients are young and wish to preserve fertility. Hysterectomy is only applicable in chemotherapy-resistant cases especially when lesion is limited to uterine. Therein, 39% of hysterectomies were performed to this end.

Sometimes hysterectomy is very hard in GTN; the high volume of pelvic vasculature and vast necrosis on tumor surface can make it harder. Some of important complications of this operation are high blood loss, postoperative fever, and damage to the other organs.¹⁵ It is recommended that hysterectomy only be conducted in a gynecology oncology center by a skillful surgeon while blood products and proper postoperative care is available.¹⁵

In this work, most patients with hysterectomy had complete response and all the patients had complete improvement. There were not any complications.

Despite the fact that GTN treatment with chemotherapy is one of the most successful chemotherapy treatments, surgery is still important in the following conditions: reducing tumor size, controlling hemorrhage in tumor, removing increased intracranial pressure, and treating resistant or recurrent disease in uterine or metastasis locations.

In a study performed by Dr. Feng, 61 patients with chemotherapy-resistant GTN underwent surgery. The statistical evaluations demonstrated that the rate of response to surgery depended on the HCG level prior to surgery.¹³ In our study, we did not find significant relations between the primary level of HCG and HCG level before surgery with response rate to surgery.

Hysterotomy

Since GTN involves women during reproductive age group, the treatments with preserving fertility are very important. In a review study conducted by Feng and Xiang, the following criteria were defined as the proper indications for the local surgery of myometrial lesion in patients with chemotherapy-resistant GTN: 1- high tendency to preserve fertility, 2- the preoperative HCG level in minimum possible level, 3- local uterine lesion, 4- the lack of evidences for extra uterine metastasis

with imaging studies, 5- metastasis which was controlled with chemotherapy.⁹

In a case report, Jenny Lynn et al. reported two patients referred with hemorrhage and willing to preserve pregnancy. Their diagnosis was uterine rapture and they underwent surgery for removing the local lesion with preserving uterine and fertility, the results of which were satisfactory.¹⁶

Based on the fact that most women in a young age tend to preserve fertility, Hasanzadeh et al. reported four cases of successful treatment GTN via hysterotomy. The indication of surgery was drug toxicity and uterine perforation chemotherapy-resistant GTN.¹⁷

In the present research, hysterotomy was performed due to the resistance to chemotherapy and severe vaginal hemorrhage and uterine rapture. All the patients were cured.

Removal of lung metastases

Local removal of lung lesions through thoracoscopy or thoracotomy in the patients with chemotherapy-resistant GTN could improve the outcome.²

Three patients in this study underwent thoracotomy to remove pulmonary lesion. In all the three patients combined chemotherapy was continued and all the patients responded to therapy.

Craniotomy

Brain metastases of GTN tend to be hyper vascular and a risk of central necrosis and hemorrhage. Hence, the patients with brain metastases are at the risk of early intracranial hemorrhage. A combination of multi-agent chemotherapy and whole-brain radiation is the main therapy in brain metastasis.³

Craniotomy in the patients with high-risk GTN with signs of increased intracranial pressure may be applicable. It is also performed rarely for patients with brain metastatic lesions resistant to chemotherapy, though its application is more for the

increased intracranial pressure or intracranial hemorrhage.

Herein, the imaging studies revealed signs of metastasis to brain and lung in one patient with high-risk GTN. The patient underwent brain metastasectomy, resulting in an overall improvement.

Conclusion

The general indications of surgery in GTN are: uterine evacuation, hysterectomy in patients older than frothy years with no desire to preserve fertility, in special cases of invasive mole, uterine rapture, severe intra-vaginal or intra-peritoneal bleeding, local removal of uterine lesion, and its rapture through the invasive mole in patients with a desire for pregnancy. Adjuvant surgeries, particularly hysterectomy and thoracotomy in patients resistant to chemotherapy, in controlling hemorrhage, to resolve bowel or urinary tract obstruction, to control infection, or to control life threatening complication, have an important application. Surgery also plays a key role in patients with PSTT. HCG level as a valuable parameter for the follow-up of patients with GTN reduced significantly after surgery in adjuvant with chemotherapy. Therefore, it seems that the results of surgery in adjuvant with chemotherapy were better in patients receiving hysterectomy or other surgical procedures. It appears that it is the time to revise the position of surgery and its applications in GTN treatment.

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Conflict of Interest

None declared.

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Table 1. Demographic characteristic of the patients

Variable	Mean	Range	Standard deviation
Age (year)	36	15-53	10.55
Number of previous pregnancies	4.5	1-11	2.88
Number of previous deliveries	3.7	0-10	2.73
Time interval from last pregnancy (except 2 patients with 72 and 96 months interval) (month)	2.36	1-6	1.35
Number of chemotherapy sessions	5.3	2-13	3.27
Follow-up time after operation (month)	15.5	5-48	10.17

Table 2. Frequency distribution of clinical and laboratory characteristics of patients

Variable		Frequency (%) in all the patients	Frequency (%) in patients with complete response	Frequency (%) in patients with relative response	P-value
Type of pregnancy	Molar 1) Hydatidiform mole	28 (90.3)	22 (71) 15 (48.4)	6 (19.3)	0.019
	2) Invasive mole 3) Choriocarcinoma	16 (51.6) 10 (32.3) 5 (16.1)	6 (19.4) 1 (3.2)	1 (3.2) 4 (12.9) 4 (12.9)	
	Term pregnancy	3 (9.7)	0	3 (9.7)	
WHO scoring	Low grade (score < 7)	25 (80.36)	22 (70.9)	3 (9.7)	0.000
	High grade (score ≥ 7)	6 (19.4)	0.000	6 (19.4)	
Metastasis location based on WHO score	Limited to uterine body	16 (51.6)	16 (51.6)	0	0.000
	Vagina or pelvic involvement	0	0	0	
	Lung	13 (41.9)	6 (19.4)	7 (22.5)	
	Extra pelvic metastasis	2 (6.5)	0	2 (6.5)	
Type of performed surgeries	Hysterectomy	21 (67.7)	16 (51.6)	5 (16.1)	0.230
	Hysterotomy	6 (19.4)	5 (16.2)	1 (3.2)	
	Thoracotomy	3 (9.7)	1 (3.2)	2 (6.5)	
	Craniotomy	1 (3.2)	0	1 (3.2)	
Reason for surgery	Resistance to chemotherapy	28 (90.3)	19 (61.3)	9 (29)	0.537
	Bleeding	3 (9.7)	3 (9.7)	0	
HCG level before surgery	<100	1 (3.2)	0	1 (3.2)	0.220
	100-1000	4 (12.9)	2 (6.5)	2 (6.5)	
	1000-10000	2 (6.5)	1 (3.2)	1 (3.2)	
	>10000	20 (64.5)	17 (54.8)	3 (9.7)	
	Missing	4 (12.9)	2 (6.5)	2 (6.5)	
Chemotherapy	Only before surgery	10 (32.3)	10 (32.3)	0	0.007
	Only after surgery	3 (9.7)	3 (9.7)	0	
	Both before and after surgery	18 (58.1)	9 (29)	9 (29)	

WHO: World Health Organization; HCG: Human chorionic gonadotropin