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Clinical evaluation of hysterectomy for the treatment of invasive mole in Southern Vietnam

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Abstract. – OBJECTIVE: This study aimed to determine the rate of salvage chemotherapy and review associated factors in invasive mole patients treated by primary or delayed hysterectomy.

PATIENTS AND METHODS: This study was carried out at the Tu Du Hospital, where a total of 189 patients were diagnosed with invasive mole based on histologic examination by hysterectomy between 01/2016 to 12/2020. We used the life table method to estimate the cumulative rate. We applied the Cox proportional hazard model to determine the factors associated with the need for salvage chemotherapy.

RESULTS: At 12-month follow-up, 47 patients had required salvage chemotherapy. The incidence was 24.87% (95% CI: 18.88-31.66). Applying the multivariate model, prophylactic chemotherapy (HR = 2.75, 95% CI: 1.20-6.30) and two weeks postoperative hCG value greater than 1,900 mIU/mL (HR = 4.30, 95% CI: 2.08-8.87) increased the risk of requiring salvage chemotherapy. Postoperative chemotherapy decreased the risk of requiring salvage chemotherapy (HR = 0.43, 95% CI: 0.22-0.83).

CONCLUSIONS: Hysterectomy can be considered safe and effective in treating invasive mole patients. Although patients were treated by hysterectomy, 24.87% of patients needed salvage chemotherapy to achieve remission. This study affirms the malignant nature of invasive mole, a subtype of gestational trophoblastic neoplasia (GTN). It is not purely a local invasion of molar villi. Postoperative chemotherapy plays an essential role in reducing the risk of requiring salvage chemotherapy.

Key Words:
Invasive mole, Gestational trophoblastic neoplasia, Hysterectomy, Postoperative chemotherapy, Salvage chemotherapy.

Introduction

Hydatidiform mole (HM) is a benign disease, in which about 80% will withdraw from the disease, but the rate of progression to gestational trophoblastic neoplasia (GTN) is relatively high, and invasive mole (IM) accounts for nearly 3/4 of GTN cases[1]. GTNs represent a heterogeneous group of pregnancy-related tumors, including invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). The GTN spectrum has recently been expanded to include atypical placental site nodule (APSN)[2]. Invasive mole is a rare, chemotherapy-sensitive, curable disease. It is a hydatidiform mole in which hydropic villi invade the myometrium or blood vessels or, more rarely, are deported to extrauterine sites. Although invasive hydatidiform mole is not an actual neoplastic disease, it is often considered clinically malignant since the lesion can invade the myometrium and metastasize. GTN responds well to chemotherapy, with cure rates of over 90% while preserving reproductive function. Although uncommon, hysterectomy is an initial treatment consideration for patients with GTN that has not metastasized and where the patient no longer wishes to have children, or that is resistant to chemotherapy. Primary or delayed hysterectomy can be integrated into management to remove central disease, and surgical extirpation of metastases may cure highly selected patients with drug-resistant disease.

For benign hydatidiform mole, some studies[3,4] have shown that hysterectomy does not reduce GTN development and the number of chemotherapy cycles. Still, there is also recent research[5,6] indicating that hysterectomy is a good treatment for patients who do not desire fertility.

According to a report[7] by the Hanoi Institute of Maternal and Infant Protection in Vietnam, the frequency of hydatidiform is high, at about 1 in 500 pregnancies. Tu Du Hospital (TDH) is the major center for HM management, treatment, and follow-up in Vietnam's southern provinces. Annual statistics by the Gynecologic Oncology Department of Tu Du Hospital disclose that the hospital provides treatment and follow-up ser-

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vices to 800-1,000 HM cases a year. At Tu Du Hospital, a hysterectomy is usually performed when the patient is over the age of 40 and no longer wishes to have children. Histology is used to confirm the interpretation of GTN, in which IM accounts for a relatively high proportion. Following hysterectomy in IM patients, the regimen of treatment would be adjuvant chemotherapy or purely monitoring of serum beta human chorionic gonadotropin (β-hCG) levels. Surgery is evaluated as a successful treatment when β-hCG values return to normal. If serum β-hCG levels elevate or plateau, the patient will receive salvage chemotherapy.

The aim of this study is to determine the rate of salvage chemotherapy and review associated factors in invasive mole patients who are treated by primary or delayed hysterectomy.

Patients and Methods

Study Design and Study Population

This study was designed as a retrospective cohort study. Medical records of all patients diagnosed with IM at TDH from January 2016 to December 2020 were reviewed. We included all IM cases with histologic confirmation of diagnosis at TDH and monitored according to the TDH regimen for at least 12 months after discharge. Patients who refused treatment monitoring were excluded from the study.

Measurements

First, IM subjects were confirmed by the records from TDH histology department. Then, in the Gynecologic oncology department, data obtained from the medical records included basic demographic information, characteristics, IM treatment following hysterectomy and the time of abnormal serum hCG. Salvage chemotherapy following hysterectomy was applied when serum quantitative hCG levels at one to two-week intervals during monitoring or adjuvant chemotherapy met one of the following criteria: (1) > 10% rise in hCG after first measuring or (2) ±10% change in hCG after second measuring[8,9]. Since this is a retrospective study, vaginal bleeding and blood loss were based on the attending physician's subjective assessment noted in medical records. Risk rating for GTN based on the classification by FIGO (2000)[10]. The uterine size was determined by the attending physician's clinical experiences with the support of ultrasound measuring.

Sample Size and Sampling Procedure

Total sampling method from January 2016 to December 2020 was applied. Data collected from inpatient, and outpatient medical records contained basic epidemiologic information in Tu Du Hospital, postoperative HM patients are monitored on β-hCG bi-weekly until three consecutive negative tests, and then, once per month for the next six consecutive months, followed by twice a month for the next 6 months and once every 3 months for the next 12 months.

Statical Analysis

We analyzed the data with Stata 14.0 (Stata Corp LLC, Lakeway Drive College Station, TX, USA). Time-to-applying salvage chemotherapy (in weeks) was defined as the time from surgical treatment of IM to the time of diagnosed requirement for salvage chemotherapy. Descriptive analyses with percentages and medians were performed to examine patients' and IM's characteristics. We used the life table method to estimate the cumulative requirement salvage chemotherapy rate. A comparison of survival time between groups was performed using the Log-rank test. We used Cox proportional hazard regression to explore the relationship between applying salvage chemotherapy and the time of IM diagnosis following hysterectomy in univariate and multivariate analyses. Variables included in multivariate models were performed after the selection of bivariate associations from univariate analysis (p-value < 0.2). Significance was set at $p < 0.05$.

Results

Among 227 cases of invasive mole between 1/2016 and 12/2020 (Figure 1), 189 case were included in the study, and 47 patients had abnormalities during monitoring of serum β-hCG levels after hysterectomy. Patients' and the diagnosed IM characteristics are described in (Table I).

The patient ages ranged from 33 to 62 years, and our patients' median age (interquartile range) was 46 years. Most patients have offspring. The rate of having more than two children accounted for 85.71%, and nulliparity accounted for 1.06%. Histology after suction was mostly complete hydatidiform mole (CHM) (47.65%) and partial hydatidiform mole (PHM) (34.71%). A small proportion of other

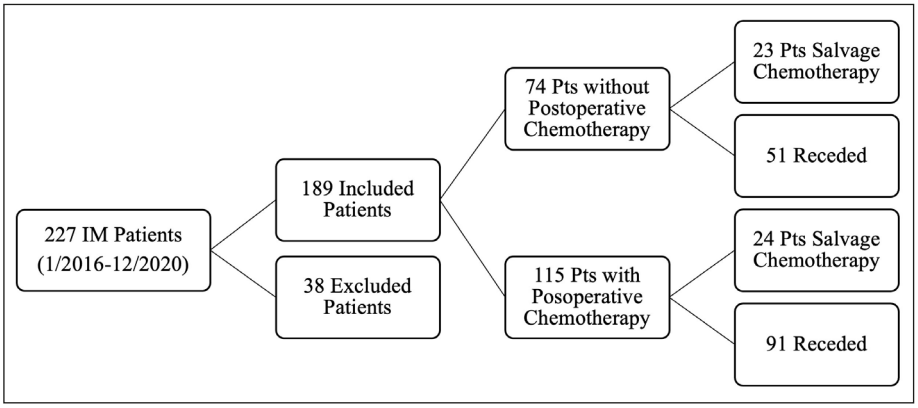

Figure 1. Patients flow diagram.

results, such as normal placental tissue, degenerative placental villi or unclassified hydatidiform mole, accounted for 17.64% of the patient population. Most diagnosed GTN were stage I. 7.41% of patients developed metastases beyond the uterus, such as in the vagina, lungs, and brain. Before total hysterectomy combined with or without oophorectomy, most patients had not been exposed to chemotherapy (81.48%). A methotrexate/Folinic acid (MTX/FA) regimen was indicated for 14.82% of patients. Senior physicians were more likely to recommend hysterectomy in the patient who was older, had enough children (92.06%) or had failed to respond to primary chemotherapy (7.94%).

At follow-up 12 months after hysterectomy, 24.87% of patients had required salvage chemotherapy, corresponding to 47 out of 189 cases treated with hysterectomy, [95% Cl: 18.88-31.66%] (Table II). The average time of diagnosis detection was 8.94 ± 4.35 weeks. The median (interquartile range) was nine weeks, the earliest as three weeks, and the latest as 21 weeks.

We used a Cox regression model to identify factors associated with the need for salvage chemotherapy. We initially used a univariate Cox proportional hazards regression model to analyze 25 pairs of univariates variables then to control confounders and co-factors, 4 statistically significant variables were added plus other 7

Table I. Invasive mole's characteristics.

Characteristics		Total hysterectomy patients. N = 189	Frequency (%)
Age	≤ 46 years	98	51.85
	> 46 years	91	48.15
Gravida	0	2	1.06
	1	25	13.23
	≥ 2	162	85.71
Pathological diagnosis		**N=170**	
	Partial mole	59	34.71
	Complete mole	81	47.65
	Other results	30	17.64
FIGO Stages	I	175	92.59
	II - IV	14	7.41
Primary chemotherapy	None	154	81.48
	Single agent	28	14.82
	Multi-agent therapy	7	3.70
Hysterectomy indication	Older than 40 years and not desire fertility.	177	92.06
	Failed response to primary chemotherapy	15	7.94

Table II. Cumulative salvage chemotherapy.

Week interval	Number of patients without salvage chemotherapy (N=142)	Number of patients with salvage chemotherapy (N=47)	Estimated cumulative of salvage chemotherapy % (95% CI)
1	189	0	0
2	189	0	0
3	186	3	1.59 (0.33-4.57)
4	183	3	3.17 (1.17-6.78)
5	178	5	5.82 (2.94-10.17)
6	172	6	8.99 (5.33-14.01)
7	168	4	11.11 (7.01-16.48)
8	167	1	11.64 (7.44-17.09)
9	159	8	15.87 (10.97-21.88)
10	155	4	17.99 (12.79-22.22)
11	153	2	19.05 (13.71-25.38)
12	150	3	20.63 (15.10-27.11)
13	148	2	21.69 (16.04-28.26)
14	148	0	21.69 (16.04-28.26)
15	148	0	21.69 (16.04-28.26)
16	147	1	22.22 (15.51-28.83)
17	144	3	23.81 (17.93-30.53)
18	143	1	21.69 (18.40-31.10)
19	143	0	21.69 (18.40-31.10)
20	143	0	21.69 (18.40-31.10)
21	142	1	24.87 (18.88-31.66)
22	142	0	24.87 (18.88-31.66)
52	142	0	24.87 (18.88-31.66)

variables with $p<0.2$ by univariable analysis into Cox multivariable regression model to carefully assess the correlation between those factors and the need for savage chemotherapy. Table III presented multivariable analysis has 11 variables over the total of 25 independent variables (Table III). In the multivariate Cox regression model, there were three significant associated factors with salvage chemotherapy after hysterectomy. The requirement of salvage chemotherapy was significantly associated with prophylactic chemotherapy, an elevated two-week postoperative serum β-hCG value over 1,900 mIU/mL, and postoperative chemotherapy. Prophylactic chemotherapy increased the risk of requiring salvage chemotherapy compared to the non-intervention group by 2.75 times [Hazard ratio, (HR) = 2.75, 95% CI = 1.20-6.30]. 2 weeks postoperative serum β-hCG value greater than 1,900 mIU/mL increased the risk of needing salvage chemotherapy by 4.30 times, (HR = 4.30, 95% CI = 2.08-8.87). Postoperative chemotherapy reduced the risk of requiring salvage chemotherapy (HR = 0.43, 95% Cl = 0.22-0.83).

Discussion

Age is one of the critical factors in the choice of treatment method, prognosis, and management of IM. Of the 189 cases that met the criteria for admission to the study, we recorded that the youngest patient diagnosed with IM was 33 years old, the oldest was 62 years old, and the average age was 46.06 years old. Our results on the efficiency of hysterectomy should be strictly limited to GTN patients when childbearing considerations have been fulfilled. It is worth noting that the median age of our patients was 46 years, which is significantly more than that of patients admitted to the study of Batti et al[11] (33 years) and less than the study of Bolze et al[9] (51 years). The patient's average age did not differ from the study of Phan et al[12]. The differences between studies from different periods of GTN may be explained by the following factors: (i) differences in study design, (ii) variable criteria and variations in the diagnosis of GTN. We performed a retrospective cohort study to collect a larger sample in order to explore the

Table III. Cumulative salvage chemotherapy.

Factors		Cox proportional hazards regression: Hazard Ratio (95% CI)			
		Univariate analyses	*p**	Multivariate analyses	*p***
Hydatidiform mole history	No	1		1	
	Yes	1.84 (0.72-4.64)	0.199	1.94(0.67-5.62)	0.225
Vaginal Bleeding	No	1		1	
	Yes	0.37 (0.17-0.83)	0.016	0.40(0.16-1.03)	0.058
Uterine tumor	No	1		1	
	Yes	0.48 (0.27-0.86)	0.013	0.63(0.34-1.18)	0.149
Suction curettage	No	1		1	
	Yes	2.8 (0.68-11.55)	0.154	1.33 (0.28-6.35)	0.718
Chemotherapy prophylaxis	No	1		1	
	Yes	2.35 (1.05-5.25)	0.037	2.75 (1.20-6.30)	**0.016**
Preoperative serum β-hCG (mIU/mL)	≤ 21,000	1		1	
	> 21,000	0.71 (0.40-1.27)	0.248	0.62 (0.29-1.34)	0.223
FIGO score	0-4	1		1	
	5-6	0.91 (0.47-1.75)	0.780	0.97 (0.46-2.05)	0.937
	7-8	1.04 (0.49-2.22)	0.916	1.20 (0.45-3.20)	0.723
Primary chemotherapy	None	1	0.174	1	
	Single agent	0.49 (0.18-1.37)	0.499	0.44 (0.05-3.49)	0.436
	Multiagent therapy	0.50 (0.07-3.66)		0.24 (0.01-5.20)	0.363
Hysterectomy indication	Not desire fertility.	1		1	
	Fail to respond primary chemotherapy	1.10 (0.40-3.08)	0.849	4.26 (0.42-43.75)	0.222
2 weeks post-operative serum β-hCG (mIU/mL)	≤ 1,900	1		1	
	> 1,900	2.42	0.003	4.30 (2.08-8.87)	**0.001**
Postoperative treatment	Non-intervention	1		1	
	Postoperative chemotherapy	0.63	0.105	0.43 (0.22-0.83)	**0.012**

*p**: Univariate analyses, *p*****: Multivariate analyses.

characteristics of IM. Medical records were compiled based on the histological result from a uterine specimen.

We identified two patients with IM who were nulliparous on extended work-up treated with hysterectomy, corresponding with 1.06% of the study population. In comparison, the nulliparous proportion in patients in the Vo et al[11] study was 29.03%. The difference between study populations is suspected to be due to differences in inclusion criteria, which were limited to low-risk GTN patients in Vo's study[13]. In short, where patients fail to respond to primary chemotherapy, a hysterectomy may be beneficial in selected patients with appropriate counseling and consultation. However, even these patients should be involved in careful shared decision-making surrounding the efficiency, benefits, and specific risks of both the chemotherapy regimen and hysterectomy.

Histological diagnoses after D&C are mainly complete hydatidiform mole (CHM) (47.65%), and partial hydatidiform mole (PHM) (34.71%). Few studies[12,14] have reported the proportion of PHM as being high, such as Vo et al[14], 2019 and Phan et al[12], 2021, with 56.49% and 65.86%, respectively. This would be reasonably expected due to a difference in inclusion criteria, with our current study population having a majority of IM patients, while the previous studies' populations were largely HM patients.

In patients with FIGO stage I disease, the selection of treatment was based primarily on whether the patient desires to retain fertility. Some patients received a chemotherapy regimen as a first-line treatment, which was typically designed according to the International Federation of Gynecology and Obstetrics (FIGO), at a rate of 18.4%. A chemotherapy regimen with sin-

gle-agent MTX/FA (14.82%) was the preferred regimen for treatment at Tu Du Hospital among patients with nonmetastatic and low-risk GTN. A multi-agent regimen, such as EMA/CO (Etoposide, MTX, Act. D, Cyclophosphamide, Vincristine), was also applied to high-risk GTN patients and FIGO stage II disease. Criteria that defined failure to respond to primary chemotherapy alone and where second-line therapy, namely hysterectomy, was offered to patients were as follows: (i) ±10% change in hCG during 1 cycle or (i) >10% rise in hCG during 1 cycle or plateau following 2 cycles of chemotherapy. The same criteria were used to define chemoresistance.

Hysterectomy was indicated mainly in patients older than 40 years old who did not wish to preserve fertility (92.06%) or had failed to respond to primary chemotherapy (7.94%). Clark et al[15] reported the hysterectomy rate due to chemoresistance was 33.33%. The discrepancy in the rate of failure to respond to primary chemotherapy was likely because Clark's population included all subtypes of GTN and was not limited to low-risk GTN patients as in our study. PSTT, ETT, and choriocarcinoma are diseases with high malignant potential and are drug resistant.

Most patients who developed gestational trophoblastic neoplasia after hydatidiform mole are detected by histologic examination. According to FIGO staging, most patients were in stage I at a rate of 92.59%. The rest of the patients were in FIGO stage II-IV, at a rate of 7.41%. Phan et al[12], 2021 reported FIGO stages I and II prevalence of 95.3% and 4.07% in their study population, respectively. At the same time, there was no data about FIGO stages III-IV. The reasons provided for this were: (i) population and (ii) the follow-up after D&C to detect progression GTN. In another study by Bolze et al[9], 2018, the local physicians chose the surgical approach of hysterectomy, and the inclusion of patients was strictly limited to the low-risk GTN group. That led to 94.6% and 5.4% of patients in the first and second stages without any stage III or IV. Through our registration data, it has been confirmed IM is a malignant subtype of GTN. Because of the possibility of distant metastasis beyond the uterus, not only penetration of molar tissue (complete or partial mole) into the myometrium but also into the vascular system, which is to implant in the vagina, lungs, brain or other organs.

In the present study, 24.87% of IM patients treated by hysterectomy needed follow-up salvage chemotherapy. Giorgione et al[4], 2017 and Clark et al[15], 2010 reported respective incidences of 28.57% and 48% requiring salvage chemotherapy[4,15], which was higher than seen in this study. Possible explanations could include the population's characteristics, high-risk GTN patients, and histology-type differences. Some other studies show the incidence of requiring salvage chemotherapy was lower, such as Bolze et al[9], 2018 at 17.57% and Feng et at[16], 2010 at 9%, because of a higher rate of patients undergoing presurgical chemotherapy. Adjuvant or primary chemotherapy is administered for three reasons: (i) to reduce the burden of viable tumor cells at the time of surgery, (ii) to treat any occult metastases that may be present at the time of surgery, and (iii) to maintain a cytotoxic level of chemotherapy in the bloodstream and tissues in case viable tumor cells are disseminated at the time of surgery[17].

The three risk factors associated in multivariate analysis with the need for salvage chemotherapy for IM patients treated with hysterectomy were: (i) prophylactic chemotherapy after suction curettage hydatidiform mole, (ii) 2-weeks postoperative hCG value greater than 1,900 mUI/mL, (iii) immediate postoperative chemotherapy. Postoperative chemotherapy should be considered helpful management for IM patients following a hysterectomy.

Limitations

The major limitation of the present retrospective cohort study is the absence of randomization. The study depends on medical records, which can lead to errors and a lack of sufficient information. Another limitation of this study is its dependence on clinician evaluation, in which some variables are subjective, such as the choice of postoperative treatment. Finally, 36 patients were excluded due to lost follow-up that might relate to lost follow-up bias. This issue may have affected the characteristics and breadth of the study sample. Despite these limitations, this study has identified the rate of salvage chemotherapy required in our study population and associated risk factors. Based on the results of this study, patients with these risk factors should be closely managed and followed up by clinicians in accordance with surveillance plans after treatment for IM as outlined by FIGO. Importantly, individualization of therapy could also be associated with reduced length of stay in the hospital, shorter durations of chemotherapy, and lower total dosage of chemotherapy. Clearly, larger studies are necessary to fully understand the potential impact.

Conclusions

The present study suggests that hysterectomy can be considered safe and effective when performed as primary or delayed treatment in GTN, as this procedure cures women who no longer wish to have offspring. The percentage of patients who did not require salvage chemotherapy was 24.87%, and no deaths were reported during the study period. The study has confirmed that IM is not merely an *in-situ* invasion of hydropic villi but can metastasize beyond the uterus, therefore making IM a malignant disease. Immediate postoperative chemotherapy plays an essential role in reducing the failure rate of surgical treatment. Understanding the factors related to the requirement of salvage chemotherapy helps clinicians choose the most appropriate treatment regimen and consult patients effectively after a hysterectomy.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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Authors' Contributions

T. Vo and T. Tran designed and managed the study.
T. Tran, T. Ho performed the analyses and wrote the manuscript.
H. Pham, N. Ho, H. Tran made contributions to the interpretation of data.
T. Vo, B. Vo provided comments on manuscript drafts.
T. Vo, C. Le, T. Tran, T. Cao revised the article.
All authors agreed to be accountable for the work.

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Availability of Data and Materials

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

Informed Consent

The informed consent was waived due to the retrospective design of the study. Data were kept anonymous and confidential during all stages of the study.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki 1964. Ethics approval for the study was obtained from the Institutional Review Board of Tu Du Hospital (No: 128/QD-BVTD 1/2022).

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