

## CLINICAL STUDY

# Invasive and metastatic hydatidiform moles in Slovakia in 1993–2022

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**ABSTRACT**

**OBJECTIVE:** A retrospective analysis of invasive and metastatic hydatidiform moles (HM) in the Slovak Republic (SR)—epidemiology, patient characteristics and treatment outcomes.

**BACKGROUND:** Invasive and metastatic mole is a highly curable type of gestational trophoblastic neoplasia. Both invasive and metastatic HM may be cured by hysterectomy without adjuvant chemotherapy.

**METHODS:** Nineteen cases of histopathologically confirmed HM (10 invasive and 9 metastatic) were treated in SR from 1993 to 2022. Patients were divided into two groups according to treatment modality (hysterectomy only – 8; hysterectomy & chemotherapy – 11). The parameters included in the analysis were patient age, antecedent pregnancy, human chorionic gonadotropin level, tumor size and time to remission.

**RESULTS:** The incidence of invasive and metastatic HM in the SR was 1:121,253 pregnancies, or 1:86,589 live births. The overall cure rate was 100%, without recurrence. Hysterectomy was performed as first-line therapy in 14 patients, with a cure rate of 57.1%. 4 out of 8 patients (50%) with metastatic moles, who underwent first-line hysterectomy, were cured without chemotherapy. There was no statistically significant difference between the two groups in all selected parameters.

**CONCLUSION:** First-line hysterectomy may lead to remission without adjuvant chemotherapy or reduce the number of chemotherapies in invasive and metastatic HM (*Tab. 4, Fig. 2, Ref. 21*). Text in PDF [www.elis.sk](http://www.elis.sk)

**KEY WORDS:** gestational trophoblastic disease, invasive and metastatic mole, hysterectomy, chemotherapy.

**Introduction**

Gestational trophoblastic disease (GTD) is a rare group of disorders associated with pregnancy, characterized by abnormal trophoblastic proliferation. The spectrum of GTD ranges from non-cancerous hydatidiform moles to malignant neoplasms – gestational trophoblastic neoplasia (GTN), such as gestational choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor, and mixed trophoblastic tumor (1).

Hydatidiform moles (HM) are further classified as complete or partial moles and are generally considered to have a benign course. However, there is a 15% risk of local invasion and 4% risk of metastases after evacuation of a complete mole, while

evacuation of a partial mole carries a 0.5–5% risk of persistent gestational trophoblastic neoplasia, usually in the form of an invasive mole (1, 2, 3, 4).

An invasive HM is a hydatidiform mole, usually complete but occasionally partial, that invades the myometrium and/or the uterine vessels. Metastatic HM is defined as lesions containing abnormal molar chorionic villi that occur outside the uterine cavity, most commonly in the vaginal wall or pelvis (3).

The exact incidence of invasive and metastatic HM is difficult to determine due to the varied approaches to diagnosis and treatment of postmolar GTN, which encompasses different types of GTN, including invasive and metastatic HM (5). The most common way to diagnose postmolar GTN is by monitoring the levels of human chorionic gonadotropin (hCG) in the follow-up period after a HM has been removed. An increase or plateau in hCG levels indicates the presence of postmolar GTN (5, 6).

Chemotherapy is typically the first-line treatment for postmolar GTN, without the need for histopathologic confirmation. The International Federation of Gynecology and Obstetrics (FIGO) anatomical staging system is used for staging, and the World Health Organization (WHO) prognostic scoring system classifies patients as low-risk or high-risk. (6). Low-risk patients are treated with single-agent chemotherapy, while high-risk patients are treated with multi-agent chemotherapy (7). The cure rates for low-risk and

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high-risk patients are 100% and 95%, respectively (5). Invasive and metastatic HM are generally sensitive to chemotherapy. Surgical therapy, such as hysterectomy, is usually reserved for patients who have completed their reproductive wishes, are resistant to chemotherapy, or have profuse hemorrhage due to perforation or massive tumor collapse during chemotherapy (8, 9, 10).

After the split of the former Czechoslovak Republic, patients with GTN started to be treated in Slovakia in 1993. GTN treatment in the Czechoslovak Republic began in 1955 with the establishment of the Center for GTD in Prague. Patients from Slovakia with GTN were treated at this center between 1955–1992 (11). The purpose of the presented study was to analyze the epidemiology, clinical characteristics and treatment results among women with histopathologically confirmed invasive and metastatic moles in the Slovak Republic.

## Patients and methods

A retrospective study was conducted to analyze cases of invasive and metastatic HM that were histopathologically confirmed and treated in the Slovak Republic from January 1st, 1993, to December 31st, 2022. 19 patients were included in the study. Patient age, largest tumour size, antecedent pregnancy, hCG levels, FIGO (International Federation of Gynecology and Obstetrics) stage, WHO (World Health Organization) prognostic risk groups, and time interval to remission were evaluated. All patients consented to the use of their records in the study. Invasive HM was defined as tumors that invaded only the uterus, while metastatic HM referred to lesions that were beyond the uterus. Pelvic ultrasound, computed tomography (CT) chest, abdomen, and pelvis scans were used to evaluate patients. Chest x-ray and brain magnetic resonance imaging (MRI) were conducted in cases where pulmonary metastases were detected on chest CT scans. Patients up to 2000/2002 were classified based on the WHO scor-

ing system (1983) and were retrospectively reclassified using the FIGO staging system and the WHO prognostic scoring system (2000) (Tabs 1, 2). Abdominal hysterectomy was performed in all patients, and remission was achieved when hCG levels were below 5 IU/l. The patients were divided into two groups based on treatment modality, namely hysterectomy only and hysterectomy with chemotherapy. The data were organized and analyzed using MS Office Excel 2023. The Shapiro–Wilk test was used to determine normality of continuous variables. The Student's t-test was used to determine significant differences for normally distributed variables and the Mann–Whitney U-test was used for non-normally distributed variables. The Fisher's exact test and the Freeman–Halton extension of the Fisher's test were used to determine significant differences for categorical variables. Significance level was set at less than 0.05.

## Results

### Incidence

Slovakia, a high-income country with a population of approximately 5.4 million, experienced a decline in live births from 73,250 to 53,209 between 1993 and 2022. During the study period, the incidence of invasive and metastatic HM in Slovakia was 1 case in 121,253 pregnancies, or 1 case in 86,589 live births. Table 3 provides the incidence of invasive and metastatic HM according to age.

### Patients' characteristic

Nineteen patients were included in the analysis, as shown in Figure 1. The average age in the hysterectomy only group was 40.3 years (range 29–52 years; SD  $\pm$ 8.5), while in the combined therapy group it was 42 years (range 18–53 years; SD  $\pm$ 10.5) ( $p=0.38$ ) (Tab. 4). The highest pretreatment hCG levels in the hysterectomy only and combined therapy groups were 135,536 IU/l

**Tab. 1. FIGO anatomical staging (6).**

FIGO stage	Description
I	Disease confined to the uterus
II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)
III	GTN extends to the lungs, with or without known genital tract involvement
IV	All other metastatic sites

FIGO – International Federation of Gynecology and Obstetrics, GTN – Gestational trophoblastic neoplasia

**Tab. 2. World Health Organization prognostic scoring system (6).**

Risk factors	Scores			
	0	1	2	4
Age (years)	< 40	$\geq$ 40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	<4	4–6	7–12	>12
Pre-treatment serum hCG (IU/l)	$<10^3$	$10^3 \leq 10^4$	$10^4 \leq 10^5$	$\geq 10^5$
Largest tumor size including uterus (cm)	–	3–4	$\geq 5$	–
Site of metastases	Lungs	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	2 or more drugs

hCG – human chorionic gonadotropin

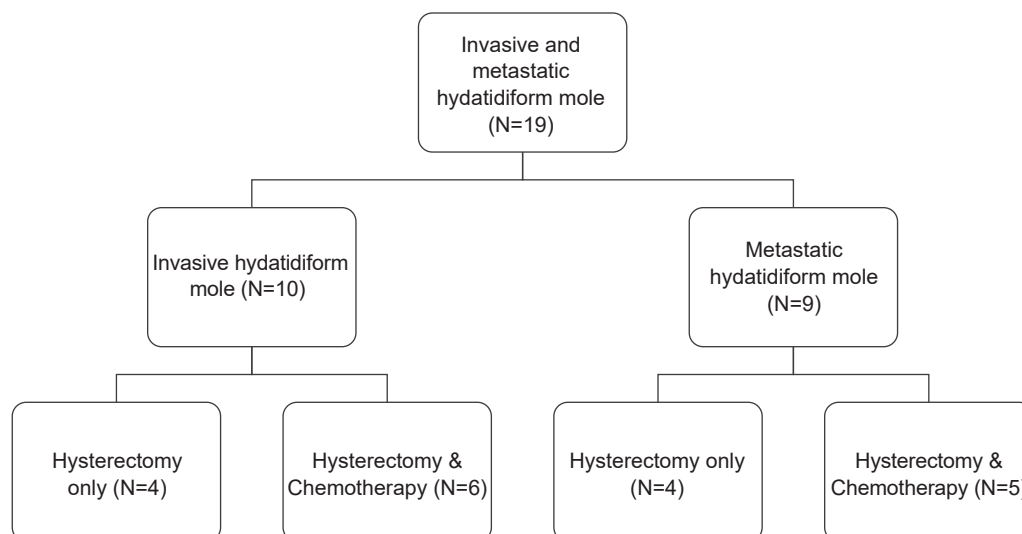


Fig. 1. Patient flow chart – distribution according to tumor type and treatment (hysterectomy only or hysterectomy & chemotherapy).

and 273,784 IU/l, respectively, while the average pretreatment hCG levels were 22,772 IU/l and 43,178 IU/l, respectively ( $p=0.38$ ). The mean tumor size in the hysterectomy only group was 4.86 cm (range 3–7 cm), and 4.83 cm (range 3.5–7 cm) in the combined therapy group ( $p=0.48$ ).

#### Therapy

In the analysis, 10 cases of invasive HM were identified, of which 6 were treated with primary hysterectomy. Out of those 6 patients, 4 were cured by hysterectomy only, while 2 required adjuvant chemotherapy after hysterectomy. 4 patients were initially

Tab. 3. Incidence of invasive & metastatic hydatidiform mole in age groups in Slovakia (1993–2022).

Age groups (years)	Patients number	Incidence	
		per pregnancies (miscarriages & total births)	per live births
15–19	1	1:148,128	1:136,431
20–29	2	1:504,060	1:472,096
30–39	4	1:147,291	1:133,857
40–49	8	1:4,301	1:3,637
50–54	4	1:11	1:10.5
<b>15–54</b>	<b>19</b>	<b>1:121,253</b>	<b>1:86,589</b>

Tab. 4. Selected parameters of invasive and metastatic hydatidiform mole in Slovakia from 1993 to 2022.

Parameter	Treatment modality						Fisher's exact test/ Freeman–Halton test <b>p</b>	
	Hysterectomy		Hysterectomy & Chemotherapy		All			
	n=8	%	n=11	%	n=19	%		
Antecedent pregnancy	Complete HM	6	75	7	63.64	13	68.42	p=0.80
	Partial HM	1	12.5	1	9.09	2	10.53	
	Miscarriage&abortion	1	12.5	3	27.27	4	21.05	
Age (years)	15–19	0	0	1	9.09	1	5.26	p=0.39
	20–29	2	25	0	0	2	10.53	
	30–39	1	12.5	3	27.27	4	21.05	
	40–49	4	50	4	36.36	8	42.11	
	>50	1	12.5	3	27.27	4	21.05	
hCG levels (IU/l)	< 10 <sup>3</sup>	2	25	3	27.27	5	26.32	p=0.85
	10 <sup>3</sup> –10 <sup>4</sup>	3	37.5	2	18.18	5	26.32	
	10 <sup>4</sup> –10 <sup>5</sup>	2	25	5	45.45	7	36.84	
	> 10 <sup>5</sup>	1	12.5	1	9.09	2	10.53	
WHO score	Low-risk	8	100	10	90.91	18	94.74	p=1.00
	High-risk	0	0	1	9.09	1	5.26	
FIGO stage	I	5	62.5	5	45.45	10	52.63	p=0.35
	II	0	0	1	9.09	1	5.26	
	III	3	37.5	5	45.45	8	42.11	
	IV	0	0	0	0	0	0	

HM – hydatidiform mole, hCG – human chorionic gonadotropin, IU – international units, WHO – World Health Organization, FIGO – International Federation of Gynecology and Obstetrics

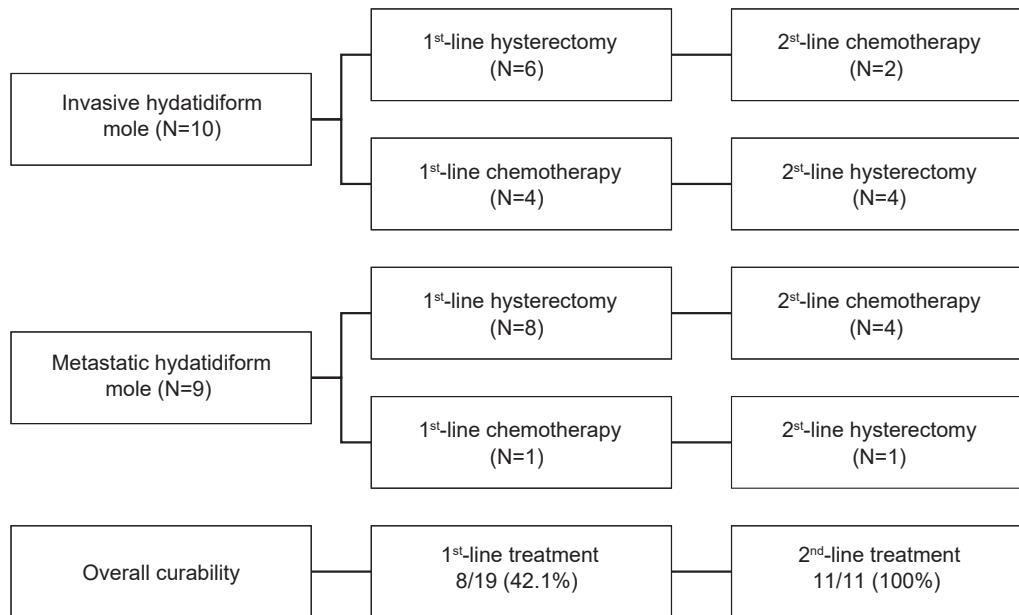


Fig. 2. Patient flow chart – division according to tumor type and treatment: overall curability with first-line and second-line treatment.

treated with primary chemotherapy, but due to bleeding complications and inadequate response to chemotherapy, hysterectomy was eventually performed. Among the 9 patients with metastatic HM, 4 were cured by hysterectomy only, while 5 required chemotherapy (Fig. 2). All 9 patients had lung metastases, and 1 patient experienced hemorrhage from a vaginal metastasis after hysterectomy which was treated with a hemostatic suture and subsequent chemotherapy.

Hysterectomy was the first-line therapy for 14 patients with invasive and metastatic HM, resulting in a cure rate of 8/14 (57.1%). Six patients experienced hCG progression after hysterectomy but were all cured by subsequent chemotherapy. Eight patients underwent only hysterectomy, while 11 received combined therapy (chemotherapy and hysterectomy). Low-risk patients were treated according to the GTD center treatment protocol with the 5-day intravenous chemotherapy regimen of Methotrexate (0.4 mg/kg/day) alternating with the 5-day intravenous regimen of Actinomycin D (10–12 ug/kg). Two patients required hysterectomy due to resistance to 1st line chemotherapy and received the EP (Etoposide, Cisplatin) chemotherapy regimen.

On average, the patients underwent 7 cycles of chemotherapy, with the range being between 5 and 9 cycles. There was only one patient classified as high-risk according to the FIGO 2002 scoring system (although she was considered medium risk according to the WHO 1983 scoring system at the time of treatment). This patient was treated with a combination of hysterectomy and MAC (Methotrexate, Actinomycin D, Cyclophosphamide) chemotherapy.

The cure rates were 8/19 (42.1%) with 1st line therapy and 11/11 (100%) with 2nd line therapy. None of the patients experienced relapse, and the average interval to remission was 8.5 weeks (4–19 weeks, SD  $\pm 4.93$ ) in the hysterectomy only group and 12.4 weeks (7–23 weeks, SD  $\pm 5.12$ ) in the combined therapy

group ( $p=0.05$ ). There were no statistically significant differences between the two groups in the evaluated parameters (Tab. 4).

## Discussion

The global incidence of hydatidiform mole (HM) is estimated to be approximately 0.57–2 cases per 1,000 pregnancies, with the incidence in Europe and North America ranging from 0.8–1.5 cases per 1,000 pregnancies (5, 12). The highest incidence of HM is in southeastern Asia at 13 cases per 1,000 pregnancies (5). The risk of gestational trophoblastic neoplasia (GTN) after a complete HM is between 15–20%, while the risk after a partial mole is 0.5–5% (4, 5). In Slovakia, the incidence of HM (complete and partial) was 0.90 cases per 1,000 pregnancies in the study period. Invasive and metastatic HM developed in 13 cases (68.4%) following a complete mole, in 2 cases (10.5%) following a partial mole, in 3 cases (15.8%) following a miscarriage, and in 1 case (5.26%) following a legal abortion.

Women over the age of 40 are at higher risk of developing HM, with a 7.5 to 10-fold higher risk than younger women and are also at higher risk of developing postmolar GTN (13, 14). In the Slovak population, 12 patients (63.2%) were over the age of 40, of whom 11 had a complete mole (91.7%) and 1 had a partial mole (8.3%).

According to medical literature, the lungs are the most common site for metastases in GTN, occurring in approximately 80% of cases. Vaginal metastases are also common, occurring in about 30% of cases, while liver and brain metastases are less frequent at 10% each, and other organs may also be affected but are rare (3,4).

In the studied population in Slovakia, there were 9 cases of metastatic mole, accounting for 47.4% of cases. Among these cases, lung metastases were present in all 9 cases (100%), while one patient (11.1%) also had a vaginal metastasis.

The primary treatment for GTN, including invasive and metastatic HM, is chemotherapy. Low-risk patients are typically treated with single-agent chemotherapy, and Methotrexate and Actinomycin D are the preferred regimens. High-risk patients are treated with multi-agent chemotherapy, with the EMA/CO regimen being the recommended choice (5, 7, 8). At the time of treatment, according to the 1983 WHO prognostic scoring system, two patients treated with MAC (one high-risk and one low-risk) were classified as medium-risk and the recommended treatment was MAC (15). A recent study reported a 5-year mortality rate of 0.3% in low-risk patients and 12% in high-risk patients when recommended chemotherapy protocols were followed (16).

Despite the efficacy of chemotherapy, adverse effects are experienced by many patients (5, 17). For patients who have completed their reproductive desires, first-line hysterectomy may decrease the number of chemotherapy cycles needed or lead to remission without chemotherapy (9, 18). Bolze et al. conducted a study in 74 low-risk patients with non-metastatic GTN who underwent first-line hysterectomy, with 82.4% of patients achieving hCG normalization without chemotherapy and the remaining 17.6% requiring chemotherapy (19). More recent studies report on the use of first-line hysterectomy for patients with metastatic GTN. In a study by Dabi et al, 30 patients with metastatic GTN were treated by first-line hysterectomy. There were 28 cases of invasive/metastatic moles and 2 cases of choriocarcinomas. Twenty-two patients (73.33%) achieved normalization of hCG without adjuvant chemotherapy, 7 patients required one single agent chemotherapy regimen and 1 patient required two single agent chemotherapy regimens (20). In a study by Eysbouts et al, all 7 patients with metastatic GTN treated with first-line hysterectomy needed adjuvant chemotherapy to achieve remission. The histopathology of the tumors was not specified (21). In our study, 14 patients (6 with invasive HM and 8 with metastatic HM) were treated with first-line hysterectomy, resulting in complete remission in 8 out of 14 patients (57.1%). The other 6 patients (42.9%) required chemotherapy. Complete response without subsequent chemotherapy was observed in 4 cases of invasive mole (66.7%) and 4 cases of metastatic mole (50%) – a total of 8 out of 19 cases (42.1%). In the studied group, there was a 100% overall cure rate with no relapses.

In conclusion, first-line hysterectomy in invasive and metastatic hydatidiform mole may produce remission without adjuvant chemotherapy or it may reduce the number of chemotherapy cycles administered. The incidence of histopathologically confirmed invasive and metastatic hydatidiform moles in Slovakia in the years 1993–2022 was 1:121,253 pregnancies, or 1:86,589 livebirths, with a 100% curability rate. Excellent curability rates can be achieved when patients are treated in specialized centers.

### Learning points

- Chemotherapy is the recommended initial treatment for women with invasive and metastatic hydatidiform mole who wish to preserve their fertility.

- Hysterectomy as a first-line treatment, without chemotherapy, can be curative even in cases of metastatic mole.
- The incidence of histopathologically confirmed invasive and metastatic hydatidiform mole in Slovakia was 1:121,253 pregnancies and the overall cure rate was 100%.

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